3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of creosote. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of creosote are indicated in Tables 3-1, 3-2, and 3-4 and Figures 3-1 and 3-2.

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

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

Wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles differ from each other with respect to their composition. Wood creosotes are derived from beechwood (*Fagus,* referred to herein as beechwood creosote) and the resin from leaves of the creosote bush (*Larrea*, referred to herein as creosote bush resin). Beechwood creosote consists mainly of phenol, cresols, guaiacol, xylenol, and creosol. It is a colorless or pale yellowish liquid, and has a characteristic smoky odor and burnt taste (Miyazato et al. 1981). It had therapeutic applications in the past as a disinfectant, a laxative, and a stimulating expectorant, but it is not a major pharmaceutical ingredient today in the United States.

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). It is not known whether the health effects associated with creosote bush resin are attributable to the phenolic components.

Coal tars are by-products of the carbonization of coal to produce coke or natural gas. Physically, they are usually viscous liquids or semisolids that are black or dark brown with a naphthalene-like odor. The coal tars are complex combinations of polycyclic aromatic hydrocarbons (PAHs), phenols, heterocyclic oxygen, sulfur, and nitrogen compounds. By comparison, coal tar creosotes are distillation products of coal tar. They have an oily liquid consistency and range in color from yellowish-dark green to brown. At least 75% of the coal tar creosote mixture is PAHs. Unlike the coal tars and coal tar creosotes, coal tar pitch is a residue produced during the distillation of coal tar. The pitch is a shiny, dark brown to black residue which contains PAHs and their methyl and polymethyl derivatives, as well as heteronuclear compounds (American Wood Preserver's Association 1988). Coal tar creosote, coal tar, and coal tar products are used as wood preservatives, herbicides, fungicides, insecticides, and disinfectants (EPA 1981a, 1984a). Volatile components of the coal tar pitch can be given off during operations involving coal tar pitch, including transporting, and in the coke, aluminum, and steel industries (Bender et al. 1988; Mazumdar et al. 1975; NIOSH 1983; Rönneberg 1995b; Rönneberg and Anderson 1995).

Although beechwood creosote, creosote bush resin, 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. Furthermore, coal tar creosote contains PAHs, some of which are carcinogenic to animals, and beechwood creosote does not. Thus, the relevance of health effects data on beechwood creosote to risk associated with exposure to coal tar creosote is not known.

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 great detail even though it is likely that the toxicity of wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles is due largely to these major individual components. However, it is understood that the toxicity of the individual components may not

be representative of the actual toxicity of the mixtures because of the possibility of synergistic and/or antagonistic interactions in the mixture. For more information on the health effects of these components, the reader can refer to the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons (Agency for Toxic Substances and Disease Registry 1992, 1995, 1998).

3.2.1 Inhalation Exposure

This section describes the health effects observed in humans and laboratory animals associated with inhalation exposure to coal tar pitch or coal tar pitch volatiles, for which reliable exposure levels could be determined. LSEs by the inhalation route presented in Table 3-1 and Figure 3-1 include studies using coal tar pitch volatiles or aerosols. All reliable exposure levels have been stated, where possible. No studies were located regarding the health effects in humans exposed solely by inhalation to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles. Studies of occupational exposure of humans (Armstrong et al. 1994; Bender et al. 1988; Bertrand et al. 1987; Bolt and Golka 1993; CEOH 1997; Costantino et al. 1995; Gibbs 1985; Gibbs and Horowitz 1979; Karlehagen et al. 1992; Kromhout et al. 1992; Kunze et al. 1992; Lloyd 1971; Lloyd et al. 1970; Mazumdar et al. 1975; NIOSH 1982; Park and Mirer 1996; Persson et al. 1989; Petsonk et al. 1988; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Romundstad et al. 2000; Rönneberg 1995b; Rönneberg and Andersen 1995; Sakabe et al. 1975; Schildt et al. 1999; Siemiatycki et al. 1994; Spinelli et al. 1991; Stern et al. 2000; Swaen and Slangen 1997; TOMA 1979, 1981, 1982; Tremblay et al. 1995; Ward 1988; Wu et al. 1998; Yadav and Seth 1998) did not distinguish between inhalation, oral, or dermal exposure. Several studies were found describing health effects in animals of inhalation exposure to aerosols of coal tar or coal tar pitch (Heinrich et al. 1994a, 1994b; Hueper and Payne 1960; MacEwen et al. 1977; Pfitzer et al. 1965; Springer et al. 1982, 1986b, 1987). Beechwood creosote, creosote bush resin, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles have some components in common, however, it is not known which of these components produce the toxic effects.

Table 3-1 Levels of Significant Exposure to Creosote - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m**3)	LOAEL Less Serious (mg/m**3)	LOAEL Serious (mg/m**3)	Reference Chemical Form
	ACUTE EXPOSURE						
	Systemic						
1	Human	8 hr (occup)	Ocular		0.18 M (conjunctivitis)		Emmett 1986 CTPV
2	Rat (CD)	5 d Gd 12-16 6 hr/d	Resp	84 F	660 F (significant increase in lung weight)		Springer et al. 1982 coal tar aerosol
			Hepatic	660 F			
			Renal	660 F			
			Endocr	660 F			
			Bd Wt	84 F	660 F (significant decrease in body weight)		
	Immuno/lymphoret						
3	Rat (CD)	5 d Gd 12-16 6 hr/d		84 F	660 F (significant decrease in thymus weight and increase in spleen weight)		Springer et al. 1982 coal tar aerosol
	Reproductive						
4	Rat (CD)	5 d Gd 12-16 6 hr/d		84 F	660 F (significant increase in the incidence of mid- and late-gestational resorptions)		Springer et al. 1982 coal tar aerosol
	Developmental						
5	Rat (CD)	5 d Gd 12-16 6 hr/d		84	660 (reduced fetal size, weight and lung size, reduced ossification)		Springer et al. 1982 coal tar aerosol
	INTERMEDIATE EXPOSURE						
	Death						
6	Rat (Wistar)	10 mo 5 d/wk 17 hr/d				2.6 F (increased mortality)	Heinrich et al. 1994a, b coal tar pitch

Table 3-1 Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m**3)	LOAEL Less Serious (mg/m**3)	LOAEL Serious (mg/m**3)	Reference Chemical Form
	Systemic						
7	Rat (Fischer-344)	6 wk 5 d/wk 6 h/d	Cardio		700 M (20% elevation in arterial blood pressure)		Sasser et al. 1989 coal mixture
			Bd Wt		700 M (17.5 % decrease in body weight)		
8	Rat (Fischer- 344)	5 wk 5 d/wk 6 hr/d	Resp		30 (histiocytosis of lung)		Springer et al. 1986b coal tar aerosol
			Cardio	690			
			Gastro	140 M 690 F	690 M (epithelial hyperplasia and chronic inflammation in cecum)		
			Hemato	30	140 (significant decrease in red blood cells, hemoglobin, and volume of packed red cells, significant increase in reticulocytes)		
			Hepatic	140 M	690 M (significant increase in relative weight of liver and serum cholesterol)		
			Renal	30 F	30 M (significant increase in relative weight of kidney) 140 F	690 M (pelvic epithelial hyperplasia)	
			Endocr	690			
			Bd Wt	30	140 (7% decrease in body weight)		

Table 3-1 Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m**3)	LOAEL Less Serious (mg/m**3)		LOAEL Serious (mg/m**3)		Reference Chemical Form
	Systemic								
9	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Resp		30	(histiocytosis of lung)	690	(lesions of olfactory epithelium)	Springer et al. 1986b coal tar aerosol
			Cardio	690					
			Gastro	140	690	(epithelial hyperplasia, ulcers and chronic inflammation of cecum)			
			Hemato	30 M	140 M				
				140 F	690 F	(significant decrease in red blood cells, hemoglobin, and volume of packed red cells)			
			Hepatic	30 F	30 M	(significant increase in relative liver weight)	690	(presence of liver lesions, elevated cholesterol, blood urea nitrogen and alteration in activities of SGPT and LDH)	
					140 F				
			Renal	30	140	(significant increase in relative kidney weight)	140 M	(pelvic epithelial hyperplasia and pigmentation of cortical tubules)	
							690 F		
			Endocr	690					
			Bd Wt	30	140	(10% decrease in body weight)			

Table 3-1 Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m**3)	LOAEL Less Serious (mg/m**3)		LOAEL Serious (mg/m**3)		Reference Chemical Form
	Systemic								
10	Mouse (CD-1)	13 wk 5 d/wk 6 hr/d	Resp	140	690	(lesions of olfactory epithelium)			Springer et al. 1987 coal tar aerosol
			Cardio	690					
			Gastro	690					
			Hemato	140	690	(significant decrease in red blood cells, hemoglobin, reticulocytes and volume of packed red cells)			
			Hepatic	29 M 140 F	140 M 690 F	(significant decrease in liver weight)			
			Renal	690					
			Endocr	690					
			Bd Wt	690					
11	Rabbit (New Zealand)	9 mo 5 d/wk 6 hr/d	Bd Wt				10 F	(31% decrease in body weight)	MacEwen et al. 1977 coal tar
	Immuno/lymphoret								
12	Rat (Fischer- 344)	5 wk 5 h/d 6 hr/d		140	690	(decreased number of megakaryocytes in spleen)			Springer et al. 1986b coal tar aerosol
13	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		30	140	(significant reduction in weight of thymus)	690	(atrophy of thymus, hypocellular bone marrow, and decreased number of megakaryocytes in marrow and spleen)	Springer et al. 1986b coal tar aerosol

Table 3-1 Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m**3)	LOAEL Less Serious (mg/m**3)	LOAEL Serious (mg/m**3)	Reference Chemical Form
	Immuno/lymphoret						
14	Mouse (CD-1)	13 wk 5 d/wk 6 hr/d		140 M 29 F	690 M (significant decrease in weight of thymus) 140 F		Springer et al. 1987 coal tar aerosol
	Neurological						
15	Rat (Fischer- 344)	5 wk 5 d/wk 6 hr/d		140 M 690 F	690 M (significant increase in relative brain weight)		Springer et al. 1986b coal tar aerosol
16	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		30	140 (significant increase in relative brain weight)		Springer et al. 1986b coal tar aerosol
17	Mouse (CD-1)	13 wk 5 d/wk 6 hr/d		690			Springer et al. 1987 coal tar aerosol
	Reproductive						
18	Rat (Fischer- 344)	5 wk 5 h/d 6 hr/d		690 M 140 F	690 F (decreased luteal tissue)		Springer et al. 1986b coal tar aerosol
19	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		30 M 140 F	140 M (significant increase in relative weight of testis) 690 F (significant decrease in relative weight of ovary and amount of luteal tissue)		Springer et al. 1986b coal tar aerosol
20	Mouse (CD-1)	13 wk 5 d/wk 6 hr/d		690 M 140 F	690 F (significant decrease in ovary weight)		Springer et al. 1987 coal tar

Table 3-1 Levels of Significant Exposure to Creosote - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m**3)	LOAEL Less Serious (mg/m**3)	LOAEL Serious (mg/m**3)	Reference Chemical Form
	Cancer						
21	Rat (Wistar)	10 mo 5 d/wk 17 hr/d				2.6 F (CEL: 39% incidence broncho-alveolar adenomas & adenocarcinomas)	Heinrich et al. 1994a, b coal tar pitch
22	Mouse CAF1- JAX	90 d 24 hr/d				10 F (CEL: 18/43 skin tumor, control = 0/225) (CEL: 27/50 lung tumor, control = 0/225)	MacEwen et al. 1977 coal tar
23	Mouse ICR CF-1	90 d 24 hr/d				2 F (CEL: 14/75 skin tumor, controls = 3/225)	MacEwen et al. 1977 coal tar
	CHRONIC EXPOSURE						
	Death						
24	Rat (Wistar)	20 mo 5 d/wk 17 hr/d				2.6 F (increased mortality)	Heinrich et al. 1994a coal tar pitch
	Systemic						
25	Monkey (Macaca mulatta)	18 mo 5 d/wk 6 hr/d	Bd Wt	10			MacEwen et al. 1977 coal tar
26	Rat (Sprague-Dawley)	18 mo 5 d/wk 6 hr/d	Bd Wt		10 (15% decrease in body weight)		MacEwen et al. 1977 coal tar
	Cancer						
27	Rat (Wistar)	20 mo 5 d/wk 17 hr/d				1.1 F (CEL: 33% incidence broncho-alveolar adenomas & adenocarcinomas)	Heinrich et al. 1994a, b coal tar pitch

Table 3-1 Levels of Significant Exposure to Creosote - Inhalation (continued)

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

aThe number corresponds to entries in Figure 3-1.

Differences in levels of health effects and cancer between males and females are not indicated in figure 3-1

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

Figure 3-1 Levels of Significant Exposure to Creosote - Inhalation

Acute (≤14 days)

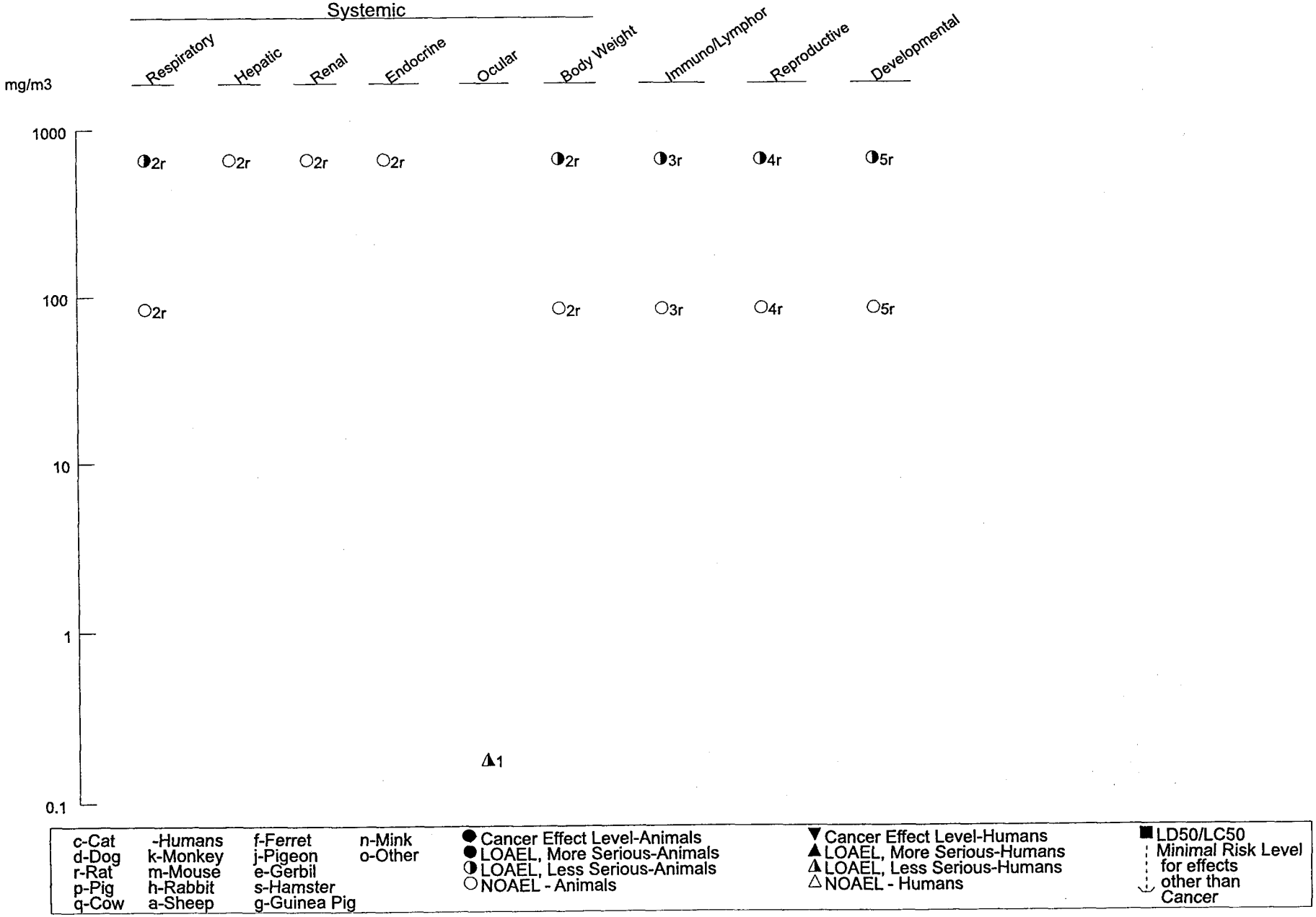


Figure 3-1 Levels of Significant Exposure to Creosote - Inhalation (*Continued*)

Intermediate (15-364 days)

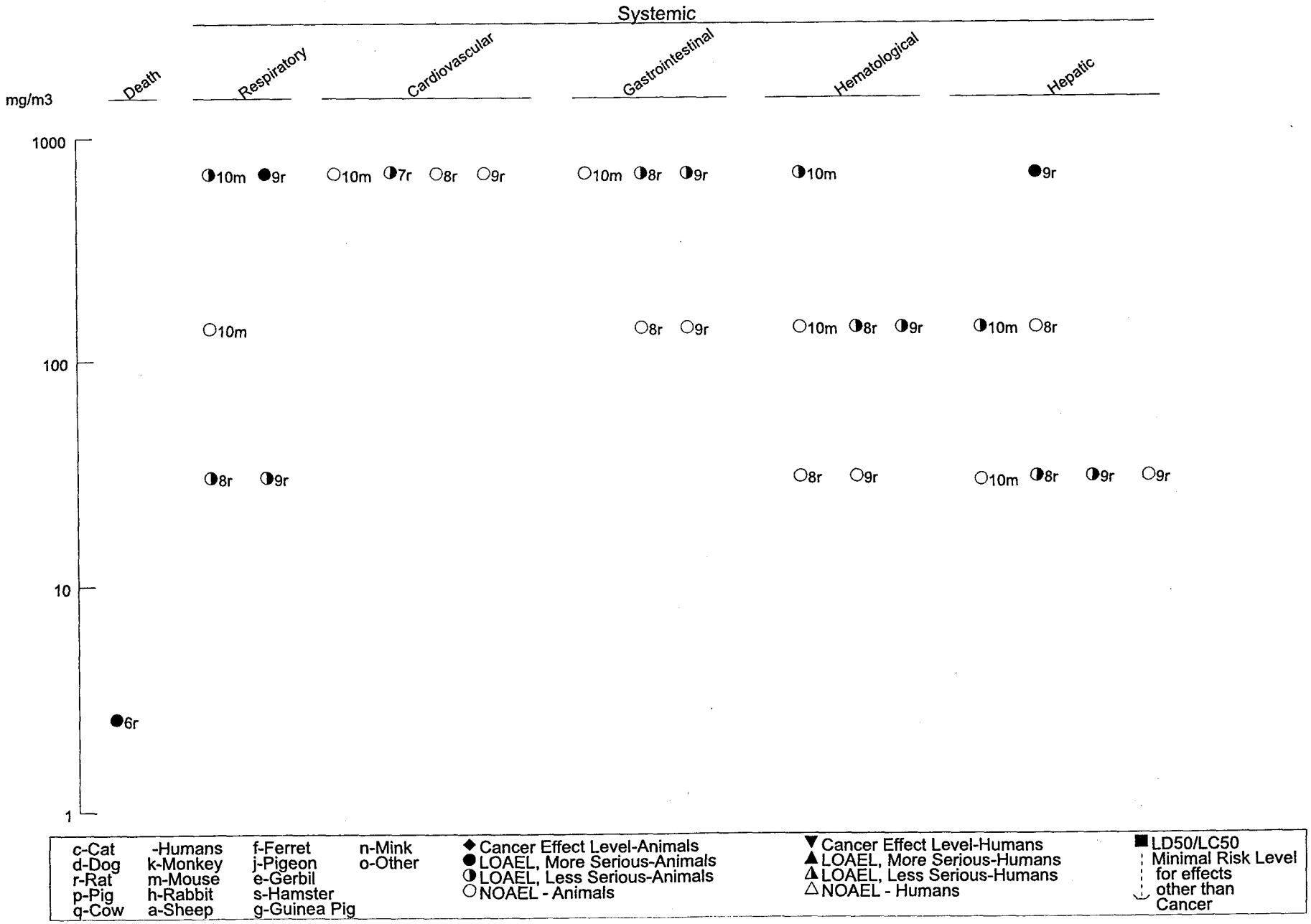


Figure 3-1 Levels of Significant Exposure to Creosote - Inhalation (*Continued*)

Intermediate (15-364 days)

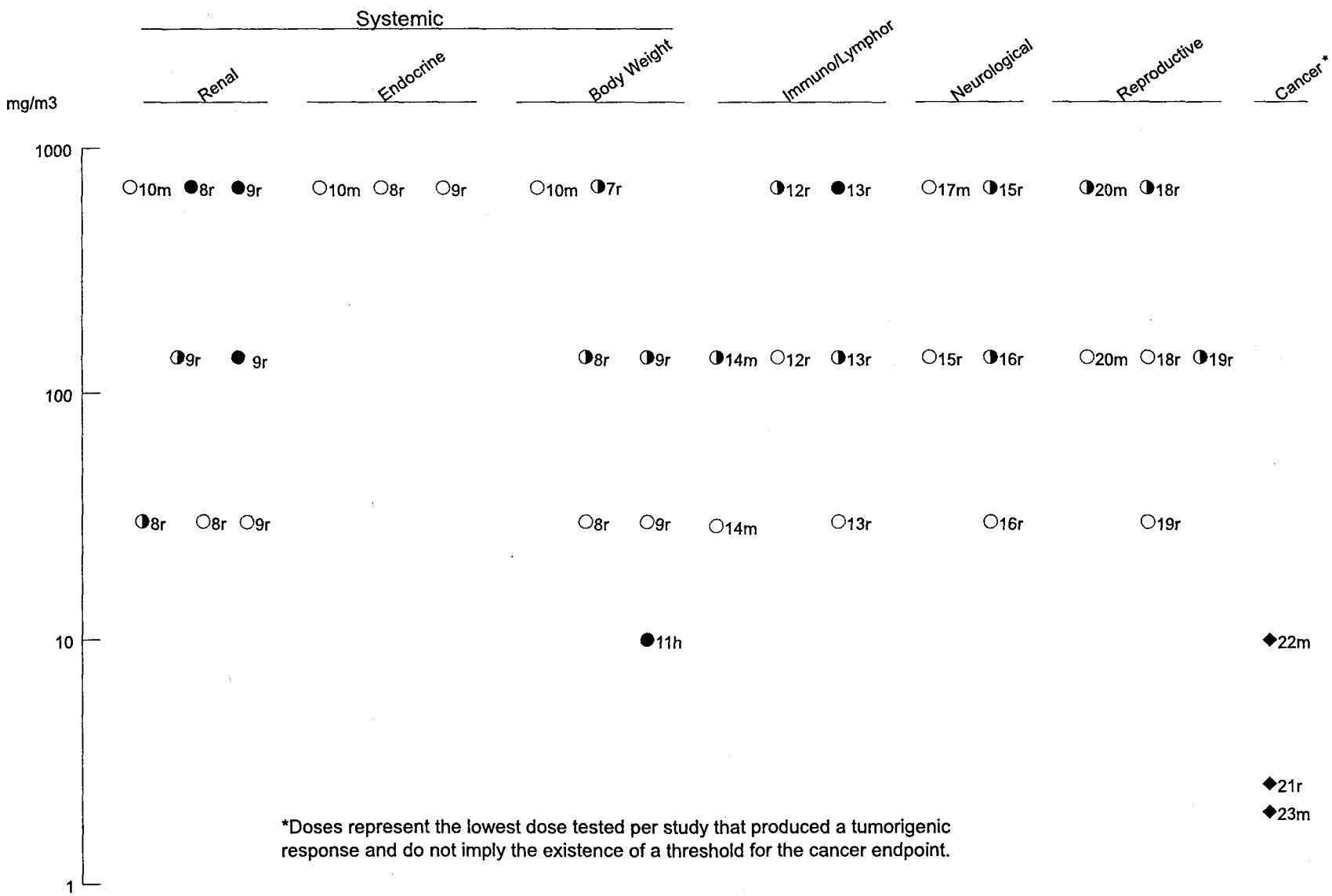
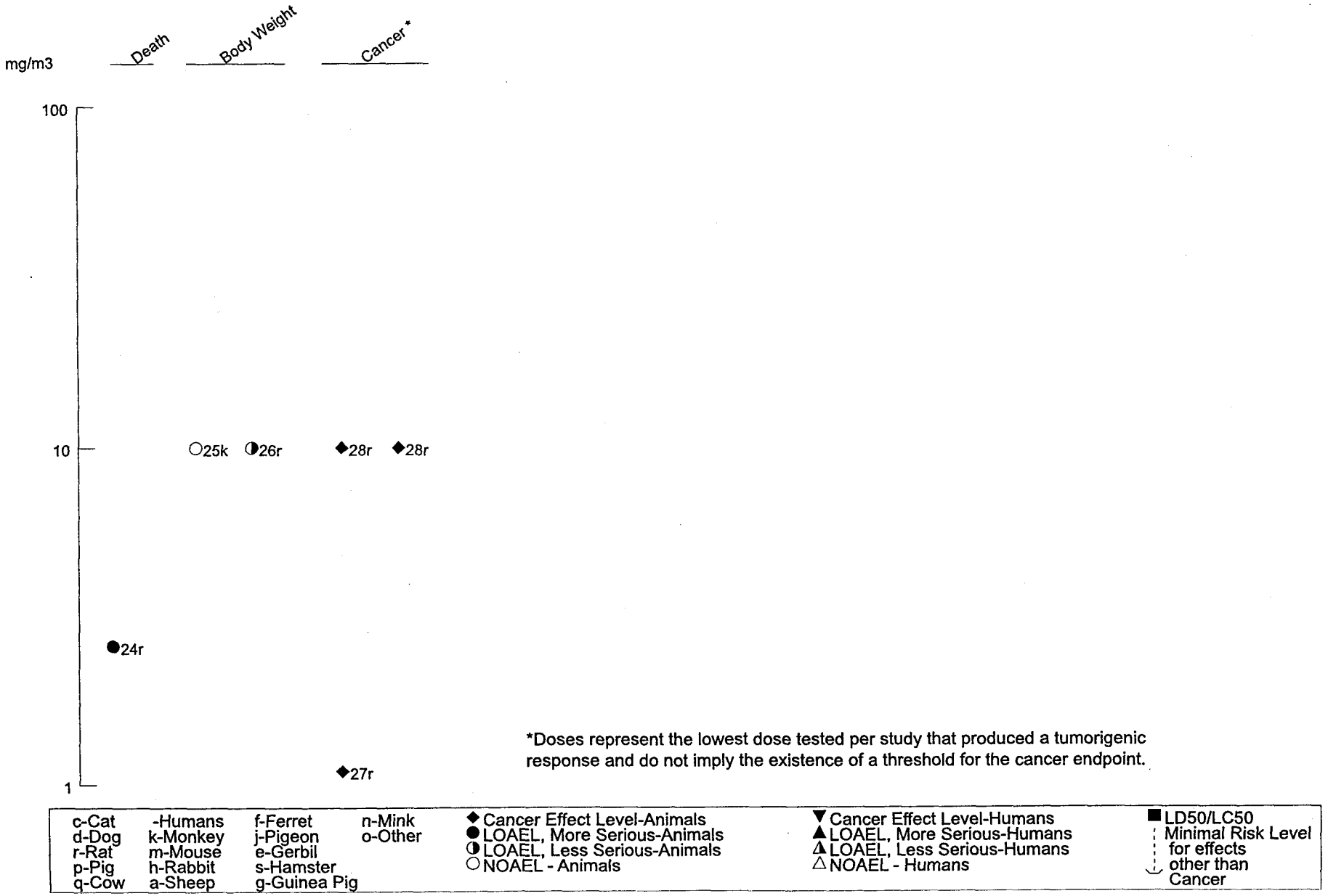


Figure 3-1 Levels of Significant Exposure to Creosote - Inhalation (*Continued*)

Chronic (≥365 days)



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

3.2.1.1 Death

No reports were located of death in humans attributed to inhalation exposure to wood creosote or the creosote bush by inhalation.

Coal Tar Products. No studies were located connecting death in humans following exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles solely by inhalation. A mortality study of human exposure during employment at eight coal tar plants indicated significant increases in cancer-related deaths, compared to the general population (TOMA 1982). No clear relationship between inhalation of coal tar and increased mortality could be established since exposure routes in addition to inhalation (e.g., dermal and oral) were likely and subjects were also exposed to other chemicals and cigarette smoke. Since the study was retrospective, no attempt was made to estimate occupational exposure levels from any source (TOMA 1982). Limitations of the study included absence of data on smoking habits, short cut-off date of 10 days of employment, use of U.S. male mortality rates for comparison as opposed to regional mortality rates, and mixed chemical exposure. The same study population was used as the basis for a nested cancer case-control study (CEOH 1997). Fifty lung-cancer cases were identified and matched with controls from the same cohort. There were three controls per case, and individuals were matched for plant, gender, race, date of hire, and age at hire. Smoking history, work and medical history data were gathered by telephone interviews with the subjects or their next of kin and used to assign workers to various exposure classes. There was no statistically significant increase in lung cancer risk in persons assessed as highly exposed to coal tar compared with those having low or no exposure. The risk associated with working for >20 years in production was lower than that of short-term employees. Controlling for smoking (data analyzed for smokers only) did not change the results, but no nonsmoking cases were identified and therefore, it was not possible to assess the effects of coal tar exposure without concurrent cigarette smoking.

In a mortality study of steelworkers employed in a coke oven plant in 1953, increased mortality from respiratory neoplasms (monitored from 1953 to 1961) was observed in coke oven workers compared to expected mortality rates (Lloyd 1971). Specifically, 20 deaths from respiratory neoplasms were observed, compared to the expected 7.5 deaths. The increase in mortality was linked to an increase in mortality from respiratory neoplasms in nonwhite oven workers who had been employed for $5 years. No increase in deaths from respiratory neoplasms was observed in nonoven workers. In a series of follow up studies of these same coke oven workers in Allegheny County, Pennsylvania, similar associations between coal tar or coal tar pitch volatile exposure and mortality, primarily from lung cancer, were

observed (Redmond 1976; Redmond et al. 1972, 1976). An increase in death due to kidney cancer was observed at the plant, although this was not limited to the coke oven workers at the steel plant (Redmond et al. 1976). Lung cancer mortality was higher in men exposed to coal tar in an aluminum smelter plant for more than 21 years, with a standardized mortality ratio (SMR) of 2.2–2.4 compared to persons not exposed to tar (Gibbs 1985; Gibbs and Horowitz 1979). Increased risk of mortality from pancreatic cancer and leukemia of more than 30% was observed for workers in the potrooms and carbon departments of 14 aluminum reduction plants, who had worked for >5 years (Rockette and Arena 1983).

A study of proportionate mortality among the 11,144 members of the United Union of Roofers, Waterproofers, and Allied Workers (Stern et al. 2000) found a significant excess in mortality due to cancers of the lung, bladder, esophagus, and larynx, and to pneumoconioses and other nonmalignant respiratory diseases in these workers compared with U.S. age-, gender-, and race-specific proportional mortality rates for the years of the study (1950–1996). These workers were occupationally exposed to asphalt fumes and asbestos as well as coal tar pitch volatiles, and cigarette smoking must also be considered as a likely confounding factor.

Spinelli et al. (1991) examined mortality and cancer incidence over a 30-year period among a cohort of 4,213 workers exposed to coal tar pitch volatiles emitted during the production of aluminum. A significant increase in the mortality rate for brain cancer was observed. However, no exposure response was seen for deaths from any form of cancer in direct relation to cumulative coal tar pitch volatile exposure. Mortality in a Norwegian aluminum smelter plant was investigated in a cohort of 1,085–1,137 men who worked between 1922 and 1975 (Rönneberg 1995b; Rönneberg and Andersen 1995). An increase in mortality from atherosclerosis and chronic obstructive lung disease were associated with 40 or more years of exposure or 20–39 years exposure to pot emissions, respectively (Rönneberg 1995b). When cancer incidence was analyzed, associations were found between tar exposure and increases in bladder, prostatic, and lung cancer (Rönneberg and Andersen 1995). In a study of exposure to coal tar pitch volatiles in coke oven plants in France, mortality due to lung cancer was 2.5 times higher in the coke plant workers (534 males) exposed for periods from <5 to >10 years compared to the French national male population (Bertrand et al. 1987). In another study of coal tar pitch volatile exposure in coke oven plants, mortality was monitored in coke oven workers in Pennsylvania who had been employed for >10 years (Mazumdar et al. 1975). An increase in mortality due to lung cancer was positively correlated with coal tar pitch volatile exposure. In a study of coal tar pitch volatile exposure in the aluminum industry, four workers from the same area of the plant died of lung cancer (Bolt and Golka 1993). The duration of exposure to coal tar pitch volatiles ranged from 3.5 to 23 years. Costantino et al.

(1995) carried out an epidemiological study of 5,321 coke oven workers and 10,497 non-oven workers. Statistically significant excess mortality was present among coke workers for several categories of death. The relative risk (RR) for all causes of death was 1.08 ($P<0.01$; 95% confidence interval [CI]=1.02–1.14). The increase in overall mortality was primarily due to increased deaths from cancers. There were highly significant trends ($P<0.001$) for increased cancer risk with increasing duration of employment and increasing exposure. The study did not control for smoking. However, the similar socioeconomic status of the controls and exposed workers suggests that it is unlikely that there was a substantial difference in smoking habits between the two groups. Further discussion of retrospective human cancer/mortality studies can be found in Section 3.2.1.7.

Animal studies were also limited in number for this route of exposure. One study was located in which rats were exposed for 1 hour to saturated vapors of coal tar creosote (Pfitzer et al. 1965). In this study, no specific concentration level was stated and no deaths were observed. In a study in Wistar rats, female rats were exposed to 1.1 or 2.6 mg/m^3 coal tar pitch aerosol for 17 hours/day, 5 days/week for 10 months, followed by exposure to clean air for 20 months (Heinrich et al. 1994a, 1994b). Increased mortality was observed in the high-concentration group, due to lung tumors (no mortality data shown). Increased mortality was also observed in Wistar rats exposed to 1.1 or 2.6 mg/m^3 coal tar pitch aerosol for 17 hours/day, 5 days/week for 20 months, followed by clean air exposure for 10 months (Heinrich et al. 1994a, 1994b). New Zealand white rabbits exposed to 10 mg/m^3 coal tar pitch aerosol in a mixture of benzene, toluene, and xylene for 6 hours/day, 5 days/week for 18 months, exhibited higher mortality than the control animals (89 versus 33%), although the authors attributed death to chronic respiratory infection (MacEwen et al. 1977). Further evaluation of these animals was not provided, so it is not known whether the inhalation exposure affected the susceptibility of the animals to respiratory infection. More importantly, the biological effect of benzene, toluene, and xylene (BTX), which were used as carrier solvents for the coal tar aerosol, was not evaluated in this study. Thus, while these solvents may have played a part in the development of the adverse effects observed in this study, the actual magnitude of the effect, if any, cannot be determined. Kock et al. (1994) reported death of 7 of 20 black rhinoceroses that had been held in creosote-treated holding pens. The animals that died had oral and gastric ulcers, widespread hemorrhages and hematoma, and uniformly swollen intensely green livers, containing excessive intrahepatic bilirubin. However, doses and routes of exposure were not established in this study.

The LOAEL values for death in each species are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No studies were located regarding the gastrointestinal, musculoskeletal, hepatic, endocrine, or body weight effects in humans or musculoskeletal effects in animals after inhalation exposure to creosotes, coal tar, coal tar pitch, or coal tar pitch volatiles. The systemic effects that have been observed in humans and animals are discussed below. LOAEL and NOAEL values for systemic effects are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects.

Coal Tar Products. A single case report describes acute bronchoconstriction in an asthmatic patient exposed to coal tar vapor while being treated with coal tar occlusive bandages for a skin condition (Ibbotson et al. 1995). The authors conclude that the effect was probably due to inhalation of coal tar vapor leading to a nonspecific irritant response. In an industrial health survey of employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, respiratory effects, including reduced lung function (forced vital capacity [FVC]), were noted in 17% (44 of 257) of the employees examined. Most of these respiratory impairments (35/44) were considered to be mild (reduction in FVC of 66–79%) (TOMA 1979). Reductions in FVC were evident in smoking and nonsmoking workers in similar proportions. Obstructive deficits were observed in 8% of smoking and 5% of nonsmoking workers; these were also generally mild to moderate (reduction in forced expiratory volume of 46–69%), but one smoker did show a severe deficit. Workers in nine coal tar plants had a 33% (150 of 453) incidence of restrictive pulmonary deficits (reduced FVC) (TOMA 1981). The study authors proposed that the elevated abnormal findings could be attributed to factors related to administration of the test and not to a disease state. However, other pulmonary function tests were, according to the authors, within the normal limits. A limitation of this study is that smoking status of the subjects was not reported (TOMA 1981). Industrial hygiene surveys of coal tar pitch volatiles at the four wood preservative plants indicated that airborne exposure to benzene-soluble components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 in 94% of the samples (TOMA 1979). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1979). Nevertheless, no clear relationship could be established because exposure routes in addition to inhalation (e.g., dermal and oral) were likely. Also, the ability to relate respiratory effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1979, 1981). Additional limitations of the studies included geographical variation in plant locations, lack of past employment history, voluntary participation in the study that could have biased it in favor of healthy

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

A study of proportionate mortality among the 11,144 members of the United Union of Roofers, Waterproofers, and Allied Workers (Stern et al. 2000) found a significant excess in mortality due to pneumoconioses and other nonmalignant respiratory diseases in these workers compared with U.S. age-, gender-, and race-specific proportional mortality rates for the years of the study (1950–1996). These workers were occupationally exposed to asphalt fumes and asbestos as well as coal tar pitch volatiles. Cigarette smoking is a potential confounding factor that, due to the nature of the study, could not be evaluated.

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

significantly higher risk of chronic bronchitis (RR=2.65, 95% CI=1.26–5.57) relative to the comparison population during the first year of the study. During the second year of the study, 11 residents from the Koppers area reported chronic bronchitis, whereas 7 were expected based on the 1990 National Health Interview Survey rates. These study results are seriously limited by the study's reliance on self reporting of health conditions for which diagnosis verification was not always available.

Pfitzer et al. (1965) exposed rats by inhalation to near-saturated vapors generated from coal tar creosote for 1 day. The rats exhibited dyspnea and slight nasal irritation. The actual exposure level was not determined (Pfitzer et al. 1965). A significant increase in lung weight was reported for female Fischer rats exposed to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12–16, but not for females exposed to 84 mg/m^3 (Springer et al. 1982). Lesions of the olfactory epithelium were reported for Fischer rats and CD-1 mice exposed to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks, but not for animals exposed to 140 mg/m^3 (Springer et al. 1986b, 1987). Rats exposed to concentrations of coal tar $30 mg/m^3 for 5 or 13 weeks also showed histiocytosis of the lung tissue (Springer et al. 1986b). No lesions of the olfactory epithelium were reported for rats exposed to up to 690 mg/m^3 coal tar aerosol for 5 weeks (Springer et al. 1986b). Respiratory symptoms, consisting of extensive chronic fibrosing pneumonitis with peribronchial adenomatosis, were observed in female Bethesda rats and guinea pigs (sex not specified) exposed to coal tar or roofing asphalt vapors (exposure level not specified) for 4 days/week for a total period of 2 years (Hueper and Payne 1960).

Cardiovascular Effects.

Coal Tar Products. In 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, cardiovascular effects, including increased diastolic blood pressure, were noted in 21% (24 of 113) of the employees examined (TOMA 1979). Industrial hygiene surveys of coal tar pitch volatiles at this and three other wood preservative plants indicated that airborne exposure to benzene-soluble components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 in 94% of the samples (TOMA 1979). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1979). Nevertheless, no clear relationship could be established because exposure routes in addition to inhalation (e.g., oral and dermal) were likely. Also, the ability to relate cardiovascular effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals including pentachlorophenol and cigarette smoke (TOMA 1979). Additional limitations of the study are noted above (see "Respiratory Effects"). However, in another industrial study, an increase in mortality from

atherosclerosis was associated with cumulative tar exposure and $40 years of exposure to pot emissions in the aluminum industry (Rönneberg 1995b).

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

Gastrointestinal Effects.

Coal Tar Products. No change in histology of the gastrointestinal tract was found in female Fischer rats exposed to up to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks or in male or female CD-1 mice exposed to up to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks (Springer et al. 1986b, 1987). Male rats exposed to exposed to 690 mg/m^3 (but not 140 mg/m^3) coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks and male and female rats exposed to 690 mg/m^3 (but not 140 mg/m^3) coal tar for 13 weeks showed epithelial hyperplasia and chronic inflammation of the cecum (Springer et al. 1986b).

Hematological Effects.

Coal Tar Products. In an industrial health survey of employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, hematological effects, including increased number of white blood cells (basophils), were noted in 6% (15 of 257) of the employees examined (TOMA 1979). Similarly, 8% of the employees in nine coal tar plants surveyed had increased white blood cells (eosinophils). However, the changes in white blood cell numbers, as well as their morphology, were apparently related to mild infections and allergies. According to the study authors, these results do not indicate any adverse hematologic effects directly related to plant hazards (TOMA

1981). Industrial hygiene surveys of coal tar pitch volatiles at the four wood preservative plants indicated that airborne exposure to benzene-soluble components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 in 94% of the samples (TOMA 1979). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1979). No determination of exposure was made at the nine coal tar plants (TOMA 1981). Nevertheless, no clear relationship could be established because exposure routes in addition to inhalation (e.g., oral and dermal) were likely. Also, the ability to relate hematological effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1981). Other limitations of the studies are noted above (see "Respiratory Effects").

In two studies by Springer et al. (1986b, 1987) Fischer rats appeared to be more sensitive to the effects of inhaled coal tar aerosol than CD-1 mice. Male rats exposed to 140 mg/m^3, but not to 30 mg/m^3, of a coal tar aerosol for 6 hours/day, 5 days/week for 5 or 13 weeks had decreased red blood cell counts, hemoglobin concentration, white blood cells, lymphocytes, eosinophils, monocytes, and increased reticulocytes (Springer et al. 1986b). Female rats also had decreased red blood cell counts, hemoglobin concentration, white blood cells, lymphocytes, eosinophils, monocytes, and increased reticulocytes when exposed to 140 mg/m^3 coal tar for 5 weeks or 690 mg/m^3 for 13 weeks, but there was no significant difference from controls for females exposed to 30 mg/m^3 coal tar for 5 weeks or 140 mg/m^3 coal tar for 13 weeks. Red blood cell counts, hemoglobin concentration, and the volume of packed red cells were also significantly decreased in CD-1 mice exposed to 690 mg/m^3 (but not 140 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks, but other hematologic parameters such as erythrocyte, leukocyte, and reticulocyte counts were unaffected by exposure (Springer et al. 1987). Kock et al. (1994) reported death of 7 of 20 black rhinoceroses which had been held in creosote-treated holding pens. The animals which died had widespread hemorrhages and anemia which may reflect the effects of hemolysis, but doses and routes of exposure were not established in this study.

Hepatic Effects.

Coal Tar Products. No significant change in liver weight was reported for female CD rats exposed to up to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12–16 (Springer et al. 1982). In two other studies, Fischer rats appeared to be slightly more sensitive to the effects of inhaled coal tar aerosol than CD-1 mice (Springer et al. 1986b, 1987). Relative liver weights were significantly increased in male rats exposed to 690 mg/m^3 (but not 140 mg/m^3) and female rats exposed to $30 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks and in male rats exposed to $30 mg/m^3 and female

rats exposed to $140 mg/m^3 (but not 30 mg/m^3) coal tar aerosol for 13 weeks (Springer et al. 1986b). Subtle changes in liver histology were also noted for males and females exposed to 690 mg/m^3 compared with controls. These included a slight increase in cytoplasmic basophilia, slightly more variability in hepatocellular size, the presence of hepatomegalocytes, increased variability in nuclear size and minimal loss of cording and lobular pattern. Minimal scattered focal necrosis was also observed in liver tissue of some exposed animals, but not in controls. Similar changes in weight and histology were also noted in mice exposed to 690 mg/m^3 (females) or $140 mg/m^3 (males) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks (Springer et al. 1987). No changes in weight or histology were observed for female mice exposed to 140 mg/m^3 or male mice exposed to 29 mg/m^3 for 13 weeks (Springer et al. 1987). Kock et al. (1994) reported death of 7 of 20 black rhinoceroses that had been held in creosote-treated holding pens. The animals that died had uniformly swollen intensely green livers, containing excessive intrahepatic bilirubin. Serum levels of aspartate transaminase (AST) and bilirubin were also elevated. However, doses and routes of exposure were not established in this study.

Renal Effects.

Coal Tar Products. Elevated red and white cell counts in urine were noted in 6–8% (29–34 of 452) of the employees examined in an industrial health survey in nine coal tar plants in which coal tar creosote and coal tar were the main treatments used (TOMA 1981). Some of these cell count elevations were attributed to urinary tract infections resulting from inadequate personal hygiene, and not to industrial exposure to toxic chemicals. However, 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. These individuals were referred to their physicians for diagnosis. No determination of exposure was made at the nine coal tar plants (TOMA 1981). Moreover, no clear relationship could be established because exposure routes in addition to inhalation (e.g., oral and dermal) were likely. Also, the ability to relate renal effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke. Additional limitations of the study included seasonal and geographical variation in plant locations, past employment history, voluntary participation in the study that could have biased it in favor of healthy workers, lack of statistical analyses, lack of adequate controls, and use of only current employees.

No change in kidney weight was reported for female CD rats exposed to up to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12–16 (Springer et al. 1982). In another two studies, Fischer rats appeared to be more sensitive to the renal effects of inhaled coal tar aerosol than CD-1 mice (Springer

et al. 1986b, 1987). Relative kidney weights were increased in female rats exposed to $140 mg/m^3 (but not 30 mg/m^3) and in male rats exposed to $30 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks and in male rats and female rats exposed to $140 mg/m^3 (but not 30 mg/m^3) for 13 weeks (Springer et al. 1986b). Male rats exposed to 690 mg/m^3 (but not 140 mg/m^3) for 5 weeks or 140 mg/m^3 (but not 30 mg/m^3) for 13 weeks and female rats exposed to 690 mg/m^3 (but not 140 mg/m^3) for 13 weeks also showed pelvic epithelial hyperplasia and pigmentation of the cortical tubules (Springer et al. 1986b). Relative kidney weights were also increased in mice exposed to 690 mg/m^3 (but not 140 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks, but the difference between exposed and control animals was not significant and no histological changes were reported (Springer et al. 1987).

Endocrine Effects.

Coal Tar Products. No adverse effect on the adrenal glands was reported for female CD rats exposed to up to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational days 12–16 or on the adrenal, pancreas, parathyroid, pituitary, or thyroid glands in Fischer rats exposed to up to 690 mg/m^3 for 5 or 13 weeks or in CD-1 mice exposed to up to 690 mg/m^3 for 13 weeks (Springer et al. 1982, 1986b, 1987).

Dermal Effects.

Coal Tar Products. In an industrial health survey of 251 employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, 82 instances of dermal effects, including skin irritation, eczema, folliculitis, and benign growths on the skin were noted (TOMA 1979). The incidence of benign growths, eczema, and folliculitis was greater than that observed in the general U.S. population, but the study authors concluded that only the incidence of folliculitis cases met the criterion of a significant skin condition such "that the examiner believes should be seen at least once by a physician for assessment or care". In another industrial health survey (TOMA 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, but the study authors concluded that the incidence of skin conditions was less than that seen in the general population. Industrial hygiene surveys of coal tar pitch volatiles at the four wood preservative plants indicated that airborne exposure to benzene-soluble components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 in 94% of the samples (TOMA 1979). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1979). No determination of exposure was made at the nine coal tar plants (TOMA 1981). Moreover, no clear relationship could be established because exposure routes in addition to

inhalation were likely (e.g., dermal contact with coal tar creosote and coal tar vapors and oral exposure). Also, the ability to relate dermal effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals (TOMA 1979, 1981). Additional limitations of the studies are noted above (see "Respiratory Effects"). In other industrial studies, dermal effects were also noted (Bolt and Golka 1993; NIOSH 1982). Four workers in an aluminum reduction plant, who had been exposed to coal tar pitch volatiles for a period of 3.5–23 years showed tar-related skin changes, including hyperkeratosis and telangiectasis (Bolt and Golka 1993). Skin lesions that were possibly pitch-related were observed in four workers involved in the transfer and transport of coal tar pitch, who had been exposed to coal tar pitch and asphalt for 2–8 years (NIOSH 1982). Warts and other lesions on the hands and face were described. Workers transferring coal tar pitch from a river barge to an ocean barge, or from a railroad car to an ocean barge were observed for 2 days to evaluate exposure conditions and health complaints after exposure to coal tar pitch volatiles (NIOSH 1982). Skin irritation, described as redness like a sunburn, lasting 2–3 days, with drying and peeling, and photosensitivity, was described by the workers. Personal air samples from the workers indicated respirable coal tar pitch vapors in concentrations up to 0.18 mg/m^3.

Dermal effects were noted in a site surveillance program conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant (Agency for Toxic Substances and Disease Registry 1994). Because of soil and groundwater contamination with PAHs and other chemicals, the EPA identified this site and placed it on the NPL in 1984. A total of 214 residents of the contaminated residential area (Koppers) were interviewed twice during a period of 2 years, and were compared to 212 residents from a nearby town. Since all of the residents from the Koppers area who were participating in the survey were African American, the chosen regional comparison population was also African American. No data were presented in this study regarding the relative importance of inhalation versus dermal exposure. Residents living on or near the Koppers area reported a higher prevalence of skin rashes (27.9%) during the first year of the surveillance than the comparison neighborhood (4.9%), with a RR of 5.72 ($P<0.05$; 95% CI=3.01–10.87). During the second year of the surveillance, the responses of the Koppers area residents were compared with the 1990 National Health Interview Survey results, and similar results were obtained, with 34 Koppers residents reporting skin rashes, compared to an expected incidence of 4. Rashes were associated with digging in the yard, having contact with the soil, or wading in or having contact with a creek in the area. Most rashes were associated with itching or burning. The recommendation of the Texas Department of Health was that residents in the Koppers area should wear protective clothing when having contact with the soil, and should wash their

skin thoroughly when contact with the soil occurs. Other dermal effects of coal tar creosote, coal tar, or coal tar pitch exposure are mentioned in Sections 3.2.3 and 3.4.1.3.

Ocular Effects.

Coal Tar Products. Workers transferring coal tar pitch from a river barge to an ocean barge, or from a railroad car to an ocean barge, were observed for 2 days to evaluate exposure conditions and health complaints after exposure to coal tar pitch volatiles (NIOSH 1982). Eye irritation, including burning, redness, swelling, and watering of the eyes lasting about 2 days was described, occasionally associated with photophobia. Personal air samples from the workers indicated respirable coal tar pitch vapors in concentrations up to 0.18 mg/m^3. However, all of the workers were wearing protective equipment, including respirators and therefore, the measurements taken do not represent actual exposures. Conjunctivitis was observed in roofers exposed to coal tar pitch volatiles at levels $0.18 mg/m^3, but no cases of conjunctivitis were observed in workers exposed to levels #0.11 mg/m^3 (Emmett 1986).

Pfitzer et al. (1965) exposed rats by inhalation to near-saturated vapors generated from coal tar creosote for 1 day. The rats exhibited slight eye irritation. The actual exposure level was not determined.

Body Weight Effects.

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

Male Fischer 344 rats were exposed to high-boiling coal liquid (heavy distillate, HD) administered by inhalation (700 mg/m^3) for 6 hours/day, 5 days/week for 6 consecutive weeks (Sasser et al. 1989). During the study, the growth of the HD-exposed animals was suppressed significantly relative to the control group. Subsequently, growth was resumed after the treatment was stopped, although HD-treated rats weighed 17.5% less than control rats at necropsy. A significant decrease in body weight was reported for female Sprague-Dawley rats exposed to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on gestational

days 12–16, but not for female Sprague-Dawley rats exposed to 84 mg/m^3 (Springer et al. 1982). In two other studies, Fischer rats appeared to be more sensitive to the effects of inhaled coal tar aerosol than CD-1 mice (Springer et al. 1986b, 1987). Body weights were significantly decreased in rats exposed to $140 mg/m^3 (but not 30 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 5 or 13 weeks, but not in mice exposed to up to 690 mg/m^3 coal tar aerosol for 13 weeks (Springer et al. 1986b, 1987).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals following inhalation exposure to wood creosote or the creosote bush.

Coal Tar Products. No studies were located regarding immunological and lymphoreticular effects in humans or animals following inhalation exposure to coal tar creosote, coal tar pitch, or coal tar pitch volatiles. A significant increase in spleen weight and a significant decrease in thymus weight was reported for female rats exposed to 660 mg/m^3 (but not 84 mg/m^3) of a coal tar aerosol for 6 hours/day on gestational days 12–16 (Springer et al. 1982). In two other already cited studies by Springer et al. (1986b, 1987), Fischer rats appeared more sensitive to the effects of inhaled coal tar aerosol than CD-1 mice. Relative thymus weights were significantly decreased in female rats exposed to 690 mg/m^3 coal tar aerosol 6 hours/day for 5 weeks and both males and females exposed to $140 mg/m^3 for 13 weeks (Springer et al. 1986b). Males exposed to up to 690 mg/m^3 and females exposed to 30 mg/m^3 for 5 weeks, and both sexes exposed to 30 mg/m^3 for 13 weeks, showed no change in thymus weight. The thymus was atrophied in male rats exposed to 690 mg/m^3 (but not 140 mg/m^3) coal tar aerosol for 6 hours/day for 5 weeks and in both male and female rats exposed for 13 weeks (Springer et al. 1986b). Examination of bone marrow smears showed that rats exposed to 690 mg/m^3 coal tar aerosol for 13 weeks had hypocellular marrows with a marked decrease in the number of megakaryocytes (Springer et al. 1986b). The number of megakaryocytes in the spleens of animals exposed to 690 mg/m^3 coal tar aerosol for 5 or 13 weeks was also decreased relative to controls. Both absolute and relative thymus weights were also significantly decreased in male mice exposed to 690 mg/m^3 (but not to 140 mg/m^3) or in female mice exposed to $140 mg/m^3 (but not to 29 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks, but no histological changes were observed (Springer et al. 1987).

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals following inhalation exposure to wood creosote or the creosote bush.

Coal Tar Products. No studies were located regarding neurological effects in humans or animals following inhalation exposure to coal tar creosote, coal tar pitch, or coal tar pitch volatiles. Inhalation of up to 690 mg/m^3 coal tar aerosol by CD-1 mice for 13 weeks had no effect on brain weight or histology (Springer et al. 1987). Inhalation of 690 mg/m^3 coal tar aerosol by male Fischer rats for 5 weeks and inhalation of $140 mg/m^3 by male and female rats for 13 weeks produced a significant increase in relative brain weights, but no change in absolute brain weight or histological abnormalities (Springer et al. 1986b). The rats had a significant reduction in body weight compared to controls, so it seems likely that the change in relative brain weight reflects the body weight loss rather than an adverse neurological effect that affected the absolute brain weight. There was no change in relative brain weight for male rats exposed to up to 140 mg/m^3 or for female rats exposed to up to 690 mg/m^3 for 5 weeks or for male and female rats exposed to 30 mg/m^3 for 13 weeks.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in animals following inhalation exposure to wood creosote or the creosote bush.

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

who also reported difficulty in becoming pregnant, but no difference in pregnancy outcome was noted during the second year of surveillance (Agency for Toxic Substances and Disease Registry 1994). It is likely that reports of difficulty in becoming pregnant were confounded by perception of risk and possibly also by the age of the mother as the difference was not significant when the results for the entire group were adjusted for concerns about chemical exposure, or when women over the age of 39 were excluded from the analysis.

A significant increase in the incidence of mid- and late-gestational resorptions was reported for female rats exposed to 660 mg/m^3 (but not to 84 mg/m^3) of a coal tar aerosol for 6 hours/day on gestational days 12–16 (Springer et al. 1982). Animals exposed to 660 mg/m^3 coal tar showed some signs of maternal toxicity. The thymus weight was significantly reduced and the weights of the lungs and spleen were significantly increased, but maternal body weights (without the products of conception) were not significantly reduced compared to controls and the weights of the liver, kidney, and adrenal glands were similar to controls. No change in the relative weights of ovary or testis were recorded for Fischer rats exposed to up to 690 mg/m^3 of a coal tar aerosol for 6 hours/day, 5 days/week for 5 weeks (Springer et al. 1986b). Relative ovary weights were significantly decreased in Fischer rats and CD-1 mice exposed to 690 mg/m^3 (but not to 140 mg/m^3) of a coal tar aerosol for 6 hours/day, 5 days/week for 13 weeks (Springer et al. 1986b, 1987). Testis weight in rats exposed to $140 mg/m^3 (but not to 30 mg/m^3) coal tar for 13 weeks was significantly increased relative to controls, while testis weight in male mice exposed to 690 mg/m^3 (but not to 140 mg/m^3) coal tar was decreased relative to controls, but the difference was not significant. Examination of ovarian sections showed a significant decrease in the amount of luteal tissue in animals exposed to 690 mg/m^3 (but not to 140 mg/m^3) coal tar for 5 or 13 weeks.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following inhalation exposure to wood creosote or the creosote bush.

Coal Tar Products. No studies were located regarding developmental effects in humans or animals following inhalation exposure to coal tar pitch or coal tar pitch volatiles. As cited above, a site surveillance program conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant on soil contaminated with creosote revealed no adverse developmental

effects on the residents (Agency for Toxic Substances and Disease Registry 1994). Specifically, there was no difference in the number of low birth weight births or in birth defects.

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

3.2.1.7 Cancer

No studies were located regarding cancer in humans or animals following inhalation exposure to wood creosote or the creosote bush.

Coal Tar Products. A number of studies have provided evidence of an association between occupational exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles and increased incidence of cancer-related mortalities and cancer in humans (Armstrong et al. 1994; Bertrand et al. 1987; Bolt and Golka 1993; Costantino et al. 1995; Gibbs and Horowitz 1979; Karlehagen et al. 1992; Kerr et al. 2000; Lloyd 1971; Lloyd et al. 1970; Martin et al. 2000; Mazumdar et al. 1975; Park and Mirer 1996; Persson et al. 1989; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Rönneberg and Andersen 1995; Sakabe et al. 1975; Spinelli et al. 1991; Stern et al. 2000; TOMA 1982; Tremblay et al. 1995), although other industrial chemicals were present. Other studies have not shown a statistically significant association between occupational exposure to coal tar products and increased incidence of specific types of cancer (CEOH 1997; Kromhout et al. 1992; Kunze et al. 1992; Romundstad et al. 2000; Schildt et al. 1999; Siemiatycki et al. 1994; Swaen and Slangen 1997). Interpretation of the data of many of the studies mentioned above is limited by a variety of factors including small study populations, concurrent cigarette smoking, and poor exposure data.

Industrial populations that have been studied include coke oven workers, aluminum smelter workers, steelworkers, and people exposed to creosote through other activities (Armstrong et al. 1994; Bertrand et al. 1987; Bolt and Golka 1993; CEOH 1997; Costantino et al. 1995; Gibbs and Horowitz 1979; Kromhout et al. 1992; Kunze et al. 1992; Lloyd 1971; Lloyd et al. 1970; Mazumdar et al. 1975; Park and Mirer 1996; Persson et al. 1989; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Romundstad et al. 2000; Rönneberg and Andersen 1995; Sakabe et al. 1975; Siemiatycki et al. 1994; Spinelli et al. 1991; Stern et al. 2000; Swaen and Slangen 1997; TOMA 1982; Tremblay et al. 1995). Following occupational inhalation exposure to coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles, cancer was observed involving a number of tissues including the respiratory tract, lips and skin, lung, pancreas, kidney, scrotum, prostate, rectum, bladder, and central nervous system; leukemia and lymphoma were also diagnosed (Armstrong et al. 1994; Bertrand et al. 1987; Bolt and Golka 1993; Costantino et al. 1995; Gibbs 1985; Gibbs and Horowitz 1979; Karlehagen et al. 1992; Liu et al. 1997; Lloyd 1971; Mazumdar et al. 1975; Park and Mirer 1996; Persson et al. 1989; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Rönneberg and Andersen 1995; Sakabe et al. 1975; Stern et al. 2000; TOMA 1982; Tremblay et al. 1995). Exposure levels in these studies were not consistently quantified. In addition, there were confounding factors. In all cases of occupational exposure, the workers were not exposed to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles as single agents, but in combination with other chemicals. For instance, some employees exposed themselves to additional carcinogens via cigarette smoking (TOMA 1982). In other studies, exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles was generally combined with other substances. Some studies had significant limitations. For example, TOMA (1982) is a retrospective study and no attempt was made to estimate occupational exposure levels from any source. Additional limitations of the study are the absence of data on smoking habits, short cut-off date of 10 days of employment, use of U.S. male mortality rates for comparison as opposed to regional mortality rates, and mixed chemical exposure.

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

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

(2) low exposure to coal tar pitch volatiles (<0.2 mg/m^3 BSM),

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

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

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

Costantino et al. (1995) carried out an epidemiological study of 5,321 coke oven workers and 10,497 non-oven workers matched for place of work and socioeconomic status. The average daily exposure to coal tar pitch volatiles was determined in previously published studies as 3.15 mg/m^3 for topside full time jobs, 1.99 mg/m^3 for topside part time jobs and 0.88 mg/m^3 for side jobs. Mortality was assessed by race for 33 categories of cause of death. All RRs were adjusted for age, race, coke plant, and period of follow up as appropriate. Statistically significant excess mortality occurred in coke workers for several categories of death. The RR for all causes of death was 1.08 (P<0.01; 95% CI=1.02–1.14). The increase in overall mortality was primarily due to increased deaths from the following cancers: all cancers (RR=1.34; P<0.001; 95% CI=1.19–1.50), cancer of the lungs, bronchus, and trachea (RR=1.95; P<0.001; 95% CI=1.59–2.33), and prostate cancer (RR=1.57; P<0.05; 95% CI=1.09–2.30). These findings were consistent across racial categories, but excess risk was higher among nonwhite than white workers. There were highly significant trends (P<0.001) for increased cancer risk with increasing duration of employment and increasing exposure. The study did not control for smoking. However, the similar socioeconomic status of the controls and exposed workers suggests that it is unlikely that there was a substantial difference in smoking habits between the two groups.

Elevated risk of death from cancer and from lung cancer was reported in a retrospective cohort study of 6,635 male workers employed for more than 15 years during the period 1970–1985 in seven factories in China (Liu et al. 1997). The main chemical exposure was to coal tar pitch volatiles. Significantly

elevated SMRs were observed in highly exposed workers for all causes of death (SMR 1.69, P<0.01), all cancers (SMR 2.53, P<0.01), digestive cancer (SMR 1.97, P<0.01), esophageal cancer (SMR 3.97, P<0.05), liver cancer (SMR 2.25, P<0.01), and lung cancer (SMR 4.3, P<0.01). The SMRs for highly exposed nonsmokers were also elevated for all cancers (SMR 2.1, P<0.01) and lung cancer (SMR 3.0, P<0.01), and there was a significant correlation between deaths from lung cancer and exposure to coal tar pitch volatiles.

A cohort study (Karlehagen et al. 1992) that examined cancer incidence among 922 workers exposed to coal tar creosote while impregnating wood (railroad cross ties and telegraph poles) at seven plants in Sweden and six plants in Norway during the period of 1950–1975 reported a significant increase in incidence of nonmelanoma skin cancer (observed=9, standardized incidence ratio (SIR)=2.37, 95% CI=1.08–4.50, P=0.02) for the entire study population and a significant increase in cancer of the lip (observed=5, expected=1.34, 95% CI=1.21–8.7, P=0.01) among individuals exposed over 20 years earlier compared with the national male population. Workers were exposed to creosote vapors when removing wood from the autoclave in which it was pressure-treated, but were also likely to receive dermal exposure while handling the wood. The conclusions that can be drawn from this study are limited by the lack of information about the smoking status or exposure to sunlight of the subjects and the absence of measurements of exposure to creosote.

A study of proportionate mortality among the 11,144 members of the United Union of Roofers, Waterproofers, and Allied Workers (Stern et al. 2000) found a significant excess in mortality due to cancers of the lung, bladder, esophagus, larynx, and to pneumoconioses and other nonmalignant respiratory diseases in these workers compared with U.S. age-, gender-, and race-specific proportional mortality rates for the years of the study (1950–1996). These workers were occupationally exposed to asphalt fumes and asbestos as well as coal tar pitch volatiles, and cigarette smoking must also be considered as a likely confounding factor. Exposure to coal tar pitch volatiles is higher for waterproofers than for roofers, and a comparison of proportional mortality of nine local unions with a large number of waterproofers found that the risk of death due to cancer, lung cancer, esophageal cancer, and pharyngeal cancer were higher in these workers (2,804 deaths) than in the workers (8,334 deaths) who did not do much of waterproofing, but these differences were not analyzed for statistical significance.

A significant association between exposure to coal tar creosotes and lung cancer was reported in a case-control study of a cohort of 1,535 male workers who were active in the French national electricity and gas company (EDF-GDF) between 1978 and 1989 (Martin et al. 2000). Controls (four per case) were

matched to the 310 cases by year of birth. Occupational exposure was estimated using a job exposure matrix, and in the absence of individual data on tobacco consumption, the socioeconomic status of the subjects was used to control for this factor. Since a positive association between exposure to asbestos and lung cancer had been previously established for this study population, an adjustment for asbestos exposure was also included in the analysis. The unadjusted odds ratios (ORs) for workers exposed to coal tar and coal tar creosotes were significantly increased. After adjusting for socioeconomic status and asbestos exposure, the odds ratio for coal tar creosotes was still significant (OR=1.56, 95% CI=1.08–2.27), but the odds ratio for coal tar was not significant. A similar pattern was seen when the data were analyzed by level of exposure. Coal tar showed a significant association with increased lung cancer risk at high exposures, but the odds ratio was no longer significant when the data were adjusted for socioeconomic status and asbestos exposure. High exposure to coal tar creosotes was significantly associated with increased odds ratios for lung cancer, both with and without adjustment for socioeconomic status and asbestos exposure, and there was also a significant exposure-response relationship between coal tar creosotes and lung cancer.

A case-control study conducted with 183 neuroblastoma cases, aged 0–14 years diagnosed among residents of New York state (excluding New York City) between 1976 and 1987, found a significant increase in risk of neuroblastoma associated with self-reported paternal exposure to creosote (21 cases, 20 controls, OR=2.1, 95% CI=1.1–4.3), coal soot (6 cases, 2 controls, OR=5.9, 95% CI=1.0–60.4), or coal tar (10 cases, 7 controls, OR=2.8, 95% CI=1.0–8.4), or maternal exposure (both certain and potential exposure combined) to coal soot (OR=10.4, 95% CI=1.2–495.3) or coal tar (OR=4.1, 95% CI=1.2–15.5) (Kerr et al. 2000). Cases were histologically confirmed and were compared with 372 controls matched by year of birth. Due to the small number of nonwhite cases, both cases and controls were limited to cases born to white mothers. Individuals with amended or sealed (adopted) birth certificates were also excluded from the study. Some specific exposure information was collected (via telephone interviews) for creosote, but in general, exposure was based on job description. Possible sources of uncertainty in this study include poor exposure information, the possibility of interviewer bias (interviewers were not blinded to the disease status of the child), and the possibility of the reported increases in risk being chance findings due to the large number of comparisons made.

In a study of the effects of coal tar pitch exposure on the respiratory system, Wistar rats received 10 weekly intratracheal instillations of 0.648, 13.56, and 20.0 mg of coal tar pitch (equivalent to 5.18, 109.2, and 160.0 mg/kg) or 2 mg charcoal powder (control group) and were sacrificed and examined at 1, 3, 6, 12, and 18 months after treatment (Chang et al. 1992). The treatment produced inflammation,

hyperplastic, and metaplastic changes. All rats with lung cancer were found in the two highest treatment groups. The pathogenesis of coal tar pitch-induced lung carcinomas seems to start from hyperplasia of bronchiole-alveolar epithelium, progressing through squamous metaplasia and/or different stages of dysplasia to carcinomas (Chang et al. 1992). According to Chang et al. (1992), the effects produced with coal tar pitch were consistent with the effects reported after similar treatment with PAHs and tobacco smoke condensate. Although the findings presented by Chang et al. (1992) suggest a correlation between coal tar pitch and lung cancer, the relevance of this relationship to potential human exposures by inhalation is questionable given the animal dosing technique.

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

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

MacEwen et al. (1977) indicated that tumor-susceptible ICR CF-1 female mice and tumor-resistant CAF1-JAX female mice exposed to coal tar aerosol-BTX mixture continuously for 90 days at concentrations of 0, 0.2, 2, and 10 mg/m^3 developed skin tumors at 2 and 10 mg/m^3, respectively. In the ICR CF-1 strain mice, tumors continued to develop for as long as 86 weeks postexposure. Skin tumor incidences in ICR CF-1 mice exposed to 0, 0.2, 2, and 10 mg/m^3 coal tar aerosol-BTX mixture for 90 days were 3 of 225 (1%), 1 of 61 (2%), 14 of 75 (19%), and 44 of 55 (80%), respectively. Skin tumor

incidences in CAF1-JAX mice exposed to 0, 0.2, 2, and 10 mg/m^3 coal tar aerosol-BTX mixture for 90 days were 0 of 225 (0%), 0 of 75 (0%), 3 of 65 (5%), and 18 of 43 (42%), respectively. Tumors were confirmed by histological examination. Tumor-susceptible ICR CF-1 female mice and tumor-resistant CAF1-JAX female mice were exposed to 0 or 10 mg/m^3 coal tar aerosol-BTX mixture intermittently for 18 months (MacEwen et al. 1977). For animals exposed intermittently, skin tumor incidences were 5 of 75 in ICR CF-1 mice and 3 of 75 in controls, and 2 of 50 in CAF1-JAX mice as compared to 1 of 50 in controls. Calculation of total exposure indicated the amount of coal tar reaching the skin of the animals was the same as in the 90-day continuous exposure study. However, the intermittent exposure allowed daily normal cleaning of the fur. The incidence of tumors was less in the animals subjected to intermittent exposure. Tumors found in control and exposed mice of both strains included alveolargenic carcinoma, alveolargenic adenoma, bronchogenic carcinoma, squamous cell carcinoma, lymphosarcoma, reticulum cell sarcoma, hemangiosarcoma, hemopoietic tumors, and subcutaneous sarcoma. The effects of the carrier solvents (BTX) used in this study were not evaluated.

Levels of exposure associated with CELs of creosote are indicated in Table 3-1 and plotted in Figure 3-1.

3.2.2 Oral Exposure

This section describes the health effects observed in humans and laboratory animals associated with oral exposure to coal tar and beechwood creosote at varying times and exposure levels. The LSEs by the oral route presented in Tables 3-2 and 3-3 and Figures 3-2 and 3-3 include studies using beechwood creosote, petroleum creosote, coal tar, and coal tar creosote. All reliable exposure levels have been reported.

Although beechwood creosote, creosote bush resin, and coal tar creosote have some components in common, such as phenols, it is not known whether these mixtures will induce the same effects. Furthermore, coal tar creosote contains a complex mixture of animal and human carcinogenic and co-carcinogenic PAHs that probably accounts for the cancer risk associated with chronic exposure to coal tar creosote while wood creosote does not.

3.2.2.1 Death

Wood Creosote. The acute toxicity of beechwood creosote in both rats and mice was studied following single gavage administration of a 10% aqueous solution (Miyazato et al. 1981). The oral LD_{50} values of beechwood creosote in Wistar rats were 885 mg/kg for males and 870 mg/kg for females. The highest dose at which no death occurred was 600 mg/kg. There was no significant difference between male and female rats with respect to mortality, and most animals died within 24 hours. However, no treatment-related deaths were observed when rats were given doses of beechwood creosote in the feed of up to

Table 3-2 Levels of Significant Exposure to Creosote - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (CD)	5 d Gd 12-16 1x/d (G)				740 F (10 of 16 animals died)	Hackett et al. 1984 coal tar
2	Rat (Wistar)	once (G)				1700 M (LD50)	Pfitzer et al. 1965 coal tar
	Systemic						
3	Rat (CD)	5 d Gd 12-16 1x/d (G)	Hepatic	370 F			Hackett et al. 1984 coal tar
			Renal	370 F			
			Endocr		90 F (significant increase in adrenal weight)		
			Bd Wt	140 F	180 F (significant decrease in body weight gain)		
4	Rat (Wistar)	once (G)	Gastro	53 F	106 F (significant decrease in peristaltic movement of intestine)		Ogata et al. 1993 wood creosote
5	Mouse (ICR)	5 d Gd 5-9 1 x/d (G)	Resp	400 F			Iyer et al. 1993 petroleum creosote
			Hepatic	400 F			
			Renal	400 F			
			Endocr	400 F			
			Bd Wt		400 F (16.1% decreased maternal body weight)		

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg)	LOAEL Less Serious (mg/kg)		LOAEL Serious (mg/kg)		Reference Chemical Form
	Systemic								
6	Mouse (CD-1)	once (G)	Gastro		0.08 M	(significant reduction in propulsive motility of the colon)			Ogata et al. 1999 wood creosote
	Immuno/lymphoret								
7	Rat (CD)	5 d Gd 12-16 1x/d (G)			90 F	(significant increase in adrenal weight and decrease in thymus weight)			Hackett et al. 1984 coal tar
	Reproductive								
8	Rat (CD)	5 d Gd 12-16 1x/d (G)		140	180	(significant increase in the number of resorptions)	370	(significant decrease in number of live fetuses/litter and increase in the number of resorptions)	Hackett et al. 1984 coal tar
9	Rat (Sprague-Dawley)	3 d Gd 12-14 1x/d (G)		740					Springer et al. 1986a coal tar
10	Mouse (ICR)	5 d Gd 5-9 1x/d (G)		400 F					Iyer et al. 1993 creosote
	Developmental								
11	Rat (CD)	5 d Gd 12-16 1x/d (G)		90	140	(significant decrease in relative fetal lung weight and a significant increase in anomalous fetuses)	370	(significant increase in the incidence of cleft palate, syndactyly/ectrodactyly and missing toenails on hind feet)	Hackett et al. 1984 coal tar
12	Rat (Sprague-Dawley)	3 d Gd 12-14 1x/d (G)					740	(significant increase in early mortality, increased incidence of cleft palate and small lungs)	Springer et al. 1986a coal tar

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Developmental						
13	Mouse (ICR)	5 d Gd 5-9 1x/d (G)			400 (12% decreased fetal weight, increased incidence of missing sternbrae)		Iyer et al. 1993 creosote
	INTERMEDIATE EXPOSURE						
	Systemic						
14	Rat (Fischer- 344)	3-5 wk 1x/d (GO)	Gastro	50 M			Chadwick et al. 1995 coal tar
			Bd Wt	50 M			
15	Mouse (B6C3F1)	28 d (F)	Bd Wt	410 M	693 M (approx 16% decreased body weight)		Culp and Beland 1994 coal tar
			Other	410 M	693 M (significantly decreased food intake)		
16	Mouse	15 d ad lib (F)	Bd Wt	659 M	1871 M (12.5% decreased body weight)		Weyand et al. 1991 coal tar
			Other	659 M	1871 M (decreased food consumption)		

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
17	Mouse (B6C3F1)	185 d (F)	Resp	462			Weyand et al. 1994 coal tar
			Cardio	462			
			Gastro	462			
			Hemato	462			
			Hepatic	462			
			Renal	462			
			Endocr	462			
			Bd Wt	462			
18	Mouse (B6C3F1)	94 d (F)	Resp	462			Weyand et al. 1994 coal tar
			Cardio	462			
			Gastro	462			
			Hemato	462			
			Hepatic	462			
			Renal	462			
			Endocr	462			
			Bd Wt	462			

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
19	Mouse A/J	260 d (F)	Bd Wt	236 F			Weyand et al. 1995 coal tar
	Immuno/lymphoret						
20	Mouse (B6C3F1)	185 d (F)		462			Weyand et al. 1994 coal tar
21	Mouse (B6C3F1)	94 d (F)		462			Weyand et al. 1994 coal tar
	Reproductive						
22	Mouse (B6C3F1)	185 d (F)		462			Weyand et al. 1994 coal tar
23	Mouse (B6C3F1)	94 d (F)		462			Weyand et al. 1994 coal tar
	Cancer						
24	Mouse A/J	260 d (F)				100 F (significant increase in incidence of lung tumors CEL: 70%/0%)	Weyand et al. 1995 Coal tar
	CHRONIC EXPOSURE						
	Death						
25	Mouse (B6C3F1)	2 yrs (F)				333 F (significantly increased incidence of early mortality)	Culp et al. 1998 Coal tar
	Systemic						
26	Mouse (B6C3F1)	2 yrs (F)	Bd Wt	628 F	1364 F (decrease in body weight)		Culp et al. 1996a coal tar

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
27	Mouse (B6C3F1)	2 yrs (F)	Resp	117 F	333 F (significantly decreased lung weight)		Culp et al. 1998 coal tar
			Gastro	1300 F			
			Hepatic	117 F	333 F (40% increase in liver weight)		
			Renal	33 F	117 F (significantly decreased kidney weight)		
			Bd Wt	117 F	333 F (20% decrease in body weight gain)		
			Other	117	346 F (significantly reduced food consumption)		
	Cancer						
28	Mouse (B6C3F1)	2 yrs (F)				200 F (increased incidence of tumors of the forestomach CEL: 61%: 0% in controls)	*Culp et al. 1996a* Coal tar
29	Mouse (B6C3F1)	2 yrs (F)				333 F (significantly increased incidence of neoplasms of the liver, lung and forestomach and of *hemangiosarcomas and* histiocytic sarcomas, CEL: 27/47 alveolar/bronchiolar adenomas)	Culp et al. 1998 Coal tar

aThe number corresponds to entries in Figure 3-2.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); *Endocr = endocrine*; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; Hemtao = hematological; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s); x = times

Figure 3-2 Levels of Significant Exposure to Creosote - Oral

Acute (≤14 days)

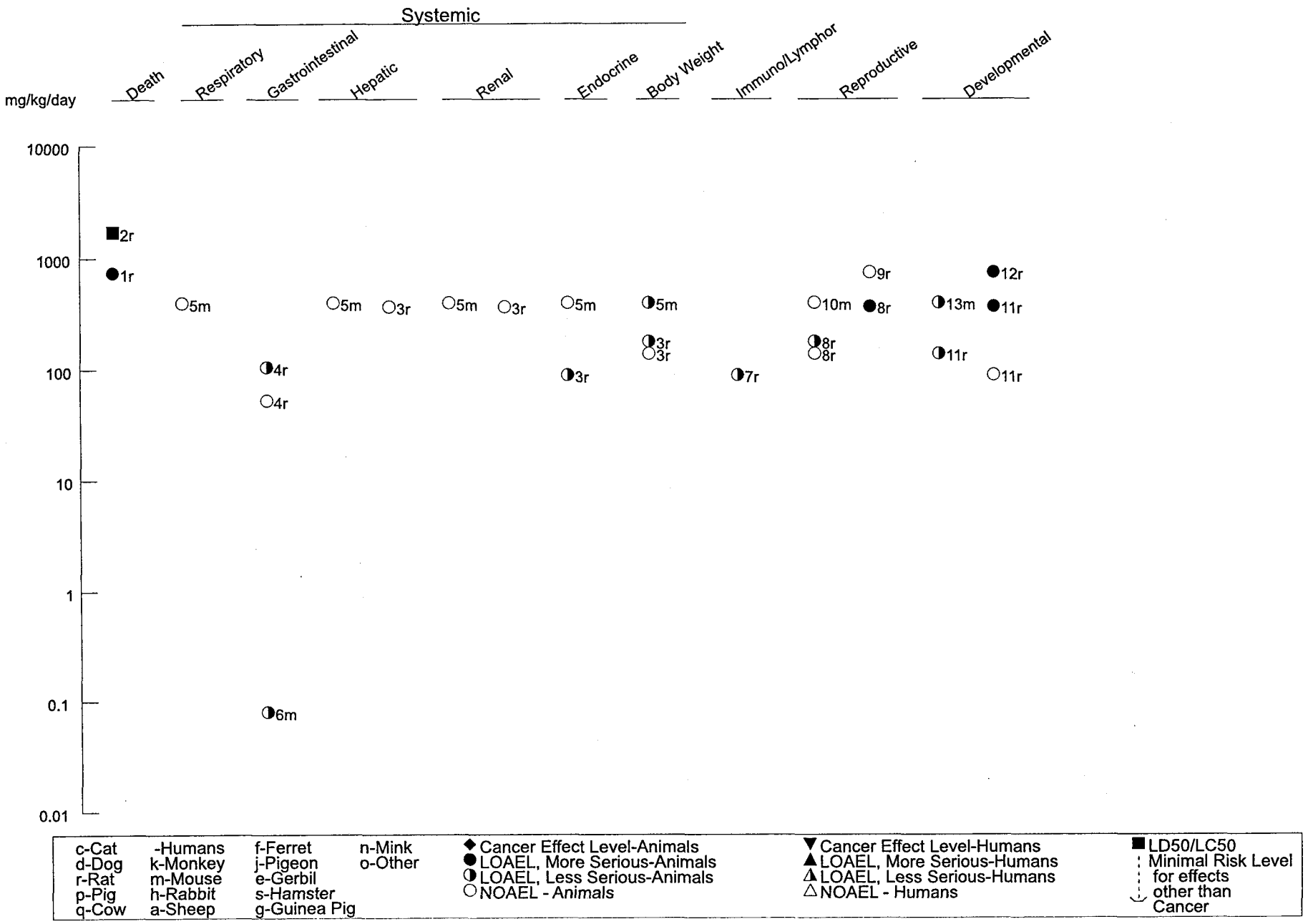


Figure 3-2 Levels of Significant Exposure to Creosote - Oral (*Continued*)

Intermediate (15-364 days)

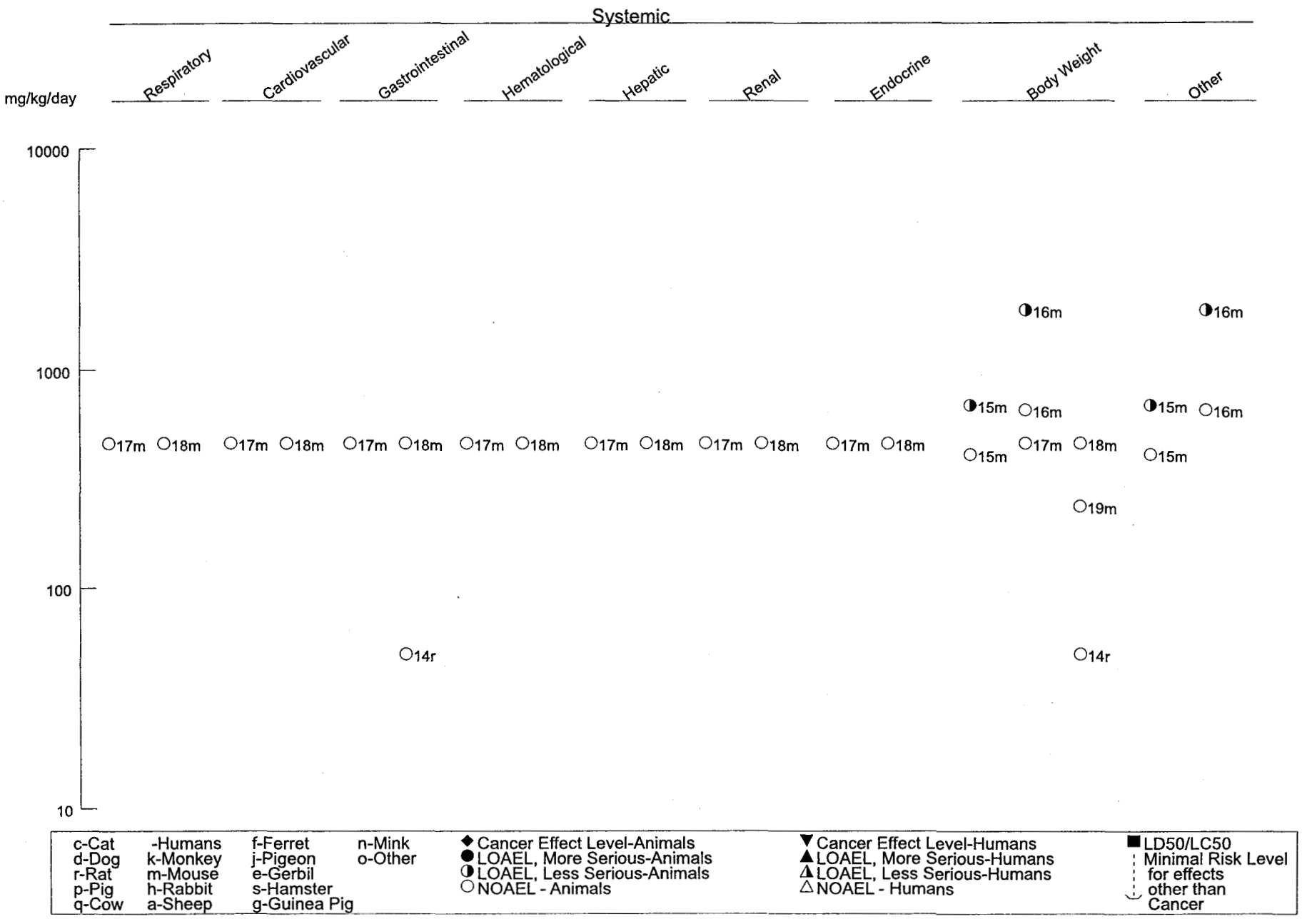


Figure 3-2 Levels of Significant Exposure to Creosote - Oral (*Continued*)

Intermediate (15-364 days)

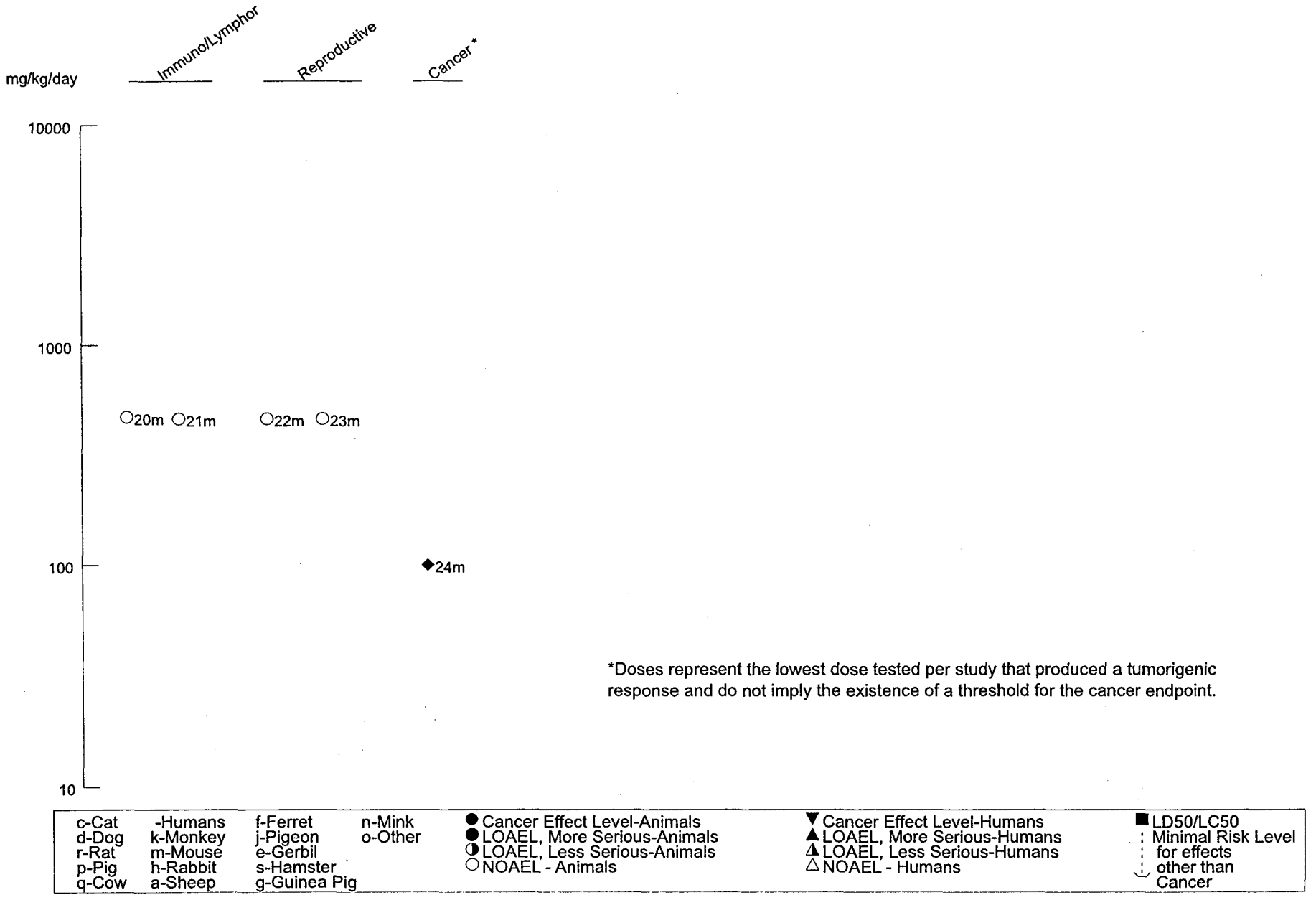


Figure 3-2 Levels of Significant Exposure to Creosote - Oral

Chronic (≥365 days)

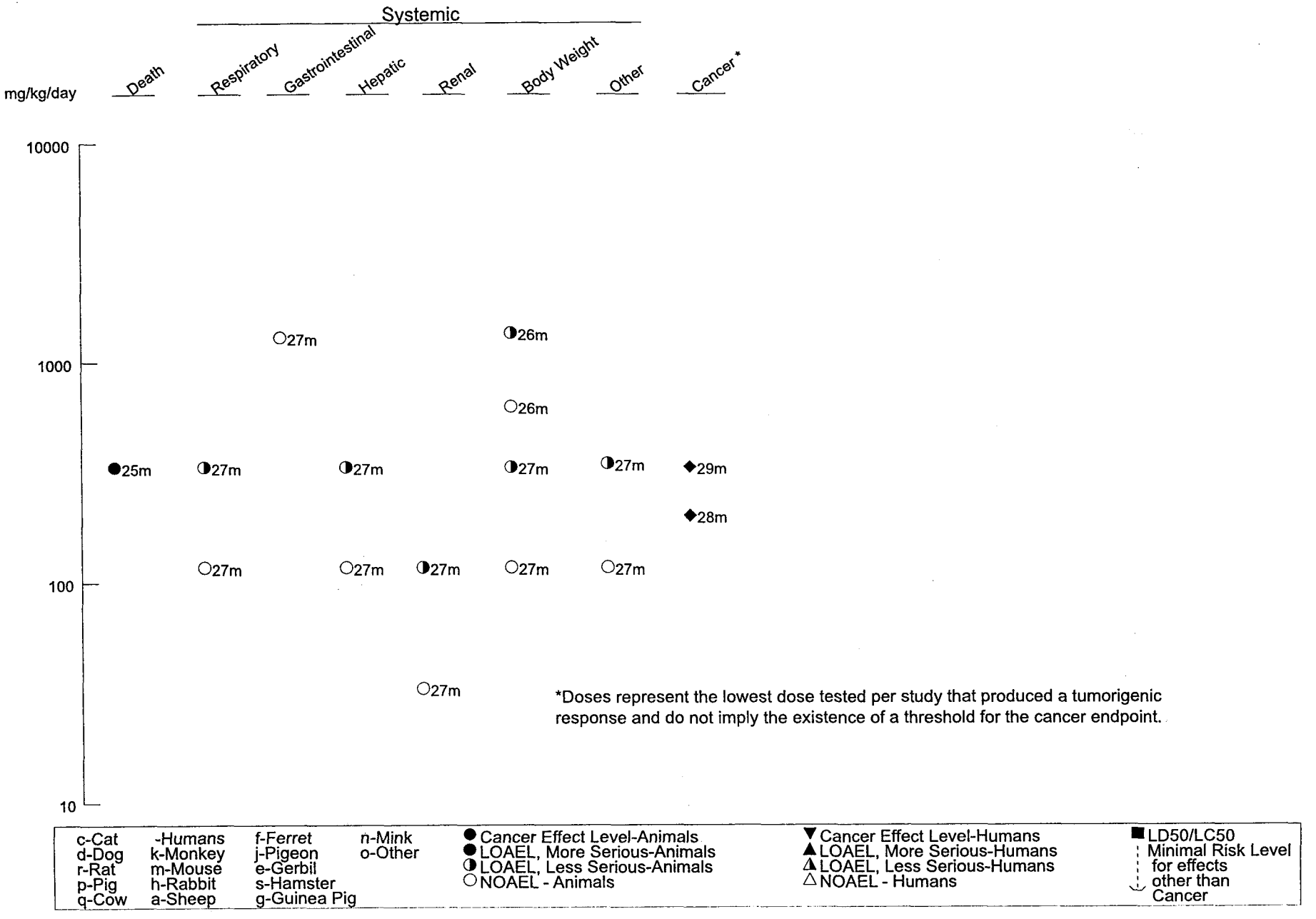


Table 3-3 Levels of Significant Exposure to Wood Creosote - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Wistar)	once (G)				885 M (LD50) 870 F	Miyazato et al. 1981 beechwood
2	Mouse (ddY)	once (G)				525 M (LD50) 433 F	Miyazato et al. 1981 beechwood
	Neurological						
3	Rat (Wistar)	once (G)				600 (convulsions)	Miyazato et al. 1981 beechwood
4	Mouse (ddY)	once (G)		313 M		376 M (convulsions) 313 F	Miyazato et al. 1981 beechwood

Table 3-3 Levels of Significant Exposure to Wood Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Systemic						
5	Rat (Wistar)	3 mo (F)	Resp	812			Miyazato et al. 1981 beechwood creosote
			Cardio	812			
			Hemato	812			
			Hepatic	163 F	168 M (increased relative liver weight)		
					215 F		
			Renal	168 M	210 M (increased relative kidney weight)		
					163 F		
			Endocr	812			
			Bd Wt	534	768 F (11% decreased body weight)	812 M (22% decreased body weight)	

Table 3-3 Levels of Significant Exposure to Wood Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
6	Mouse (ddY)	3 mo (F)	Resp	1427			Miyazato et al. 1981 beechwood creosote
			Cardio	1427			
			Hemato	1427			
			Hepatic	768 M 1127 F	1065 M (significant increase in relative liver weight) 314 F		
			Renal	1427			
			Endocr	1427			
			Bd Wt	450 M 1127 F	768 M (16% decreased body weight) 1427 F (11% decreased body weight)		
	Immuno/lymphoret						
7	Rat (Wistar)	3 mo (F)		317 M 768 F	805 M (increased relative spleen weight)		Miyazato et al. 1981 beechwood
8	Mouse (ddY)	3 mo (F)		1810			Miyazato et al. 1981 beechwood
	Neurological						
9	Rat (Wistar)	3 mo (F)		768 F	257 M (increased relative brain weight)		Miyazato et al. 1981 beechwood
10	Mouse (ddY)	3 mo (F)		1810			Miyazato et al. 1981 beechwood

Table 3-3 Levels of Significant Exposure to Wood Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Reproductive						
11	Rat (Wistar)	3 mo (F)		317 M 768 F	805 M (increased relative testes weight)		Miyazato et al. 1981 beechwood
12	Mouse (ddY)	3 mo (F)		1810			Miyazato et al. 1981 beechwood
	CHRONIC EXPOSURE						
	Death						
13	Rat (Sprague-Dawley)	95 or 102 wk G				200 Significant increase in mortality in male and female rats.	Kuge et al. 2001 Seirogan
14	Rat (Wistar)	96 wk (F)				313 M (30/51 died)	Miyazato et al. 1984b beechwood
	Systemic						
15	Rat (Sprague-Dawley)	95 or 102 wk G	Cardio			200 M Significant reduction in heart weight.	Kuge et al. 2001 Seirogan
			Bd Wt			200 F Significant reduction in mean terminal body weight and body weight change.	

Table 3-3 Levels of Significant Exposure to Wood Creosote - Oral (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
16	Rat (Wistar)	96 wk (F)	Cardio	143 M 394 F	313 M (increased relative heart weight)		Miyazato et al. 1984b beechwood creosote
			Hepatic		143 M (increased relative liver weight and serum cholesterol) 179 F (increased serum cholesterol)		
			Renal		143 M (increased relative kidney weight, increased BUN, nephrosis) 179 F		
			Endocr	143 M 394 F	313 M (increased relative weight of adrenal glands) 313 F		
			Bd Wt	394			
17	Mouse (ddY)	52 wk (F)	Resp	532			Miyazato et al. 1984a beechwood creosote
			Hemato	532			
			Hepatic	532			
			Renal	532			
			Bd Wt	532			
	Immuno/lymphoret						
18	Rat (Sprague-Dawley)	95 or 102 wk G			200 M Significant reduction in spleen weight.		Kuge et al. 2001 Seirogan

Table 3-3 Levels of Significant Exposure to Wood Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Immuno/lymphoret						
19	Rat (Sprague-Dawley)	95 or 102 wk G			200 F	Significant reduction in thyroid-parathyroid weight.	Kuge et al. 2001 Seirogan
20	Rat (Wistar)	96 wk (F)		394			Miyazato et al. 1984b beechwood
21	Mouse (ddY)	52 wk (F)		532			Miyazato et al. 1984a beechwood
	Neurological						
22	Rat (Wistar)	96 wk (F)		179 F	143 M	(increased relative brain weight)	Miyazato et al. 1984b beechwood
					394 F		
23	Mouse (ddY)	52 wk (F)			247 M	(increased relative brain weight)	Miyazato et al. 1984a beechwood
					297 F		
	Reproductive						
24	Rat (Sprague-Dawley)	95 or 102 wk G			200 M	Significant increase in testis weight	Kuge et al. 2001 Seirogan
25	Rat (Wistar)	96 wk (F)		394			Miyazato et al. 1984b beechwood

Table 3-3 Levels of Significant Exposure to Wood Creosote - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
26	Mouse (ddY)	52 wk (F)		532			Miyazato et al. 1984a beechwood

aThe number corresponds to entries in Figure 3-3.

Differences in levels of health effects and cancer between males and females are not indicated in figure 3-3

Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; Hemtao = hematological; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s); x = times

Figure 3-3 Levels of Significant Exposure to Wood Creosote - Oral

Acute (≤14 days)

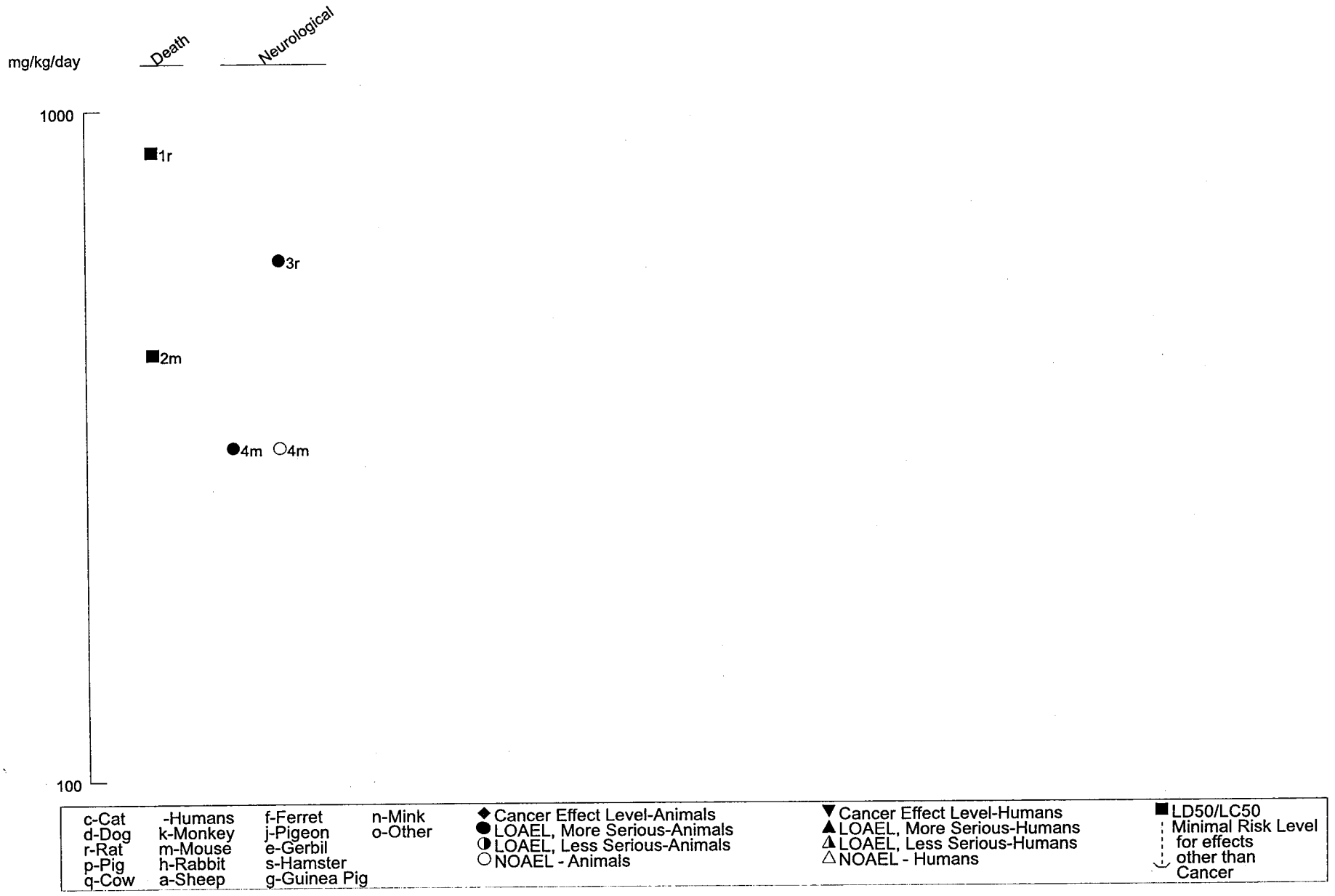


Figure 3-3 Levels of Significant Exposure to Wood Creosote - Oral (*Continued*)

Intermediate (15-364 days)

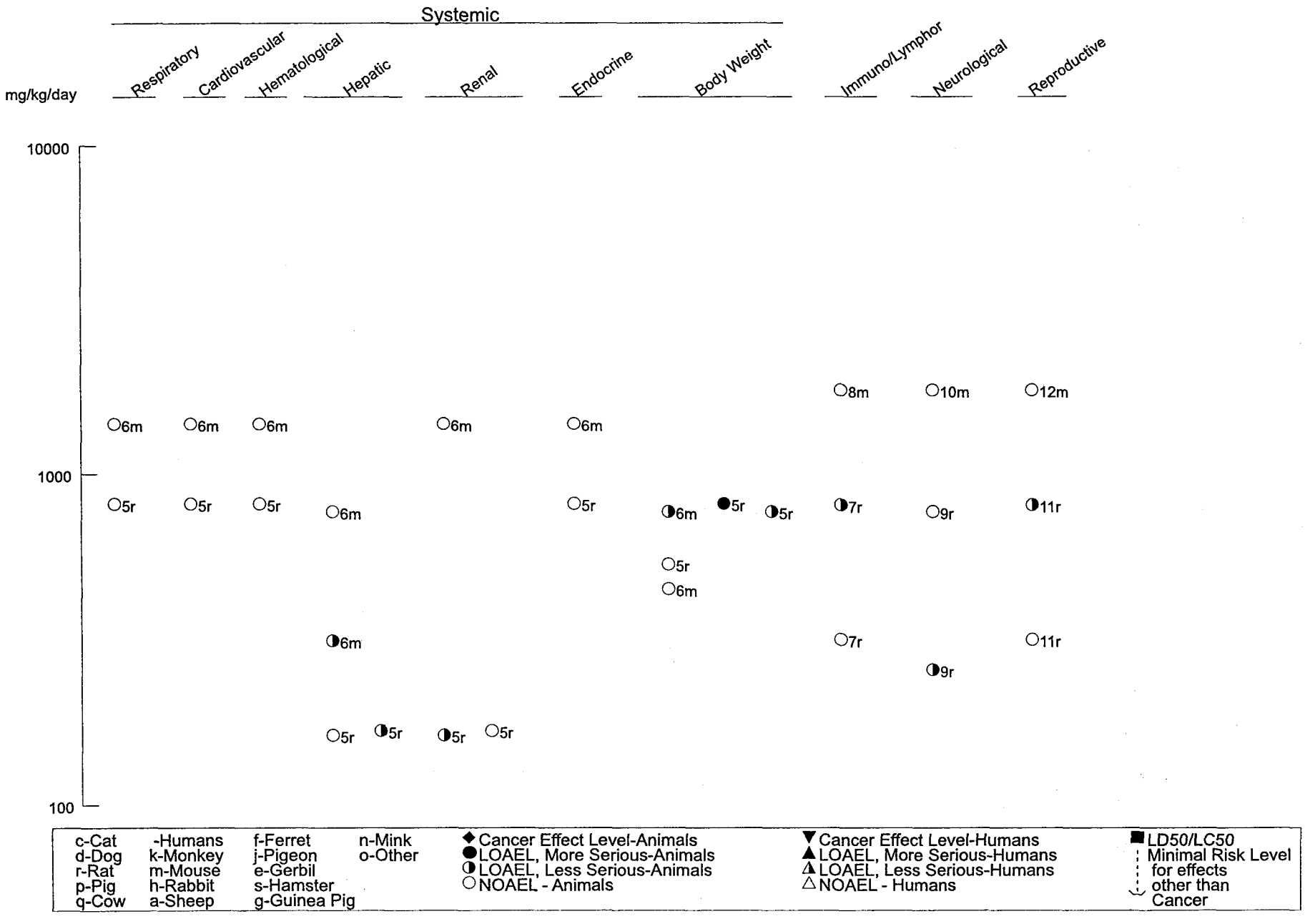
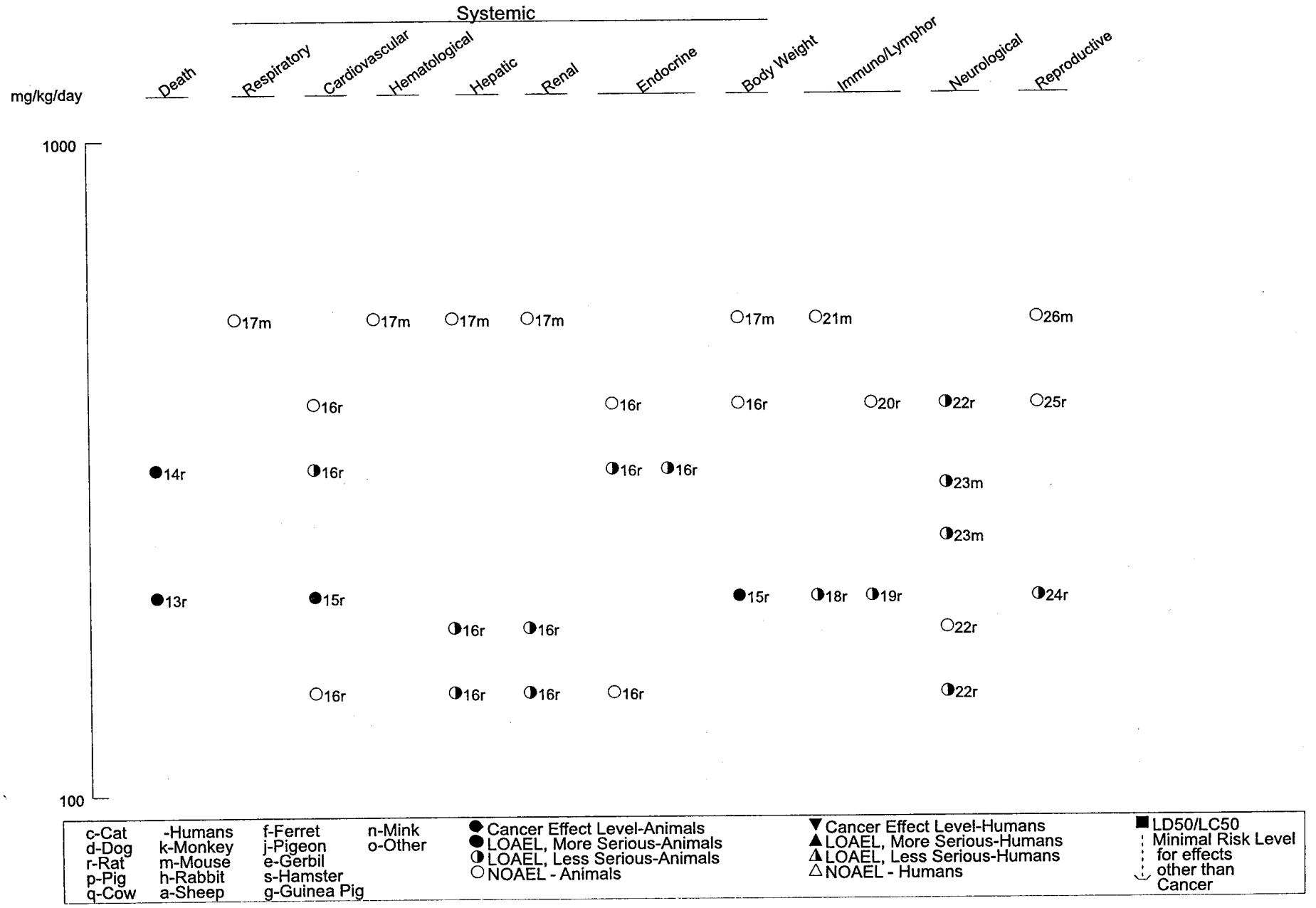


Figure 3-3 Levels of Significant Exposure to Wood Creosote - Oral (*Continued*)

Chronic (≥365 days)



812 mg/kg/day (males) or 768 mg/kg/day (females) for 3 months (Miyazato et al. 1981). Male and female Wistar rats fed diets that contained up to 313 or 394 mg/kg/day beechwood creosote for 96 weeks exhibited deaths in all groups (Miyazato et al. 1984b). There was no treatment-related increase in mortality in the females; the major cause of death in the females including controls was bronchpneumonia and leukemia. The high-dose males had a slightly higher mortality rate than controls and low-dose males; and this was due to chronic progressive nephropathy. Significant increases in mortality were observed in male and female Sprague-Dawley rats administered wood creosote by gavage at 200 mg/kg/day for 40 or 80 weeks, respectively (Kuge et al. 2001). Mortality in groups of rats administered 20 or 50 mg/kg/day did not exceed the mortality rate in the control group. Based on necropsy examinations, it was suggested that mortality in the experimentally exposed animals may have been associated with aspiration of the test material.

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

The LD_{50} values from each reliable study for each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

Coal Tar Products. A 70-year-old man died following ingestion of an unspecified amount of "industrial" creosote (presumably coal tar creosote) (Bowman et al. 1984). Death was attributed to multi-organ failure and occurred 30 hours after admission to the hospital. It is not known if this man had a history of prior coal tar creosote ingestion. Death has been reported to occur in adults and children 14–36 hours after the ingestion of about 7 and 1–2 g coal tar creosote, respectively (Lewin 1929). Thus, ingestion of creosote can be fatal to humans, but the dose level required to produce death cannot be accurately estimated from these reports.

The acute oral LD_{50} for coal tar creosote is reported to be 1,700 mg/kg in male Wistar rats (Pfitzer et al. 1965). No deaths were reported in $B6C3F_1$ mice after oral treatment with doses of manufactured gas

plant (MGP) residue, a form of coal tar, up to 462 mg/kg/day (males) or 344 mg/kg/day (females) for 94 or 185 days (Weyand et al. 1994). Cases of lethal poisoning resulting from ingestion of large amounts of coal tar creosote have been reported in larger farm animals (Cribb 1968; Davis and Libke 1968; Giffee 1945; Graham et al. 1940; Harrison 1959; Luke 1954). Some of the reports are anecdotal and do not include quantification of the amount of creosote ingested (Cribb 1968; Giffee 1945; Graham et al. 1940; Luke 1954). Experimental feeding of powdered clay pigeon targets containing an unspecified amount of coal tar pitch (15–30 g of powdered material daily for up to 15 days) caused death in 8 of 9 pigs (Davis and Libke 1968). The acute fatal doses are 4 g/kg for sheep and over 4 g/kg for calves (Harrison 1959). Based on these data, coal tar creosote can be classified as mildly to moderately toxic in acute and intermediate duration studies.

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

The LD_{50} and LOAEL values for death from each reliable study for each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

There is relatively little information available regarding the systemic effects of ingested wood creosote, coal tar creosote, coal tar, or coal tar pitch. The database consists primarily of old anecdotal reports or animal studies that would be considered inadequate by current standards. Some clinical reports describe oral exposure of humans to wood creosote, but the amounts ingested are only estimates (Alderman et al. 1994; Clark and Reed 1992; Gordon et al. 1995). Three studies published by Miyazato et al. (1981, 1984a, 1984b) that evaluated the acute, intermediate, and chronic effects of beechwood creosote in rats and mice and a chronic study in rats by Kuge et al. (2001) comprise the bulk of reliable information on

the systemic effects of ingested beechwood creosote. Based on the results of these studies, the liver, kidney, and central nervous system appear to be target organs of creosote toxicity. Effects have also been observed in the gastrointestinal, respiratory, and cardiovascular systems. No studies were located regarding musculoskeletal, endocrine, ocular, or body weight effects in humans or musculoskeletal or dermal effects in animals after oral exposure to creosote. Studies regarding systemic effects that have been observed in humans and animals after oral exposure to coal tar creosote or coal tar are discussed below. Culp et al. (1996a, 1998), Goldstein et al. (1998), Hackett et al. (1984), Iyer et al. (1993), and Weyand et al. (1994, 1995) comprise the bulk of the data for these compounds. The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Tables 3-2 and 3-3 and plotted in Figures 3-2 and 3-3.

Respiratory Effects.

Creosote Bush. A report was found in the literature describing the medical condition of a 60-year-old woman hospitalized after taking 1–2 capsules of chaparral (prepared by grinding leaves of an evergreen desert shrub known as creosote bush or "greasewood;" active ingredient is nordihydroguaiaretic acid [NDGA]) daily for 10 months (Gordon et al. 1995). The patient developed "flulike syndrome" and increased her chaparral intake to six capsules/day 3 weeks before admission. She developed aspiration pneumonia requiring antibiotic therapy and endotracheal intubation.

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

No adverse effect on lung weight was noted for Wistar rats given up to 812 mg/kg/day (males) or 768 mg/kg/day (females) beechwood creosote or ddY mice given up to 1,065 mg/kg/day (males) or 1,427 mg/kg/day (females) beechwood creosote in the feed for 3 months (Miyazato et al. 1981). In a chronic study, rales were observed in Sprague-Dawley rats administered wood creosote by gavage at

200 mg/kg/day (Kuge et al. 2001). These signs were not seen in rats administered wood creosote at 20 or 50 mg/kg/day. After 95 weeks, reddened lungs were evident in all groups of rats in this study, including the control group, but were more prevalent in rats administered the high dose of wood creosote. The cause of this lung reddening was not determined, but the authors suggested that it may have been associated with aspiration of the test material. There were no increases in lung weight in any of the experimental groups.

A slightly higher incidence of bronchitis or thickening of the tracheal mucous membrane was observed in ddY mice that ingested feed containing 0.3% (equivalent to 247 mg/kg/day for males and 297 mg/kg/day for females) and 0.6% (equivalent to 474 mg/kg/day for males and 532 mg/kg/day for females) beechwood creosote for 52 weeks (Miyazato et al. 1984a). However, the authors attributed this to irritation from long-term inhalation exposure to volatile components of beechwood creosote in the feed, and not to a direct toxic effect on the respiratory tissue from oral exposure.

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

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

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

Wood Creosote. No adverse effect on heart weight was noted for rats given up to 812 mg/kg/day (males) or 768 mg/kg/day (females) beechwood creosote or mice given up to 1,065 mg/kg/day (males) or 1,427 mg/kg/day (females) beechwood creosote in the feed for 3 months (Miyazato et al. 1981), or female rats given up to 394 mg/kg/day and male rats given 143 mg/kg/day beechwood creosote for 96 weeks (Miyazato et al. 1984b) or male or female Sprague-Dawley rats administered 20 or 50 mg/kg/day of wood creosote by gavage for 102 weeks (Kuge et al. 2001). However, male, but not female, rats administered 200 mg/kg/day for 95 weeks showed a significant reduction in heart weight. Male rats given 313 mg/kg/day beechwood creosote for 96 weeks exhibited an increase in heart weight (Miyazato et al. 1984b).

Coal Tar Products. In a feed study of MGP coal tar by Weyand et al. (1994) using B6C3F_1 mice, there was no adverse effect of treatment on the aorta after 94 or 185 days exposure to 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females). One pig that died after ingesting an unknown amount of coal tar pitch exhibited pericarditis (Luke 1954).

Gastrointestinal Effects.

Wood Creosote. The antidiarrheal effect of beechwood creosote was studied in rats (Ogata et al. 1993, 1999). Female Wistar rats were dosed orally with creosote in concentrations of 0, 7, 13, 27, 53, 107, 213, and 427 mg/kg mixed with 7.7 mg/kg of saline (Ogata et al. 1993). After 1 hour, 5.6 mg/kg castor oil was administered through the stomach cannula to all groups of rats to induce diarrhea. Feces excreted were then observed at 1 hour intervals during the next 7 hours. To assay antimotility effects, female Wistar rats were given creosote at the same concentrations as above. After 1 hour, 0.2 mL of a charcoal meal (12% wet weight [w/w] charcoal powder and 2% [w/w] gum arabic in water) was administered through the stomach cannula and the rats sacrificed 20 minutes later; the small intestine was examined to determine how far the charcoal meal had traveled from the stomach. Creosote administered 1 hour before

the castor oil treatment prevented diarrhea with an ED_{50} of 53 mg/kg. The gastrointestinal transit time of the charcoal meal given to rats was significantly suppressed by 106 and 213 mg/kg (but not by 53 mg/kg) creosote, which showed creosote inhibited peristaltic propulsive movement of the intestine.

In a second study by Ogata et al. (1999), the effect of orally administered wood creosote on propulsive motility of the intestine and the colon were tested in male CD-1 mice using a charcoal meal test and a colonic bead expulsion test. The effect of treatment with wood creosote was compared with untreated mice or mice treated with loperamide (a known antidiarrheal agent). Postdose plasma samples were removed from mice 30 minutes after dosing and tested for the ability to suppress colonic propulsive movement. Wood creosote showed only a slight inhibitory effect on the propulsive motility of the small intestine at administered doses of 0.08 and 0.4 mg/kg, but not at an ordinary human therapeutic dose level (2–10 mg/kg). In the colonic bead expulsion test orally administered wood creosote significantly ($p<0.05$) increased bead expulsion time at doses of 0.08, 0.4, and 2 mg/kg; it was most marked at the dose of 2 mg/kg. The reduction in colonic propulsive motility produced by wood creosote occurred within 15 minutes of dosing. Postdose plasma samples from creosote treated mice produced a significant reduction in colonic propulsive motility when injected into untreated mice. This suggests that the effect is mediated by wood creosote (or its metabolites) in the blood rather than wood creosote from the lumen of the colon as the time period would not be sufficient for creosote to have reached the colon.

Coal Tar Products. 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.

Wistar rats that died following the administration of single gavage doses of coal tar creosote in an acute range-finding study (doses ranged from 613 to 5,000 mg/kg) exhibited hyperemia and distention of the stomach upon necropsy (Pfitzer et al. 1965). No adverse gastrointestinal effects were noted in male Fischer 344 rats treated with 50 mg/kg/day creosote by gavage for 1–5 weeks, including no change in the weight of the small intestines, large intestines, or caecum (Chadwick et al. 1995). In a feed study of MGP coal tar by Weyand et al. (1994) using $B6C3F_1$ mice, there was no adverse effect of treatment on the glandular stomach or forestomach after 94 or 185 days exposure to 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females). In another feeding study, 5-week-old female $B6C3F_1$ mice were fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from

manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day (0.03, 0.1, and 0.3%) of coal tar 2. No effect on the weight or histology of the stomach or small intestine was observed at any dose (Culp et al. 1998). Pigs that died after ingesting an unknown amount of coal tar pitch exhibited blood-stained fluid in the abdominal cavity (Luke 1954).

Hematological Effects.

Creosote Bush. A report was found in the literature describing a 45-year-old woman who developed painless jaundice, fatigue, anorexia, and pruritus after taking chaparral tablets, 160 mg/day for around 2 months (Alderman et al. 1994). Complete blood count, platelet count, and clotting times were normal. A 60-year-old woman was hospitalized with a 1-week history of upper quadrant abdominal pain, anorexia, and jaundice (Gordon et al. 1995). The patient had been taking 1–2 capsules of chaparral daily for the past 10 months. The patient developed "flulike syndrome" and increased her chaparral intake to 6 capsules a day 3 weeks before admission. The patient's prothrombin time increased from 15.9 to 28 seconds (normal values 10.9–13.7 seconds).

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

that the values were within normal physiological ranges (Miyazato et al. 1984a). An unspecified set of hematologic parameters were not affected in Sprague-Dawley rats administered wood creosote at 20, 50, or 200 mg/kg/day for up to 102 weeks (Kuge et al. 2001).

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

Hepatic Effects.

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

A 45-year-old woman developed painless jaundice, fatigue, anorexia, and pruritus after taking chaparral, 160 mg/day, for about 2 months (Alderman et al. 1994). Physical examination confirmed jaundice and a 14-cm liver with a smooth, nontender border. Serum enzyme levels were elevated; serum ALT was 1,611 IU (normal 0–65 IU); AST was 957 IU (normal 0–50 IU); alkaline phosphatase was 265 IU (normal 35–130 IU); GGT was 993 IU (normal 0–65 IU), and total bilirubin was 11.6 mg/dL (normal <1.4 mg/dL). Tests for anti-hepatitis A IgG and IgM, hepatitis B surface antigen, antibody against hepatitis B surface antigen and hepatitis B core antigen, and acute antibody against hepatitis virus were all negative. Ultrasonography showed no abnormality. Endoscopic retrograde cholangiopancreatigraphy (ERCP) showed sparse, smooth, but severely narrowed biliary ducts without sclerosing cholangitis, distal obstruction, tumor, or stenosis. Specimens from percutaneous liver biopsy showed prominent acute inflammation with neutrophil and lymphoplasmocytic infiltration, diffuse hepatocyte disarray and necrosis, focal acute pericholangitis, some ductal dilatation, and proliferation of bile ductules in portal-

periportal regions. The patient was started on Prednisone at 60 mg/day, tapered to 10 mg/day and discontinued in 7 weeks; the patient remained well with normal laboratory findings. The patient was diagnosed with chaparral-induced toxic hepatitis after reports of two cases of chaparral hepatotoxicity were published. In another report, a 60-year-old woman was hospitalized with a 1-week history of upper quadrant abdominal pain, anorexia, and jaundice (Gordon et al. 1995). The patient had been taking 1–2 capsules of chaparral daily for the past 10 months. The patient developed "flulike syndrome" and increased her chaparral intake to 6 capsules a day 3 weeks before admission. Jaundice occurred 2 weeks later. On admission, she was confused and deeply jaundiced. Her total serum bilirubin increased from 212 mmol/L (12.4 mg/dL) to 607 mmol/L (35.5 mg/dL) (normal values 2–20 mmol/L [0.1–1.2 mg/dL]). The patient's liver failure was considered to be chaparral-induced toxic hepatitis. Viral hepatitis was ruled out because antibodies to hepatitis A virus IgM, antibody to hepatitis B core antigen, and hepatitis C virus were undetectable. An exploratory laparotomy performed 1 week after admission showed ascites and a nodular liver. Liver biopsy showed severe acute hepatitis with areas of lobular collapse and nodular regeneration, mixed portal inflammation and marked bile ductular proliferation. Her total serum bilirubin increased to 607 mmol/L. The patient underwent orthotopic liver transplantation. The patient slowly recovered and was discharged.

Serum liver enzymes, blood urea nitrogen, 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 in 90% ethanol were within the normal range and were unchanged by exposure to the extract of creosote bush (Heron and Yarnell 2001). The authors also reported that an additional eight patients who had been prescribed an extract of creosote bush had no noticeable adverse effects, but no information as to blood chemistry was available for these patients.

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

were unaffected in Sprague-Dawley rats administered wood creosote at 20 or 50 mg/kg/day for 102 weeks or 200 mg/kg/day for 95 weeks (Kuge et al. 2001).

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

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

No adverse effect on liver weight was observed in female ICR mice treated by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5–9 (Iyer et al. 1993). In a feed study of MGP coal tar by Weyand et al. (1994), B6C3F_1 mice were exposed to 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females) in the feed for 94 or 185 days. Plasma clinical chemistry parameters determined were as follows: glucose, creatine, blood urea nitrogen, total protein, ALT, ALT, and alkaline phosphatase activity. Tissues obtained from the animals were examined for microscopic lesions. There was no adverse effect of treatment on liver histopathology or serum enzymes.

Anecdotal reports of mortality in pigs after ingestion of clay pigeons containing coal tar pitch from pastures formerly used for target shooting were found in the literature (Giffee 1945; Graham et al. 1940). Lack of appetite, sluggishness, rough coat, and weakness, followed by death were reported. Autopsy revealed degenerative hepatic changes. Experimental feeding of powdered clay pigeon targets containing

an unspecified amount of coal tar pitch (15–30 g powdered material daily for up to 15 days) caused death in eight of nine pigs (Davis and Libke 1968). Twenty-four to 48 hours prior to death, a decrease in hemoglobin, packed blood cell volume, and blood sugar concentration was noted. Autopsy revealed centrilobular hepatic necrosis and hemorrhage of the liver. Four pigs that ingested an unknown amount of coal tar pitch exhibited, at necropsy, marked enlargement of the liver (Luke 1954). The hepatic surface was pitted, the lobules very prominent and the whole organ extremely friable. Fibrinous strands were found on the liver, the cut surface of which presented a mottled mosaic-like pattern. Three pigs were fed a small quantity of pitch ground up in their feed (Luke 1954). These three pigs received 2 pounds (approximately 0.38 ounces/day) of pitch over a period of 28 days. At the end of the 28th day, the pigs were sacrificed and examined. The addition of pitch did not interfere with their appetite and no marked symptoms were observed. Enlargement of the liver was seen together with a varying degree of liver damage. The liver lesions were extensive and there was a marked excess of peritoneal fluid. Histological examination of the affected liver tissue showed marked central necrosis of the lobules, which, in some cases, had completely destroyed the normal liver cells. These liver changes had a somewhat patchy distribution with badly affected and normal lobules often occurring side by side. The factors in the pitch responsible for the lesions were not identified.

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

Renal Effects.

Creosote Bush. No adverse renal effects were noted in a 45-year-old woman who took 160 mg/kg/day chaparral for approximately 2 months (Alderman et al. 1994). A 60-year-old woman was hospitalized with a 1-week history of upper quadrant abdominal pain, anorexia, and jaundice (Gordon et al. 1995). The patient had been taking 1–2 capsules of chaparral daily for the past 10 months. The patient increased her chaparral intake to six capsules/day 3 weeks before admission. Renal failure ensued, which required hemodialysis. The patient underwent cadaveric renal transplantation. The patient slowly recovered and was discharged.

Wood Creosote. Kidney-to-body-weight ratios were significantly increased in Wistar rats exposed to $210 (male) or $163 (female) mg/kg/day or more beechwood creosote in the diet for 3 months or to $143 (males) or $179 (females) mg/kg/day or more for 96 weeks (Miyazato et al. 1981, 1984b), although the trend was not strictly dose-related. No effect on the relative weight of the kidney was observed in mice exposed to up to 1,065 mg/kg/day (males) or 1,427 mg/kg/day (females) for 3 months, mice exposed to 474 mg/kg/day (males) or 532 mg/kg/day (females) for 52 weeks, or male rats exposed to 168 mg/kg/day for 3 months (Miyazato et al. 1981). This response is of minimal pathologic significance in the intermediately treated rats of both sexes and the chronically treated female rats since no treatment-related changes were noted at histopathological evaluation. Blood urea nitrogen and serum inorganic phosphorus were elevated in the chronically treated male rats, which is indicative of uremia. Chronic progressive nephropathy, which occurs spontaneously in old male rats, was also observed at a higher incidence in the chronically treated male rats than in the control male rats, and probably accounts for the biochemical changes observed. The authors concluded that long-term exposure to beechwood creosote at the high dose (1.2% in feed or 534 mg/kg/day) accelerated the occurrence of chronic progressive nephropathy in male rats (Miyazato et al. 1984b). These results suggest that beechwood creosote has the potential to induce adverse effects in the kidney. Kidney weights were unaffected in Sprague-Dawley rats administered wood creosote at 20 or 50 mg/kg/day for 102 weeks or 200 mg/kg/day for 95 weeks (Kuge et al. 2001).

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

No adverse effect on kidney weight was observed in female ICR mice treated by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5–9 (Iyer et al. 1993). No change in kidney weight was observed in female CD rats gavaged on gestational days 12–16 with up to 370 mg/kg/day coal tar (Hackett et al. 1984). In a feed study of MGP coal tar by Weyand et al. (1994) using $B6C3F_1$ mice, there was no adverse effect of treatment on the kidney or bladder after 94 or 185 days exposure to 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females). In another feeding study 5-week-old female $B6C3F_1$ mice were fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day

(0.03, 0.1, and 0.3%) of coal tar 2. The dietary level of 0.1% coal tar produced a significant decrease in kidney weight compared with controls, but lower dietary levels did not (Culp et al. 1998).

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

Endocrine Effects.

Wood Creosote. No adverse effect on adrenal weight was noted for Wistar rats given up to 812 (males) or 768 mg/kg/day (females) beechwood creosote or ddY mice given up to 1,065 (males) or 1,427 mg/kg/day (females) beechwood creosote in the feed for 3 months (Miyazato et al. 1981). Male rats given 313 mg/kg/day beechwood creosote for 96 weeks exhibited an increase in relative adrenal weight, but males receiving 143 mg/kg/day and females receiving up to 394 mg/kg/day did not (Miyazato et al. 1984b). Significant reductions in thyroid-parathyroid weight were observed in female Sprague-Dawley rats administered wood creosote by gavage at 200 mg/kg/day for 95 weeks, but not in female rats administered 20 or 50 mg/kg/day for 102 weeks (Kuge et al. 2001). There were no dose-related changes in adrenal or pituitary weights in male or female rats in any dose group.

Coal Tar Products. Adrenal weights were significantly increased in pregnant rats gavaged with $90 mg/kg/day coal tar on gestational days 12–16 (Hackett et al. 1984). No adverse effect on adrenal weight was observed in female ICR mice treated by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5–9 (Iyer et al. 1993). Weyand et al. (1994) conducted a feed study of MGP coal tar using B6C3F_1 mice. There was no adverse effect of treatment on the salivary glands, pancreas, thymus, parathyroid, or adrenal glands after 94 or 185 days exposure to 0, 51, 251, or 462 mg/kg/day for males and 0, 42, 196, or 344 mg/kg/day for females.

Dermal Effects.

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

Body Weight Effects.

Wood Creosote. Body weight gain was decreased 11–22% in Wistar rats given 768 (males) or 812 (females) mg/kg/day beechwood creosote, and 11–16% in ddY mice given 768 (males) or 1,427 (females) mg/kg/day beechwood creosote in the feed for 3 months (Miyazato et al. 1981). No effect on body weight was observed in rats or mice exposed to lower doses (534 mg/kg/day, male rat; 578 mg/kg/day, female rat; 450 mg/kg/day, male mouse; 1,127 mg/kg/day, female mouse) of beechwood creosote for 3 months. No effect on body weight was observed in rats or mice exposed to up to 313 (males) or 394 (females) mg/kg/day for 96 weeks, or to 474 (males) or 532 (females) mg/kg/day for 52 weeks (Miyazato et al. 1984a, 1984b). Significant body weight reductions were observed in male (7% weight reduction) and female (15% weight reduction) Sprague-Dawley rats administered wood creosote by gavage at 200 mg/kg/day for 95 weeks (Kuge et al. 2001). Terminal body weights were unaffected in rats administered 20 or 50 mg wood creosote/kg/day for 102 weeks.

Coal Tar Products. No adverse effect on body weight was noted in male Fischer 344 rats treated with 50 mg/kg/day coal tar creosote by gavage for 3–5 weeks (Chadwick et al. 1995). However, body weight was significantly decreased in female CD rats gavaged on gestational days 12–16 with 180 mg/kg/day (but not 140 mg/kg/day) coal tar (Hackett et al. 1984). A 16% decrease in body weight gain was also observed in female ICR mice after gavage treatment with 400 mg/kg petroleum creosote in DMSO on gestational days 5–9; however, a similar reduction in weight gain was seen in the group treated with DMSO only (Iyer et al. 1993). In another study, male B6C3F_1 mice were given 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar in feed for 28 days (Culp and Beland 1994). Food consumption and change in body weights were monitored for the coal-tar-fed animals. Dose-related decreases in body weight were observed in all dose groups. Animals treated with 693 and 1,067 mg/kg/day coal tar showed average body weights significantly decreased by approximately 16% from controls. Body weights for other treated groups were not significantly different from those of controls.

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

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

Culp et al. (1996a) fed diets containing 0, 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar to female B6C3F$_1$ mice for 2 years and noted a decrease in body weight (data not shown) at the two highest doses (1,364 and 2,000 mg/kg/day) compared with controls. No decrease was noted for animals exposed to #0.3% (628 mg/kg/day) compared with controls. In another feeding study, 5-week-old female B6C3F$_1$ mice were fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day (0.03, 0.1, and 0.3%) of coal tar 2. The dietary level of 0.3% coal tar (333 mg/kg/day coal tar 1 or 346 mg/kg/day coal tar 2) produced a significant decrease in body weight gain (20%) compared with controls, but lower dietary levels did not (Culp et al. 1998).

Other Systemic Effects.

Wood Creosote. Dose-related clinical signs consisting of salivation, decreased activity, signs of apparent abdominal discomfort, and significant reductions in food consumption and food efficiency (food consumption divided by body weight gain) were observed in Sprague-Dawley rats administered 200 mg wood creosote/kg/day by gavage for 95 weeks, but not in rats administered 20 or 50 mg/kg/day for 102 weeks (Kuge et al. 2001).

Coal Tar Products. Consumption of food containing MGP residue was evaluated in male $B6C3F_1$ mice by measuring whole animal body weight and food consumption (Weyand et al. 1991). Coal tar samples collected from four different coal gasification sites were incorporated separately at varying concentrations into the diet and fed to the mice for 15 days. Food consumption was not affected in groups fed up to 0.2% (659 mg/kg/day) coal tar. However, animals fed diets containing 0.5% (1,871 mg/kg/day) or 1.0% (3,125 mg/kg/day) coal tar refused to eat for 2 or 4 days, respectively, while animals fed 2% or more coal tar continued to refuse to eat for the duration of the experiment. In another feeding experiment, male $B6C3F_1$ mice were given 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar in feed for 28 days (Culp and Beland 1994). Dose-related decreases in food consumption were observed in all treated groups. Animals treated with 693 and 1,067 mg/kg/day coal tar showed significantly decreased food consumption compared to controls over a period of 28 days, animals receiving lower doses did not. Similar reductions in food consumption were seen in another study of female $B6C3F_1$ mice fed a control gel diet or diets containing 0.01, 0.03, 0.1, 0.3, 0.6, and 1% coal tar samples from manufactured gas plant waste sites for 2 years (Culp et al. 1998). This diet provided approximately 12, 33, 117, 333, 739, or 1,300 mg/kg/day of coal tar 1 and 40, 120, or 346 mg/kg/day (0.03, 0.1, and 0.3%) of coal tar 2. Mice fed coal tar 1 ate significantly less food than controls. The reduction in food consumption was approximately 30% for mice fed 1% coal tar 1 and 25% for mice fed 0.6% coal tar 1. Mice fed 0.3% coal tar 2 also ate significantly less food than controls and had approximately a 20% reduction in food consumption.

3.2.2.3 Immunological and Lymphoreticular Effects

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

Wood Creosote. In rats, the spleen may be affected by beechwood creosote exposure, although the data are not conclusive (Miyazato et al. 1981). In particular, exposure to beechwood creosote at 805 mg/kg/day in the diet for 3 months resulted in increased relative spleen weight of male Wistar rats. Spleen weights of male rats exposed to lower levels of beechwood creosote in the diet and female rats at doses up to 768 mg/kg/day indicated no consistent trend of either increase or decrease (Miyazato et al. 1981). In companion experiments using ddY mice, no effect on relative spleen weight was seen at doses up to 1,810 (male) or 1,570 (female) mg/kg/day, in the feed (Miyazato et al. 1981). No effect on spleen weight was observed in rats exposed to doses up to 394 mg/kg/day for 96 weeks, or mice exposed to doses of 532 mg/kg/day for 52 weeks (Miyazato et al. 1984a, 1984b). Spleen weight was unaffected in male and female Sprague-Dawley rats administered 20 or 50 mg wood creosote/kg/day by gavage for 102 weeks. Spleen weight in female rats administered 200 mg/kg/day for 95 weeks was similarly unaffected, but male rats at the latter dose and duration showed a significant reduction in spleen weight (Kuge et al. 2001).

All reliable NOAEL and LOAEL values for immunological and lymphoreticular effects for each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

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

All reliable NOAEL and LOAEL values for immunological and lymphoreticular effects for each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

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

Creosote Bush. A 45-year-old woman developed fatigue and anorexia after taking 160 mg/kg/day chaparral for around 2 months (Alderman et al. 1994). The patient was diagnosed with chaparral-induced toxic hepatitis. In another report, a 60-year-old woman was hospitalized with a 1-week history of upper quadrant abdominal pain, anorexia, and jaundice (Gordon et al. 1995). The patient had been taking 1–2 capsules of chaparral daily for the past 10 months. The patient developed "flulike syndrome" and increased her chaparral intake to 6 capsules per day 3 weeks before admission. On admission, she was confused; her encephalopathy worsened, and she developed seizure activity. The patient was diagnosed with toxic hepatitis secondary to chaparral ingestion.

Wood Creosote. In rats and mice, the first sign of poisoning following the gavage administration of single high doses (600 mg/kg in Wistar rats; 378 [male] or 313 [female] mg/kg in ddY mice) of beechwood creosote was muscle twitching followed by convulsions within 1–2 minutes. This was followed by asphyxiation, coma, and death (Miyazato et al. 1981). These effects were not observed in male mice gavaged once with 313 mg/kg beechwood creosote (Miyazato et al. 1981). Dose-related increased brain-to-body-weight ratios were observed in male rats exposed to doses of $257 mg/kg/day beechwood creosote in the diet for 3 months, but not female rats exposed up to 768 mg/kg/day or male and female mice exposed to up to 1,810 (male) or 1,570 (female) mg/kg/day (Miyazato et al. 1981). Increased relative brain weights were observed in male and female mice exposed to doses up to 247 (male) or 297 (female) mg/kg/day for 52 weeks in the diet, and in male rats exposed to 143 mg/kg/day and female rats exposed to 394 mg/kg/day (but not 179 mg/kg/day) for 96 weeks in the diet (Miyazato et al. 1984b). This response is of questionable toxicological significance because of the lack of a dose-response trend and/or the lack of treatment-related pathological findings at necropsy.

All reliable NOAEL and LOAEL values for neurological effects for each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

Coal Tar Products. Several cases of acute poisoning in cattle have been attributed to ingestion of coal tar creosote. Six cattle believed to have licked creosote-treated electrical light poles as evidenced by burning over the mucosa of the mouth, tongue, and lips showed the following signs: extremely rapid respiration,

contracted pupils, cold skin, apparent severe pain, and coma (Hanlon 1938). However, it is probable that some of these effects may have been due to ingestion of pentachlorophenol. Pentachlorophenol, like creosote, is an oil-borne wood preservative with extensive use in the public utility industry for treatment of utility poles. Some of the effects observed by Hanlon (1938) are more compatible with the metabolic effects (i.e., uncoupling of phosphorylative oxidation) associated with pentachlorophenol. For more information on the effects of pentachlorophenol, please refer to the ATSDR *Toxicological Profile for Pentachlorophenol* (Agency for Toxic Substances and Disease Registry 1999). Thus, it is not possible to determine conclusively whether coal tar creosote is toxic to the central nervous system of animals based on this report. In another report, one of two bulls that had ingested an unknown amount of creosote died and the second one was observed to be walking stiffly (Cribb 1968). The surviving animal recovered fully several days after being removed from the creosote.

All reliable NOAEL and LOAEL values for neurological effects for each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

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

Wood Creosote. An increase in relative testis weight was observed in Wistar rats administered 805 mg/kg/day beechwood creosote in the diet for 3 months, but not in rats receiving 317 mg/kg/day or in mice treated with up to 1,810 mg/kg/day beechwood creosote for 3 months (Miyazato et al. 1981). There were no accompanying gross or histopathological lesions of the testes in these animals. No adverse effects on ovary weight were noted in female rats (768 mg/kg/day) or mice (1,570 mg/kg/day) in the same study. No effect on testis or ovary weight was observed in rats exposed to doses up to 394 mg/kg/day for 96 weeks, or mice exposed to doses of up to 532 mg/kg/day beechwood creosote for 52 weeks (Miyazato et al. 1984a, 1984b). Ovary weights were unaffected in female Sprague-Dawley rats administered 20 or 50 mg wood creosote/kg/day for 102 weeks or 200 mg wood creosote/kg/day by gavage for 95 weeks (Kuge et al. 2001). Testis weight was significantly increased in male rats administered 200 mg wood creosote/kg/day for 95 weeks, but not in male rats administered 20 or 50 mg/kg/day for 102 weeks.

All reliable NOAEL and LOAEL values for reproductive effects for each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

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

No significant difference in the number of live births was observed in female Sprague-Dawley rats gavaged with 740 mg/kg/day coal tar on gestational days 12–14 (Springer et al. 1986a). Only moderate maternal toxicity was observed. Body weight gain was significantly reduced in treated dams, but the estimated weights of the products of conception were similar for control and treated animals, and no significant reduction in litter size was observed. No adverse effects on reproductive indices, including the number of live fetuses, dead fetuses, and resorptions were observed in female ICR mice dosed by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5–9 (Iyer et al. 1993). Moderate maternal toxicity in the form of reduced body weight gain was observed for both creosote-treated and vehicle control mice compared with untreated controls, but no differences in organ weights were observed for any group. $B6C3F_1$ mice fed a control gel diet or adulterated diets containing 0, 51, 251, or 462 mg/kg/day (males) and 0, 42, 196, or 344 mg/kg/day (females) MGP residue as a by-product of coal gasification, exhibited no adverse effect on the epididymides, preputial gland, ovaries, uterus, or clitoral gland after treatment for 94 or 185 days (Weyand et al. 1994).

Coal tar creosote was tested for estrogenic activity using an assay in ovariectomized (OVX) ICR and DBA/2 mice (Fielden et al. 2000). Immature OVX mice were used to assess the ability of creosote to induce an increase in uterine weight, and mature OVX mice were used to assess the ability of creosote to induce both increased uterine weight and vaginal cell cornification. OVX mice were gavaged with 0, 10, 50, or 100 mg/kg creosote in sesame oil or 0.1 mg/kg 17α-ethynylestradiol (positive control) once a day for 4 days beginning when mice were 30 (OVX ICR immature), 32 (OVX DBA/2 immature), 77 (OVX ICR mature), or 85 (OVX DBA/2 mature) days old. Mice were sacrificed 24 hours after the last treatment; body and uterine weights were recorded for all mice and vaginal smears were taken from the mature mice. Treatment with 17α-ethynylestradiol produced a significant increase in uterine weight and vaginal cell cornification compared with animals receiving only sesame oil, but no significant increase in uterine weight or vaginal cell cornification was observed in animals treated with creosote.

All reliable NOAEL and LOAEL values for reproductive effects for each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

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

Coal Tar Products. A significant decrease in relative fetal lung weight and a significant increase in anomalous fetuses was observed in female CD rats gavaged with 140 mg/kg/day (but not 90 mg/kg/day) coal tar on gestational days 12–16 (Hackett et al. 1984). Further abnormalities, a significant increase in the incidence of cleft palate, syndactyly/ectrodactyly and missing toenails on hind feet, were observed in offspring of females treated with 370 mg/kg/day coal tar. In this study, maternal body weight gain was significantly reduced at the three highest dose groups and the weight of the adrenal glands was significantly increased. However, the weights of the spleen, liver, kidneys, and ovaries of all dose groups were similar to controls. Maternal body weight gain, excluding uterine weight, was significantly reduced at all doses. These findings suggest that maternal toxicity may have played a role in the development of teratogenic effects in this study.

In another developmental study, female Sprague-Dawley rats were gavaged with 740 mg/kg/day coal tar on gestational days 12–14 and allowed to deliver their pups (Springer et al. 1986a). Only moderate maternal toxicity was observed. Body weight gain was significantly reduced in treated dams, but the estimated weights of the products of conception were similar for control and treated animals, and no significant reduction in litter size was observed. Pup development was followed for 21 days after birth. Early mortality was significantly increased in treated pups; within the first 3 days after birth, 54% of the treated pups died compared with 9% of the untreated pups. Body and lung weights of treated pups that died or were sacrificed at 1 or 3 days postdelivery were significantly reduced compared with controls. Body weight gain was significantly reduced (15%) for treated pups compared with controls at all time points. Treated pups that died showed signs of severe dehydration and this became more pronounced as the time to death increased. Thymus and lung weights in treated animals were significantly lower than in the corresponding control animals. Lungs were defined as "small lungs" if their size was more than two standard deviations below the mean of the control group. No controls had small lungs or cleft palates. In treated pups that died, the incidence of small lungs was 27% (in 90% of litters), 10% (in 80% of litters) had cleft palates, and 33% of pups (in 80% of litters) had both small lungs and cleft palates. Median

survival times for pups with cleft palate, both cleft palate and small lungs, and only small lungs were 2, 2, and 10 hours, respectively. No malformations were detected in 30% of the treated pups that died and microscopic examination of fetal lung tissue revealed no overt histological differences between treated and control animals. The data from this study suggest that coal tar is a teratogen in Sprague-Dawley rats; however, given the moderate, yet statistically significant, maternal toxicity, the possibility of fetal effects secondary to maternal toxicity cannot be excluded.

A 12% decrease in mean fetal body weight was observed in the offspring of female ICR mice dosed by gavage with 400 mg/kg petroleum creosote in DMSO on gestational days 5–9 compared to the solvent control group (Iyer et al. 1993). An increase in the incidence of a skeletal anomaly (i.e., missing sternebrae) was also observed in the creosote-treated litters, but the difference in the frequency of occurrence was not significant compared to the control group. Moderate maternal toxicity in the form of reduced body weight gain was observed for both creosote-treated and vehicle control mice compared with untreated controls, but no differences in organ weights were observed for any group. The authors suggest that creosote is embryotoxic but not teratogenic; however, interpretation of the results of this study is complicated by the apparent toxicity of the carrier solvent (DMSO).

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

Although some teratogenic effects were observed in the studies discussed in this section, it is not clear that they were directly induced by creosote. In some studies, the observed fetal deformities appeared to be related to maternal toxicity. If creosote is a teratogen, it would be a weak one. Some of the studies suggest that creosote is fetotoxic. In particular, the study by Schipper (1961) showed an increase in fetal mortality without apparent maternal toxicity.

The LOAEL and NOAEL values for developmental effects in mice and rats after oral exposure to creosote are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located that dealt directly with an association between cancer and ingested coal tar or coal tar pitch in humans.

Creosote Bush. A 56-year-old woman who had been consuming 3–4 cups daily of chaparral tea (an infusion of the leaves of the creosote bush) for a period of 3 months approximately 1.5 years prior to surgery was found to have cystic renal disease and cystic adenocarcinoma of the kidney (Smith et al. 1994). One of the components of chaparral tea is nordihydroguaiaretic acid. This chemical has been shown to produce cystic nephropathy in rats fed a 2% concentration for 6 weeks (Evan and Gardner 1979; Goodman et al. 1970). The concentration of nordihydroguaiaretic acid in chaparral tea is considerably higher than that used to cause cystic nephropathy in animals and the authors conclude that the renal disease seen in their patient was most likely to have been due to consumption of chaparral tea.

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

Dietary exposure of male and female ddY mice to beechwood creosote at concentrations up to 532 mg/kg/day (which induced signs of toxicity) for 52 weeks induced no treatment-related increase in the incidence of tumors (Miyazato et al. 1984a). This study is limited, in that 52 weeks may not be a sufficient treatment duration to observe an increase in the incidence of tumors in mice. However, these same authors reported that dietary exposure of male and female rats to 394 mg/kg/day beechwood creosote (which induced signs of toxicity) for 96 weeks also failed to result in any treatment-related increase in the incidence of tumors (Miyazato et al. 1984b). Kuge et al. (2001) conducted a chronic study of the carcinogenicity of wood creosote using 20, 50, or 200 mg wood creosote/kg/day administered by gavage to Sprague-Dawley rats for up to 102 weeks. There was a significant increase in mortality in the

200 mg/kg/day group. Significant increases in the incidence of mammary gland adenocarcinoma, adenoma, and fibroadenoma were observed in some groups of female rats, but the increases did not appear to be dose-related. In male rats, there was an increase in pituitary gland adenoma in the animals administered 20 mg wood creosote/kg/day, but not 50 mg wood creosote/kg/day. There was a high incidence of neoplastic changes in the control group of rats that was were not administered wood creosote. Based on the lack of dose-related increases in neoplasms in these studies, there is no clear evidence that ingested beechwood creosote is carcinogenic to mice or rats.

Coal Tar Products. Excess cases of breast cancer have been observed in St. Louis Park, Minnesota, that were tentatively associated with coal tar creosote contamination of the water supply (Dean et al. 1988). Coal tar creosote-derived PAHs were first detected in the water supply of St. Louis Park in November 1978, but may have been there for decades. A 100-acre plot of coal tar creosote-contaminated soil on which stood a plant that used coal tar creosote and operated from 1917 to 1972 is believed to be the source of contamination. The levels of coal tar creosote or creosote-derived PAHs in the contaminated drinking water of St. Louis Park were not specified. There were 113 cases per 100,000 of breast cancer in St. Louis Park compared to 78 cases per 100,000 in the metropolitan Minneapolis-St. Paul area during 1969–1971. An attempt was made to demonstrate that these excess cases could be explained by known risk factors for breast cancer, such as age at first birth, parity, age at menarche and menopause, body mass index, history of benign breast disease, and familial history, and thus had no association with environmental exposure variables (Dean et al. 1988). The authors presented a method to adjust the breast cancer morbidity in St. Louis Park using data from a larger population with documented risk factors for breast cancer ("standard population"). These more stable rates based on breast cancer risk factors were determined in a larger study conducted by Helmrich et al. (1983). Dean et al. (1988) determined that the attributable risk due to the risk factors was higher for the breast cancer cases in St. Louis Park (0.598) than in the metropolitan Minneapolis-St. Paul area (0.311). They then used these attributable risks to calculate an adjusted morbidity ratio to estimate expected numbers of breast cancer cases in the community. After this adjustment, there appeared to be a higher expected number of breast cancer cases (n=134 per 100,000) than the observed number (113 per 100,000) in St. Louis Park, thereby negating any association with creosote in the water supply. It is necessary when using any standardization method in adjusting rates to ensure comparability among the groups in the study population that are being compared and between the study population and the standard population. It would appear that differences do exist between women in St. Louis Park, the metropolitan Minneapolis-St. Paul area, and the larger cohort studied by Helmrich et al. (1983). These differences were not thoroughly examined by Dean et al. (1988) and could include differences in demographic, economic, and/or environmental factors. However, Dean

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

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

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

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

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

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

In the later study, coal tar samples from manufactured gas plant waste sites were added to the feed of 5-week-old female B6C3F_1 mice at the following concentrations; 0.01, 0.03, 0.1, 0.3, 0.6, and 1% (12, 33, 117, 333, 739, and 1,300 mg/kg/day) coal tar 1 and 0.03, 0.1, and 0.3% (40, 120, or 346 mg/kg/day) coal tar 2 (Culp et al. 1998). Coal tar 1 was a mixture of samples from seven waste sites and coal tar 2 was a mixture from two of the sites included in coal tar 1 plus a third site with a very high benzo[a]pyrene content. Control mice received either unadulterated feed (negative control) or feed containing 5, 25, or 100 ppm benzo[a]pyrene. Mice fed coal tar 1 or 2 showed a significant concentration-related increase in incidence of neoplasms of the liver, lung, and forestomach and of hemangiosarcomas, histiocytic sarcomas, and sarcomas. Mice treated with coal tar 1 also showed a significant concentration-related increase in incidence of neoplasms of the small intestine. In contrast mice treated with benzo[a]pyrene

showed a significant concentration-related increase in incidence of neoplasms of the forestomach, esophagus, tongue, and larynx. The authors concluded that the forestomach neoplasms produced by coal tar treatment may be due to the presence of benzo[a]pyrene, but that the other tumors produced by coal tar are likely to be due to the presence of genotoxic compounds other than benzo[a]pyrene. The small intestine-tumors produced by coal tar 1 may be due to chemically-induced cell proliferation that occurred at high doses of coal tar.

A risk assessment based on the data from Culp et al. (1998) discussed the validity of using the concentration of a single component of coal tar (benzo[a]pyrene) to estimate the relative cancer risk for coal tar (Gaylor et al. 2000). 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 authors conclude 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.

Levels of exposure associated with CELs of creosote are indicated in Table 3-2 and Figure 3-2.

3.2.3 Dermal Exposure

This section describes the health effects observed in humans and laboratory animals associated with dermal exposure to coal tar creosote. All reliable exposure levels have been reported. Several reports were found that describe the occurrence of dermal and ocular irritation, burns, and "warts" (i.e., squamous papillomas) following acute or prolonged skin contact with coal tar creosote. Coal tar creosote also induces phototoxicity of the skin, and has been demonstrated to be a skin carcinogen in animals. Conclusions that can be drawn from the results of animal studies are limited by the possibility of concurrent oral ingestion of creosote from the skin via normal preening behavior and by the fact that few studies reported accurate doses. Details of these reports are given below.

3.2.3.1 Death

No studies were located regarding death in humans following dermal or skin contact with creosotes, coal tar, coal tar pitch, or coal tar pitch volatiles solely by this route.

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

In test animals, a dermal LD_{50} in rabbits of >7,950 mg/kg was estimated following a 24-hour application of coal tar creosote to both intact and abraded skin; two of four rabbits died at the high dose of 15,800 mg/kg (Pfitzer et al. 1965). This LOAEL value is recorded in Table 3-4. Additional reports of deaths in test animals, after dermal application of coal tar or coal tar pitch volatiles, can be found in the literature, although specific details of the studies are missing (Bonser and Manch 1932; Deelman 1962). Wallcave et al. (1971) treated groups of Swiss albino mice topically with 9% benzene solutions of two coal tar pitches of known PAH content. An additional group of 15 male and female mice were painted with benzene only and served as controls. Zones of approximately 1 square inch were shaved in the skin of the back of each animal and the solutions of coal tar pitch were painted in this area 2 times/week with 25 mL of solution (approximately 1.7 mg coal tar pitch per treatment). Mean survival time for animals painted with coal tar pitch and control animals was 31 and 82 weeks, respectively. The effect, if any, of benzene on the dermal absorption of asphalt components was not evaluated in this study. Asphalt (500 mg/mL) and coal tar pitch (30–84 mg/mL) were the materials used in assessing skin carcinogenesis in nonpigmented Swiss CD-1 and pigmented C3H/HeJ male mice (Niemeier et al. 1988). The mean survival time for treated C3H/HeJ ranged from 44.3 to 68.7 weeks compared to 65.6–73.9 for the controls. The mean survival time for the treated CD-1 mice ranged from 52.6 to 67.8 weeks compared to 63.9–67.8 weeks for controls.

3.2.3.2 Systemic Effects

No studies were located regarding the musculoskeletal, endocrine, or body weight effects in humans or respiratory, musculoskeletal, or endocrine effects in animals after dermal exposure to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles. Studies regarding the systemic effects that have been observed in humans and animals after dermal exposure to creosotes are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Tables 3-4 and 3-5.

Respiratory Effects.

Coal Tar Products. In an industrial health survey of employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, decreased pulmonary function was noted (TOMA 1979). Restrictive deficits in pulmonary function, as indicated by decreases in FVC, were noted in 44 of 257 employees (10 of 47 nonsmokers). Obstructive deficits, as indicated by decreases in percentage forced expiratory volume in one second (FEV1) were noted in 19 of 257 employees (3 of 54 nonsmokers). Nevertheless, no clear relationship could be established because exposure routes in

Table 3-4 Levels of Significant Exposure to Creosote - Dermal

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

Table 3-4 Levels of Significant Exposure to Creosote - Dermal (continued)

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

Table 3-4 Levels of Significant Exposure to Creosote - Dermal (continued)

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

Table 3-4 Levels of Significant Exposure to Creosote - Dermal (continued)

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

Table 3-4 Levels of Significant Exposure to Creosote - Dermal (continued)

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

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

Table 3-5 Levels of Significant Exposure to Wood Creosote - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL			Reference Chemical Form
				Less Serious		Serious	
INTERMEDIATE EXPOSURE							
Systemic							
Rabbit (Australian albino)	10 wk 5 d/wk	Dermal		10 M Percent (%)	(small visible comedones in 2 wks)		Kligman and Kligman 1994 birch tar

d = days(s); LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; wk = week(s)

addition to dermal were likely, such as inhalation and oral. Also, the ability to relate respiratory effects to coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1979). Additional limitations of the studies included seasonal and geographical variation in plant locations, past employment history, voluntary participation in the study that could have biased it in favor of healthy workers, lack of statistical analyses, lack of adequate controls, and use of only current employees.

A site surveillance program was conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant (Agency for Toxic Substances and Disease Registry 1994). The plant had ceased creosoting activities in 1961, after operating for 51 years. A sand and gravel company had operated on part of the abandoned site during the 1970s and 1980s. Because of soil and groundwater contamination with PAHs and other chemicals, the EPA identified this site and placed it on the NPL in 1984. Several residential lots were observed to have soil concentrations of benzo[a]pyrene in excess of 325 mg/kg, or oily-stained areas, and were subject to emergency resodding by the EPA. Contaminated soils were scheduled to be treated for clean-up. A total of 214 residents (123 males, 91 females) of the contaminated residential area (Koppers) were interviewed twice during a period of 2 years, and were compared to 212 residents (122 males, 93 females) from a nearby town. Since all of the residents from the Koppers area who were participating in the survey were African American, the chosen regional comparison population was also African American. No data were presented in this study regarding the relative importance of inhalation versus dermal exposure. During the second year of the surveillance, the responses of the Koppers area residents were compared with the 1990 National Health Interview Survey results. Residents of the Koppers area showed a significantly higher risk of chronic bronchitis (RR=2.65, 95% CI=1.26–5.57) relative to the comparison population during the first year of the study. During the second year of the study, 11 residents of the Koppers area reported chronic bronchitis, whereas 7 were expected based on the 1990 National Health Interview Survey rates. These study results are seriously limited by the study's reliance on self reporting of health conditions for which diagnosis verification was not always available.

Cardiovascular Effects.

Coal Tar Products. In 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, cardiovascular effects, including increased diastolic blood pressure, were noted in 21% (24/113) of the employees examined

(TOMA 1979). Nevertheless, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate cardiovascular effects to coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals such as pentachlorophenol and cigarette smoke (TOMA 1979). Additional limitations of the study are listed above under Respiratory Effects.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following dermal exposure to creosotes, coal tar, or coal tar pitch.

Coal Tar Products. In an acute animal study, New Zealand white rabbits that died following single dermal applications of undiluted coal tar creosote (15,800 mg/kg) exhibited hyperemia of the intestines, but animals treated with 7,950 mg/kg did not (Pfitzer et al. 1965).

Hematological Effects.

Coal Tar Products. In an industrial health survey of employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, hematological effects, including increased number of white blood cells (basophils), were noted in 6% (15 of 257) of the employees examined (TOMA 1979). Similarly, 8% of the employees in eight of nine coal tar plants surveyed had increased white blood cells (eosinophils) (TOMA 1981). Industrial hygiene surveys of coal tar pitch volatiles at the four wood preservative plants indicated that in 94% of the samples, airborne exposure to benzene-soluble components of the coal tar pitch volatiles was within the OSHA permissible limit of 0.2 mg/m^3 (TOMA 1979). The other 6% of the samples ranged from 0.21 to 3.6 mg/m^3 (TOMA 1979). No determination of exposure was made at the nine coal tar plants (TOMA 1981). Furthermore, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate hematological effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1979, 1981). Additional limitations of the studies are noted above (see "Respiratory Effects").

In a clinical study, 15 patients (Group A) with chronic plaque psoriasis were treated with increasing concentrations (1–4%) of topical coal tar paste (Gilmour et al. 1993). These patients did not receive ultraviolet (UV) therapy and served as controls. Seventeen subjects (Group B) received UV-B phototherapy and four subjects (Group C) received psoralen photochemotherapy (PUVA). Another

control group (Group D) consisted of 4 nonpsoriatic subjects who were receiving UV-B as part of another study. Samples of blood were collected before irradiation and 48 hours after irradiation, and full blood counts were determined. Samples taken from Group A were taken before treatment and again 4 weeks later. Samples taken from Group B and C were taken before treatment, 4 weeks after treatment (48 hours after irradiation), and finally 4 weeks after irradiation. The blood counts were all normal. A similar lack of adverse effect on the hematological system was observed by Tham et al. (1994) in psoriasis patients who applied a total of 120 g of coal tar over a period of 2–6 weeks to the skin of one side of their body.

Hepatic Effects.

Coal Tar Products. Fifteen patients (Group A) with chronic plaque psoriasis were treated with increasing concentrations (1–4%) of topical coal tar paste (Gilmour et al. 1993). An additional 17 subjects (Group B) received UV-B phototherapy and 4 subjects (Group C) received psoralen photochemotherapy (PUVA). Another control group (Group D) consisted of 4 nonpsoriatic subjects who were receiving UV-B as part of another study. Liver function was determined. Samples taken from Group A were taken before treatment and again 4 weeks later. Samples taken from Group B and C were taken before treatment, 4 weeks after treatment (48 hours after irradiation), and finally 4 weeks after irradiation. Liver function was within normal limits. A similar lack of adverse effect on liver function was observed by Tham et al. (1994) in psoriasis patients applying 120 g of coal tar to their skin twice daily for 2–6 weeks.

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

Renal Effects.

Coal Tar Products. In an industrial health survey of employees in nine coal tar plants in which coal tar creosote and coal tar were the main treatments used, renal effects, including protein and cells in the urine, were noted in 1–8% (3–34 of 452) of the employees examined (TOMA 1981). Nevertheless, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate renal effects to coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1981). A study performed by Wright et al. (1992b) evaluated the nephrotoxic effects of commercial coal tar preparation for the scalp. The preparation was applied to healthy human subjects either for 15 minutes,

twice a week, for 8 weeks to uncovered skin, or for 30 minutes, every second day for 4 weeks under occlusive bandage. The preparations tested contained 5 or 10% beechwood tar. The concentration of coal tar in the preparation was not specified. Renal function and urinary phenol levels were assayed before, during, and after treatment. No impairment of renal function was detected, nor was urinary phenol content found to be related to the coal tar treatment (Wright et al. 1992b). No adverse effect on urinalysis was observed for 15 patients with chronic plaque psoriasis were treated with increasing concentrations (1–4%) of topical coal tar paste in urine samples taken before treatment and 4 weeks after treatment (Gilmour et al. 1993).

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

Renal effects were also noted in a study conducted by Deelman (1962), in which mice were exposed dermally to an unspecified amount of tar applied 6–18 times over 6–7 weeks. "Seriously affected" kidneys were noted, although no details or data were presented. Ten groups of Swiss albino mice received topical applications of 10% benzene solutions of eight petroleum asphalts of known polynuclear aromatic hydrocarbon content (Wallcave et al. 1971). An additional group of 15 males and females were painted with benzene only and served as controls. Zones of approximately 1 square inch were shaved in the skin of the back of each animal and the solutions of asphalt were painted in this area 2 times/week with 25 mL of solution (approximately 2.5 mg asphalt per treatment). Amyloidosis was frequently observed in animals receiving asphalt, particularly in the kidney. The potential effect of benzene on the dermal absorption of asphalt components was not evaluated in this study.

Endocrine Effects.

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

Dermal Effects.

Creosote Bush. Leonforte (1986) reported six confirmed cases of acute allergic dermatitis subsequent to contact with the creosote bush. Two cases were the result of "casual occupations," two were the result of household remedies, and two were the result of burning the bush. Based on his findings, the author concluded that the allergens are probably contained in the plant's perfume, are volatile, and are not destroyed by heat. In contrast, no adverse treatment-related effects were reported for 23 patients treated topically with an extract of creosote bush (concentration not stated) in castor oil (Heron and Yarnell 2001).

Wood Creosote. Beechwood creosote has been found to irritate tissue other than skin. The effects of beechwood creosote (dose not specified) on the periapical tissue (the connective tissue surrounding the apex of the tooth) were studied in 10 teeth from 4 different dogs 7 days after its application following root canal surgery (Attalla 1968). Beechwood creosote application resulted in localized inflammatory changes and occasional abscess formation in the periapical region, presumably due to tissue damage caused by coagulation of proteins. Bone resorption was observed in the alveolar process. The authors concluded that beneficial disinfectant properties of beechwood creosote may be outweighed by irritant effects following root canal surgery. Birch tar (10%) was applied to the ear of male Australian albino rabbits 5 days/week for 3 weeks (Kligman and Kligman 1994). Comedones were visible on the ear after 2 weeks of treatment.

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 (1978b), burns from hot pitch are relatively common in occupational settings. Burn scars and other sites of epidermal atrophy may later be sites for skin cancer. Creosote chemical burns were observed in construction workers who handled wood treated with creosote (presumably coal tar creosote) (Jonas 1943). Exposure levels were not specified. It was found that 70% of the burn cases were mild and were characterized by erythema of the face. These symptoms were more marked on the cheeks, nose, forehead, and posterior part of the neck. The remainder of the burn cases (30%) were more severe and were characterized by intense burning, itching, and considerable subsequent pigmentation followed by desquamation. There is no way to determine, given the information provided, whether this response was due to primary irritation or an allergenic response.

Other reports of skin irritation after contact with coal tar (Cusano et al. 1992) were found. Patients admitted over a 4-month period to the dermatology wards of Manchester Skin Hospital for the treatment of psoriasis were patch tested with 3% coal tar (Burden et al. 1994). A positive reaction to coal tar was followed by dilution series testing down to a 0.1% concentration of coal tar. Patients were asked about previous psoriasis treatment and adverse reactions from topical preparations. Mean duration of psoriasis was 20 years and many patients had been treated as inpatients previously on numerous occasions; 91% of patients recalled previous treatment with coal tar. Thirteen patients showed clinical intolerance to coal tar and two had positive patch test reaction to coal tar confirmed by serial dilutions.

In another study, 5% crude coal tar (CCT) was applied to the backs of eight subjects in six distinct sites for 15, 30, 60, 90, 120, and 180 minutes (Diette et al. 1983). Tar was then vigorously removed with a washcloth, Ivory® soap, and water. Immediately following tar removal, the minimal phototoxic dose (MPD) of UV-A was determined at each site using 1-cm diameter apertures. In all subjects, the minimal erythema dose (MED) and MPD were defined as the minimal dose of UV-A causing 1+ erythema with distinct borders read at 24 hours after exposure. In addition, 5% CCT was applied to four separate sites on the backs of 13 subjects for 1 hour. The following methods of tar removal were compared: (1) water, (2) Ivory® soap and water, (3) mineral oil, and (4) Ivory® soap and water followed by mineral oil. Immediately after tar removal, all sites were exposed to UV-A and the MPD of UV-A was determined. UV-A exposure doses were identical to those used above. A 5% CCT ointment was applied to the backs of 19 subjects and removed 1 hour later with a washcloth, Ivory® soap, and water. The subjects were informed prior to testing about the photosensitizing effect of tar plus UV-A in producing a burning, stinging, or smarting reaction at an unspecified time during UV-A exposure. These subjects would signal the onset of symptoms and were encouraged not to wait until the burning sensation became unbearable. Subjects were tested immediately and at 0.5, 2, 4, 6, 24, and 30 hours following tar removal. At least 8 subjects were tested at each time; only at 24 and 30 hours were <10 subjects tested. Using the same UV-A exposure times, the MED of UV-A was determined in those eight subjects tested at 24 and 30 hours. The minimal UV-A dose required to induce delayed erythema (the MPD) and the minimal UV-A dose required to induce an immediate smarting reaction (minimal smarting dose or MSD) were recorded. The effects of the following variables on MPD were noted: (1) interval of time tar is left on the skin (TA); (2) methods of tar removal; and (3) time between removal of tar and UV-A irradiation. Tar application for 30 minutes was photosensitizing in all eight subjects; six of the subjects showed photo-sensitization after only 15 minutes of tar application. The photosensitizing effect of tar increased rapidly up to 60 minutes of application. MPD increased from 3.77±1.55 to 6.1±4.0 J/cm^2 after 30 minutes of application. Longer time intervals between tar removal and UV-A exposure were accompanied by more

gradual, but consistent, increases in MPD. The MSD also significantly increased with increasing intervals between tar removal and UV-A exposure. At times, the smarting reaction was associated with an immediate erythema, which faded in several hours; this was not a consistent finding with 1 MSD of UV-A. No urticarial response was noted at this dose level.

Other studies confirm that coal tar creosote is capable of increasing skin sensitivity to sunlight. Phototoxicity is an exaggerated response to sun exposure characterized by excessive sunburn. The usual sunburn is produced by UV-B light, whereas a phototoxic skin response occurs following absorption of UV-A light by chemicals in or on the skin (NIOSH 1981a). Coal tar creosote exposure was evaluated in six male dock builders of Scandinavian descent with fair skin. These builders had worked on this particular construction site for 5 months, but had an average of 16.6 years of work as pile-drivers (NIOSH 1981a). The dermal burning and irritation experienced by these workers upon dermal contact with wood treated with coal tar creosote was exacerbated on hot or sunny days. Skin examinations of these dermally exposed workers revealed erythema and dry peeling skin on the face and neck with irritation and folliculitis on the forearms. These symptoms were worse on hot or sunny days, at which time red, swollen, and puffy eyes were observed. Thus, phototoxicity compounds the irritative response of the skin to coal tar creosote. No skin tumors were observed in this study, but it is not clear if the exposure duration in the group of workers was sufficient to allow development of skin tumors. Nevertheless, some studies have reported latency periods for the development of dermatoses, such as squamous papillomas, ranging from several months to 16 years or more (Cookson 1924; Henry 1946, 1947; O'Donovan 1920; Shambaugh 1935). Effects similar to those seen in the NIOSH (1981a) study were noted in workers transferring coal tar pitch from a river barge to an ocean barge (NIOSH 1982). Exposure levels of coal tar pitch volatiles measured were considered to represent the minimum ambient air exposure in the barge area because of unusual environmental sampling conditions. These levels ranged from below the detectable limit to 0.06 mg/m^3 for breathing zone samples and from below the detectable limit to 0.02 mg/m^3 for area samples. Other studies have been published that describe similar effects of coal tar exposure, although exposure levels are not specified (Emmett 1986).

Coal tar creosote has been reported to produce types of noncancerous skin lesions other than burns and irritation following dermal exposure (Haldin-Davis 1935; NIOSH 1982; Schwartz 1942; Shambaugh 1935). Haldin-Davis (1935) described the case of a man employed in the activity of dipping wood in creosote tanks who received "heavy" dermal exposure to coal tar creosote (level not determined) on the face, trunk, and thighs. He subsequently developed a number of lesions on the hands, forearms, and thighs. One of these lesions was excised and examined, and classified as a benign squamous cell

papilloma. A study was made of the cases of cancer of the lip at various New England hospitals (Shambaugh 1935). Men who were constantly exposed to tars were those who worked in "net lofts" where the fishing nets are repaired and tarred. It was common practice to hold the large wooden shuttle-like needle in the mouth while the tarred nets are being mended. The needle soon becomes smeared with the tar, which is thus carried to the lip. It was found that the older workers who had been exposed to the tar for many years showed typical tar warts on the hands and forearms. An irritative condition on the forearms, which they call "pinginitis," evidently a pustular folliculitis (not cancerous), was observed. Three workers in factories erected for manufacturing armaments developed symptoms 1–2 weeks after beginning work which were attributed to the creosote that evaporated off the wooden floors (Schwartz 1942). It was likely that the fresh creosote on the blocks came in contact with the ends of the trousers and rubbed against the ankles. These employees noticed that their ankles began to itch above the shoe tops and later an erythematous, papular, and vesicular eruption appeared. The lesion extended 4 or 5 inches above the shoe tops, and when seen, presented the appearance of a scratched eczematoid dermatitis. Their condition improved over the weekend. One patient, before the etiology of the condition was discovered, had been treated with a coal tar ointment and the dermatitis became worse. Patch tests were not performed with scrapings from the wooden blocks. It has been reported that chronic hyperpigmentation, a darkening of the skin also known as pitch melanosis, may develop after $5 years of exposure to coal tar pitch (EPA 1978b). Even unexposed areas may be affected.

In an industrial health survey of 251 employees in four wood preservative plants in which coal tar creosote and coal tar were the main treatments used, 82 cases of dermal effects, including skin irritation, eczema, folliculitis, and benign growths on the skin were reported. It is not stated in the report whether multiple conditions were evident in any of the workers examined (TOMA 1979). Workers in nine coal tar plants had a 20% incidence of dermal effects including keratosis, eczema, folliculitis, and chloracne (TOMA 1981). The incidence of benign growths, eczema, and folliculitis was greater than that observed in the general U.S. population, although the authors concluded that only the cases of folliculitis were sufficiently severe to be significant. However, no clear relationship could be established because exposure routes in addition to dermal were likely, such as inhalation and oral. Also, the ability to relate dermal effects to coal tar creosote and coal tar exposure was further confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (TOMA 1979, 1981). Additional study limitations are noted above under “Respiratory Effects.”

The National Institute for Occupational Safety and Health (NIOSH) has investigated potential employee-related health effects in mixers and laborers exposed to coal tar/coal tar creosote/clay products in a

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

A site surveillance program conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant revealed dermal effects of creosote exposure in the residents (Agency for Toxic Substances and Disease Registry 1994). Since all of the residents from the Koppers area who were participating in the survey were African American, the chosen regional comparison population was also African American. No data were presented in this study regarding the relative importance of inhalation versus dermal exposure. Residents living in or near the Koppers area reported a higher prevalence of skin rashes (27.9%) during the first year of the surveillance than the comparison neighborhood (4.9%), with a RR of 5.72 ($P<0.05$; 95% CI=3.01–10.87). During the second year of the surveillance, the responses of the Koppers area residents were compared with the 1990 National Health Interview Survey results, and similar results were obtained, with 34 Koppers residents reporting skin rashes, compared to an expected incidence of 4. Rashes were associated with digging in the yard, having contact with the soil, or wading in or having contact with a creek in the area. Most rashes were associated with itching or burning. The recommendation was that residents in the Koppers area should wear protective clothing when having contact with the soil, and should wash their skin thoroughly when contact with the soil occurs.

Skin irritation is also observed in laboratory animals following dermal exposure to coal tar creosote. The effects of dermally applied coal tar fractions, derived from creosote and anthracene oils by high-temperature boiling, were studied in mouse tail skin at concentrations of 5 and 10% (acids) in paraffin by Wrench and Britten (1975). Several of the fractions caused irritation, and some caused peeling and epidermal thickening. The authors concluded that the acids that boiled in the range from 280 to 340 EC have a more specific action in inducing granular layers than the parent tars, oils, or whole acids at similar concentrations. This study is of limited value because the chemical composition of the acid fractions was not defined, and no dose levels could be quantified. It can only be concluded that certain fractions of coal tar creosote irritate mouse skin.

Three samples of Scottish blast-furnace tar (I, II, and III), one sample of English tar, and an ether extract of English tar were applied in a clipped area of skin in the region between the shoulder blades of 60 mice (Bonser and Manch 1932). Tar was applied biweekly for the first 14 weeks, and thereafter once weekly. This change in the frequency of the tar applications was necessitated by the rather marked tendency to ulceration of the skin exhibited by many of the mice. This experiment was continued for 56 weeks, by which time all mice had died. At 30 weeks, 35 of 60 mice applied with ether extract of English tar died and among the 25 survivors, 50% bore tumors. The first appearances of warts in mice applied with Scottish tar (samples I, II, and III), English tar sample, and ether extract of English tar was in 16 (7 of 60 animals), 21 (8 of 60 animals), and 12 (24 of 60 animals) weeks, respectively. Warts were confirmed histologically in 4, 3, and 16 mice (per sample), treated with Scottish tar (samples I, II, and III), English tar, and ether extract of English tar, respectively.

The skin of 10 groups of Swiss albino mice was treated with 9% benzene solutions of two coal tar pitches of known PAH content (Wallcave et al. 1971). An additional group of 15 males and females were painted with benzene only and served as controls. Zones of approximately 1 square inch were shaved in the skin of the back of each animal and the solutions of coal tar pitch were painted in this area 2 times/week with 25 mL of solution (approximately 1.7 mg coal tar pitch per treatment). Animals exhibited hyperplasia of the epidermis as a general phenomenon, frequently accompanied by inflammatory infiltration of the dermis and on several occasions ulceration with formation of small abscesses. This effect was also seen after application of a 10% solution of petroleum asphalts (Wallcave et al. 1971). The effect, if any, of benzene on the dermal absorption of asphalt components was not evaluated in this study.

Guinea pigs also exhibited phototoxicity after dermal treatment with coal tar pitch distillates and UV light (Emmett 1986). In addition, the histological effects of coal and birch tar on guinea pig teat epidermis treated over a period of 22 days have been investigated (Schweikert and Schnyder 1972a, 1972b). Preparations of both coal and birch tar induced a proliferate acanthosis.

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

Coal tar was applied to the ear of male Australian albino rabbits 5 days/week for 3 weeks (Kligman and Kligman 1994). Comedones were visible on the ear after 3 weeks of treatment with 0.1 or 1.0% coal tar.

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

Ocular Effects.

Coal Tar Products. Direct exposure of the eye to coal tar creosote is irritating to the superficial tissues. Factory and construction workers, roofers, and other workers who handle coal tar, or wood treated with coal tar creosote have experienced conjunctiva burns and irritation resulting from accidental exposure (Birdwood 1938; Emmett 1986; Jonas 1943; NIOSH 1980a, 1981a). Exposure to the sun exacerbated eye irritation from exposure to creosote or coal tar fumes. It was reported in a review by EPA (1978b) 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. The likelihood of adverse effects on the eye may be reduced by maintaining the levels of coal tar pitch volatiles in air below 0.2 mg cyclohexane solubles per cubic meter. In one study, conjunctivitis was not observed at coal tar pitch levels below 0.11 mg cyclohexane solubles per cubic meter (EPA 1978b).

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

Body Weight Effects.

Coal Tar Products. In a developmental study of Sprague-Dawley rats and CD-1 mice exposed to 0, 500, or 1,500 mg/kg coal tar on gestational days 11–15, rats had significant decreases in extragestational body weight compared with controls, while mice had no significant change in extragestational body weight compared with controls (Zangar et al. 1989). Body weight effects were noted in a study conducted by Deelman (1962), in which mice were exposed dermally to an unspecified amount of tar applied 6–18 times over 6–7 weeks. "Diminished weight" was noted, although no details or data were presented. Asphalt (50 µL of a 500 mg/mL solution) and coal tar pitch (50 µL of a 30–84 mg/mL solution) applied

to an unspecified area of the skin of Swiss CD-1 and pigmented C3H/HeJ male mice 2 times/week for 78 weeks had no adverse effect on body weight (Niemeier et al. 1988).

3.2.3.3 Immunological and Lymphoreticular Effects

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

Coal Tar Products. Contact dermatitis has also been reported after short-term contact with coal tar (Cusano et al. 1992). No adverse immunological effects were observed in patients with chronic plaque psoriasis who were treated with increasing concentrations (1–4%) of topical coal tar paste (Gilmour et al. 1993). Autoantibodies, serum immunoglobulin and complement levels were measured; two patients with psoriasis had slightly elevated IgE levels and several had slightly raised concentrations of serum immunoglobulin isotopes and complement components, but these were within normal ranges in most psoriasis patients. Percentages of subsets of peripheral blood mononuclear cells (PBMC) were normal and were not altered by treatment. Lymphocytic infiltration was noted in the pathological evaluation of a tar carcinoma excised from the eyelid of a tar and pitch worker (Goulden and Stallard 1933).

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

with controls, while thymus weights were similar in control and treated animals (Zangar et al. 1989). Amyloidosis of the spleen and inflammatory infiltration of the dermis were observed in Swiss mice after topical application of 2.5 mg asphalt in 10% benzene solutions twice weekly for 81–82 weeks (Wallcave et al. 1971). The effect, if any, of benzene on the dermal absorption of asphalt components was not evaluated in this study.

3.2.3.4 Neurological Effects

No studies were located regarding neurological effects in animals following dermal exposure to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles.

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

3.2.3.5 Reproductive Effects

No studies on the reproductive effects produced by dermal exposure to wood creosote, coal tar pitch, or coal tar pitch volatiles in human or animals were located.

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

A site surveillance program conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc., creosote wood treatment plant revealed no adverse reproductive effects in the residents (Agency for Toxic Substances and Disease Registry 1994). There was no difference in the reproductive outcome of female residents of the Koppers area compared to the comparison neighborhood or the 1990 National Health Interview Survey. In particular, there was no effect on number of pregnancies, live births, premature births, spontaneous abortions, or still births. Koppers women who reported having problems becoming pregnant during the first year of surveillance had an average of 1.3 pregnancies compared to an average of 3.4 pregnancies from women in the comparison neighborhood who also reported difficulty in becoming pregnant. No difference in pregnancy outcome was noted during the second year of surveillance, and rates of stillbirth, low weight birth, or spontaneous abortions were similar to those of unexposed populations (Agency for Toxic Substances and Disease Registry 1994). It is likely that reports of difficulty in becoming pregnant were confounded by perception of risk and possibly also by the age of the mother as the difference was not significant when the results for the entire group were adjusted for concerns about chemical exposure, or when women over the age of 39 were excluded from the analysis. A retrospective study of dermal exposure to coal tar found no increased risk of spontaneous abortion associated with exposure to coal tar during pregnancy, but this was a small study and was unlikely to have sufficient resolution to detect a modest increase in risk (Franssen et al. 1999).

In a developmental study of Sprague-Dawley rats and CD-1 mice, exposure to 500 or 1,500 mg/kg coal tar on gestational days 11–15 resulted in significant decreases in uterine weight (Zangar et al. 1989). No difference in extragestational body weight gain of the mouse dams was observed, but some maternal toxicity in the form of significantly increased weights of the liver, kidney, and spleen was seen. The extragestational body weights of treated rats were significantly decreased compared to controls and the relative weights of maternal liver and kidney were significantly increased while those of the thymus were significantly decreased. The relative weights of the spleen and adrenal glands were unaffected by treatment. Resorptions were significantly increased for all exposed rats and high dose mice compared to controls. Early resorptions (occurred before dosing) were similar in all groups, but middle resorptions (which corresponded to the dosing period) were significantly increased in exposed rats and high dose mice. Late resorptions were also significantly increased in exposed rats.

3.2.3.6 Developmental Effects

No studies on the developmental effects produced by dermal exposure to wood creosote, coal tar, coal tar pitch, or coal tar pitch volatiles in humans were located.

Coal Tar Products. A site surveillance program was conducted by the Texas Department of Health beginning in 1990 at a housing development in Texarkana, Texas, that had been built on part of an abandoned Koppers Company, Inc. creosote wood treatment plant (Agency for Toxic Substances and Disease Registry 1994). There was no difference in the number of low birth weight births or birth defects. One retrospective human study of dermal exposure to coal tar was located in which 64 women who had been treated with coal tar for psoriasis or dermatitis were issued questionnaires (Franssen et al. 1999). Fifty-six of the women returned the questionnaires. The ratio of dermatitis to psoriasis was 1:2 with a mean percentage treated body area of 78–90%, and the women were between 18 and 35 years of age for the period of the study (1981–1985). In total, the women had been pregnant 103 times. In 59 out of 103 pregnancies no coal tar had been used, in 21 pregnancies it was unclear whether coal tar had been used or not and in the remainder coal tar had been used at some point during pregnancy. Untreated pregnancies resulted in 5% congenital disorders while treated pregnancies resulted in 4% congenital disorders. The authors pointed out that their sample size was small and this study probably did not have sufficient resolution to detect a small increase in risk.

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

was observed in exposed rat fetuses and a significantly increased incidence of cleft palate, dilated ureter, and renal pelvic cavitation was observed in exposed mouse fetuses.

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

3.2.3.7 Cancer

Coal Tar Products. Various case reports and the results of cross-sectional occupational surveys associate chronic occupational creosote (coal tar) exposure with the development of skin cancer (Cookson 1924; Goulden and Stallard 1933; Henry 1947; Lenson 1956; Mackenzie 1898; O'Donovan 1920; Shambaugh 1935; Shimauchi et al. 2000). These papers reported similar neoplastic skin lesions for different groups of workers exposed to creosote. Lesions included the development of dermatoses (e.g., squamous papillomas), which progressed to carcinoma, usually squamous-cell carcinoma. Tumor locations included regions of the face, head and neck, and upper limb. Cancer of the scrotum has also been associated with prolonged exposure to coal tar creosote (Henry 1946). The latency period for the development of dermatoses, such as squamous papillomas, was varied, ranging from several months to 16 years or more (Cookson 1924; Henry 1946, 1947; O'Donovan 1920; Shambaugh 1935). Worker exposure in the past was much greater than it is now because of less-sophisticated industrial practices, the lack of knowledge concerning occupational hygiene, and the current recognition of the dangers of excessive exposure to the health of workers. For example, chimney sweeps had a lower incidence of scrotal cancer after limiting their exposure to coal tar creosote by regular washing of their skin. Other factors that should be considered when extrapolating the findings of this older literature to present conditions are the role of exposure to UV radiation in the form of sunshine in these workers (UV radiation is now known to be a major cause of skin cancer), the composition of the creosote products, and other health factors that differ in Great Britain prior to 1940 and the present. Although these studies lack information concerning specific exposures and do not consider other risk factors for the development of skin cancer, when taken

as a group, they suggest a relationship between chronic dermal coal tar creosote exposure, phototoxicity, and the development of skin carcinoma in humans.

The effect of treatment with tar and/or artificial UV radiation on the risk of developing cutaneous carcinoma was evaluated on skin cancer patients (59 cases) with severe psoriasis (Stern et al. 1980); 924 subjects without skin cancer were selected as unmatched controls. A matched group (58 cases and 126 matched controls) was also selected from the same group of controls. Patients were categorized according to amount of tar use (<30, 30–90, or >90 months) and levels of radiation exposures (low, moderate, or high). The relationship between tar exposure and UV radiation treatment and the development of skin cancer both before and after 8-methoxypsoralen photochemotherapy (PUVA) were evaluated. The estimated crude relative rate of cutaneous carcinoma for all patients with high exposure to tar or UV radiation, or both, was 2.4, compared with patients without high exposure. The reported relative rates were 1.8 for high-exposure groups of the prevalence cases and 3.0 for incidence cases. For the matched set of cases and controls, the estimated relative rate for all cases was 4.7. Prevalence and incidence cases in matched sets showed significantly increased risk. However, the conclusions that can be drawn from this study regarding the association of coal tar exposure and skin cancer are limited by the fact that the association of cancer risk and coal tar or UV radiation exposure was not examined separately for each agent.

Bhate et al. (1993) reported that incidence of cancer (total, skin, breast, cervix, genitourinary tract, bronchus, gastrointestinal tract, lynphoma, or other) was not significantly greater in 2,247 patients with psoriasis than in 4,494 age-matched controls without psoriasis. However, they noted that there was a statistically significant increase in skin cancer in the subgroup of 1,252 female psoriasis patients (24/1,228 psoriasis, 25/2,479 controls, P=0.032) and postulated that this might be associated with the fact that women were generally exposed to more treatments for psoriasis than men. The numbers of patients exposed to particular treatments (1,641 psoriasis patients had received coal tar treatment, but many patients had received more than one form of treatment) was too small to allow a statistical analysis of therapeutic risk factors. The authors calculated that although their study population was large, cancer incidence in psoriasis patients would have to be increased to 163% of control levels to be statistically significant at the P=0.05 level.

Fisher (1953) examined a group of 241 tar workers who had not been previously exposed to other carcinogens and found an increase in the number of “tar warts” (defined by the author as early squamous-celled epitheliomas) with duration of exposure. The percentage of workers with warts rose from 5% in

men with <5 years of exposure to 50% in men with 20–25 years exposure and 100% in men with more than 40 years exposure. The author stated that age on starting exposure also influenced susceptibility to tar warts, but did not present the data supporting this statement. No statistical analysis of the data was performed.

Other investigators who have examined the possibility of increased skin cancer incidence in psoriasis patients (Jones et al.1985; Menter and Cram 1983; Torinuki and Tagami 1988) have concluded that coal tar treatment did not produce an increase in cancer incidence, but all of these studies are limited in scope and it is not likely that they would be sufficiently sensitive to detect a small increase in risk. Jones et al. (1985) reported no increase in cancer incidence in 719 tar-treated psoriasis patients compared with the general population. Torinuki and Tagami (1988) reported no effect of tar on cancer rates in patients treated with coal tar and UV light, but only 5 of 43 patients had a follow-up duration of >6 years and this is likely to be insufficient to detect a possible cancer effect. Menter and Cram (1983) reported their opinion that there was no increase in incidence of skin cancer in patients treated with UV light and coal tar, but this was a study of the efficacy of the treatment regime and thus, no untreated controls were included for comparison and no statistical analysis was performed.

Several other studies are available that suggest that there is no association between exposure to coal tar creosote or other coal tar products and cancer in humans. Data from a population-based case-control interview study of 1,867 white men (622 cases and 1,245 controls) in Iowa and Minnesota conducted during 1980–83 were examined (Blair et al. 1993). Interviews were conducted with individuals or their next of kin to obtain information on agricultural exposures, residential history, medical history, family history of cancer, and a detailed occupational history. White men without hematopoietic or lymphatic malignancy were selected as controls. Risks of non-Hodgkin's lymphoma (NHL) were evaluated by intensity or probability of exposure to specific substances. No increased risk was noted with exposure to creosote or asphalt. No increased incidence of nonmelanoma skin cancer was observed in 426 patients 25 years after they had undergone 4 years of coal tar medicinal therapy in combination with UV light for the treatment of atopic dermatitis and neurodermatitis (Maugham et al. 1980). This study is limited in that follow up occurred in only 72% of the patients, and there was no discussion of recall bias or of the effects of mobility (i.e., relocation of the study participants) on the results. In a 25-year retrospective study of 280 psoriatic patients treated with crude coal tar in combination with UV radiation at the Mayo clinic, it was found that the incidence of skin cancer in these patients was not significantly increased above the expected incidence for the general population (Pittelkow et al. 1981). Chemical and biological analysis of coal tar-based therapeutic agents and industrial grade coal tar indicated that the therapeutic

agents and the industrial materials were similar (Wright et al. 1985). The authors suggest that the lack of carcinogenic effects after therapeutic exposure may be due to the presence of solvents and surfactants in the preparations, which may alter deposition and absorption by the skin. Reducing the contact with the therapeutic agents by regular washing may also be a factor (Wright et al. 1985). A case-control study was carried out on 24 PUVA-treated patients with squamous cell cancer of the skin and 96 PUVA-treated patients as matched controls (Lindelof and Sigurgeirsson 1993). Information on past therapies was obtained by questionnaire designed to determine if previous therapy was a risk factor for skin cancer in PUVA-treated patients. For subjects using previous tar therapy, there were 17 of 24 cases of skin cancer (70% exposed) with an estimated RR of 1.3 (95% CI=0.5–3.5); control subjects reported 62 of 96 cases (64% exposed). Prior treatment with tar was not considered to be a risk factor for skin cancer in PUVA-treated patients.

Another study was located that reported that there was no increase in the risk of skin, bladder, or lung cancer in wood treatment plant workers, where coal tar creosote and coal tar pitch were the chemicals used (TOMA 1980). Nevertheless, these findings are of limited value since the study population was limited to those currently working at the plant, was small, and comprised of 46.5% blacks, who experience a very low incidence of skin cancer compared to whites. In addition, the exposure and follow up periods did not allow a long enough latency period for tumor development and there was no verification provided that those studied were actually exposed to coal tar creosote or coal tar. No association was found between bladder cancer and occupational exposures to coal tar and pitch or creosote in a case-control study of 484 persons with confirmed bladder cancer (Siemiatycki et al. 1994).

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 coal tar is carcinogenic following dermal application to rodent skin. The more detailed dermal carcinogenicity studies are reviewed below, and the relevant CELs are presented in Table 3-4.

The tumor-promoting potential of coal tar creosote was evaluated by applying various fractions (e.g., basic, phenolic, and neutral) to the skin of albino mice in conjunction with benzo[a]pyrene (Cabot et al. 1940). The various fractions of creosote oil were prepared by distillation and separation; 90% of the

creosote oil distilled between 160 and 300 EC. The basic fraction was removed with aqueous hydrochloric acid. The phenolic fraction was removed with aqueous sodium hydroxide. The remaining neutral fraction was then steam distilled. The composition of the various fractions was not specified. The tumorigenic effect of benzo[a]pyrene was retarded by the creosote oil, neutral distillate, neutral residue, and phenolic fractions. However, in three instances this effect was apparently related to skin damage associated with the treatments rather to a specific inhibitory effect. Only the phenolic fraction seemed to exhibit a primary antagonistic effect. Three other fractions (basic, neutral, and a low concentration of neutral distillate) exhibited apparent tumor promoting effects.

Ten groups of Swiss albino mice were exposed topically with 9% benzene solutions of two coal tar pitches of known PAH content (Wallcave et al. 1971). An additional group of 15 males and females was painted with benzene only and served as controls. Zones of approximately 1 square inch were shaved in the skin of the back of each animal and the solutions of coal tar pitch were painted in this area 2 times/week with 25 mL of solution (approximately 1.7 mg coal tar pitch per treatment). Animals were weighed once a week (no data shown) and all tumors arising in the skin were charted. Animals were sacrificed when moribund or when they developed highly advanced tumors on the skin. A complete autopsy was performed on all animals, and sections of the skin as well as all grossly pathological organs were studied histologically. Coal tar-painted animals developed squamous cell carcinomas and benign tumors in the form of squamous cell papillomas and keratoacanthomata; 91.4% of animals bore some kind of skin tumor. The potential effects of benzene on the dermal absorption of asphalt components were not evaluated in this study.

Weanling C3H/HeJ mice were exposed to 50 mg solutions containing 25 mg of roofing materials (traditional coal tar pitch, coal tar bitumen, standard asphalt from roofing operation, coal tar bitumen from roofing operation, or roofing dust) 2 times/week for 80 weeks, or until a skin lesion was diagnosed as a papilloma (Emmett et al. 1981). The material was dissolved or suspended in redistilled toluene in a 1:1 ratio (w/w) and applied to the intrascapular region of their backs, where hair had been previously removed. A vehicle control group received 50 mg of toluene 2 times/week, and a positive control group received 50 mg of 0.1% solution of benzo[a]pyrene in toluene 2 times/week. When the papilloma progressed and was diagnosed grossly as a carcinoma, the mouse was sacrificed and autopsied. Selected histopathologic examination of tumors was made to confirm the gross diagnosis. It was found that traditional coal tar pitch and dust from removal of an old roof were significantly more carcinogenic than coal-derived roofing bitumen, but all were strongly carcinogenic. The average times of the appearance of papillomas (and percentage of mice developing tumors) were at 18 (98%), 21.5 (98%), 20.5 (93%),

16.5 (86%), and 31.8 (79%) weeks for traditional coal tar pitch, coal tar bitumen, coal tar bitumen from roofing operation, roofing dust, and positive control, respectively. No tumors were caused by standard roofing asphalt or toluene. The percentage of benzo[a]pyrene in the materials was as follows: traditional coal tar pitch, 0.064%; coal tar bitumen, 0.072%; standard asphalt, <0.004%; coal tar bitumen from roofing operation, 0.064%; roofing dust 0.08%; toluene, 0%; and positive control, 0.1%.

Asphalt and coal tar pitch were the materials used in assessing skin carcinogenesis in nonpigmented Swiss CD-1 and pigmented C3H/HeJ male mice (Niemeier et al. 1988). Animals were divided into 48 experimental groups and treated as follows: (a) 32 groups treated for the primary factorial experiment (i.e., 2 strains x 4 materials x 2 generation temperatures [232 and 316 EC] x 2 light exposure conditions [presence or absence of simulated sunlight]); each animal dosed 2 times/week with 50 µm of the appropriate test material; (b) 4 groups for the solvent control (i.e., 2 strains x 2 light exposure conditions; each animal dosed 2 times/week with 50 µL of cyclohexane/acetone [1:1] vehicle); (c) 2 groups for cage control (i.e., 2 strains x 2 light exposure conditions, dosed 2 times/week with 50 mL solvent and not sham irradiated but always maintained in their individual cages); (d) 4 groups for the positive control (i.e., 2 strains x 2 light exposure conditions, dosed 2 times/week with 50 µL of the solution of 0.01% benzo[a]pyrene in cyclohexane:acetone [1:1]); (e) 4 groups for a combination treatment of asphalt and coal tar pitch fume condensate (i.e., 2 strains x 2 light exposure conditions; each animal dosed 2 times/week with the high temperature condensate from Type III asphalt and Type I coal tar pitch, on alternate weeks); and (f) 2 groups (i.e., 2 strains, for light exposure 2 times/week with no skin painting treatment). Mice were observed daily for systemic toxicity and gross appearance of tumors. Mice found dead were necropsied and those that were moribund were sacrificed and necropsied. Surviving mice at the end of 78 weeks were also necropsied. Tissues were examined and skin lesions excised and prepared for microscopic examination. The theoretical air concentrations of PAH from coal tar pitch at 232 and 316 EC were $5.0x10^6$ and $55.1x10^6$ mg/m^3, respectively. The theoretical air concentrations of benzo[a]pyrene from coal tar pitch at 232 and 316 EC were $55.6x10^3$ and $366.7x10^3$ mg/m^3, respectively. The theoretical air concentrations of PAH from asphalt at 232 and 316 EC were 3,300 and 15,000 mg/m^3, respectively. The theoretical air concentrations of benzo[a]pyrene from asphalt at 232 and 316 EC were 21 and 122 mg/m^3, respectively.

Administration of condensed fumes from both types of coal tar pitches and both types of asphalt resulted in benign tumors (papillomas, kerato-acanthomas, fibromas, and unclassified benign epitheliomas) and malignant tumors such as squamous cell carcinoma and fibrosarcomas (seen more often in C3H/HeJ mice) (Niemeier et al. 1988). CD-1 mice had a much lower incidence of malignant tumors than C3H/HeJ

mice (about 5 versus 60%). The average latent period ranged from 39.5 to 56.1 weeks among C3H/HeJ groups and from 47.4 to 76.5 weeks among the CD-1 groups. The tumorigenic response of C3H/HeJ in the coal tar pitch Type III group with concomitant exposure to light increased with high temperature. Both strains when exposed to condensed coal tar pitch fumes or benzo[a]pyrene in the presence of simulated sunlight had inhibited tumorigenic responses; C3H/HeJ strain treated with 0.01% benzo[a]pyrene and coal tar pitch showed increased tumorigenic response. In the CD-1 strain, only the solar exposed pitch fume groups showed significantly increased tumorigenic response when compared to the positive control. The tumorigenic response of C3H/HeJ to the condensed asphalt fumes increased with high temperature, but no significant change in tumorigenic response was observed for CD-1 mice exposed to fumes at the higher temperature. Simulated sunlight significantly inhibited tumorigenic response in C3H/HeJ mice to both types of asphalt fumes collected at the lower temperature and no overall significant effects were noted in the CD-1 strain. Both strains when exposed to benzo[a]pyrene in the presence of simulated sunlight had inhibited tumorigenic responses; C3H/HeJ strain treated with 0.01% benzo[a]pyrene and those exposed to the high temperature asphalt fumes showed increased tumorigenic response. In the CD-1 strain, only the nonsolar exposed asphalt fume exposed groups showed significantly increased tumorigenic response when compared to the positive control. In comparing the combination group to their respective controls, the C3H/HeJ strain showed no differences in latency, but the combination group showed a significantly increased response by the onset rate analysis method as compared to the asphalt group (Type III-316 EC) without light. The responses in CD-1 mice were similar, in that the nonsolar exposed combination group had a significantly increased tumor response, as assessed by the onset rate method, compared with the asphalt group. They also died earlier (no data shown) and developed tumors at a significantly earlier time than the asphalt group. When the combination groups were compared to the responses of the pitch groups, onset rate analysis showed that the sham irradiated pitch group (Type I-316 EC) had a significantly greater tumor response than the combination group. No other differences were noted. Both strains when exposed to benzo[a]pyrene or combination of pitch and asphalt in the presence of simulated sunlight showed inhibited tumorigenic responses; C3H/HeJ strain treated with 0.01% benzo[a]pyrene and the combination groups and those exposed to the high temperature asphalt fumes showed increased tumorigenic response.

In conclusion, both coal tar pitch and asphalt produced benign and malignant skin tumors in mice (Niemeier et al. 1988), but C3H/HeJ mice were more susceptible to the formation of malignant tumors than CD-1 mice. Concomitant exposure to sunlight reduced tumor production by coal tar pitch, or asphalt, or the combination of coal tar pitch and asphalt compared with nonsolar exposed animals. The

combination of exposure to both asphalt and coal tar pitch increased tumor formation compared with asphalt alone, but was reduced compared with coal tar pitch alone.

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

This is in contrast to the results of a tumor initiation study by Springer et al. (1989) in which Charles River CD-1 female mice (30 per group) were treated with crude coal tar and a variety of coal tar fractions in an initiation assay. The backs of the mice were shaved and the skin treated with 50 µL of an acetone solution of the various test materials. Two weeks after initiation, the animals were promoted with twice-weekly applications of 5 µg of 12-O-tetradecanoylphorbol-13-acetate (TPA) (also known as phorbol myristate acetate or PMA) in 50 µL of acetone for 24 weeks. Tumors were identified visually and were not characterized further by histopathology. The time of tumor appearance and the number of tumors were recorded as measures of response. Test materials included: 5 mg (approximately 203 mg/kg body weight) crude coal tar (boiling point: 300–850 EF); coal tar temperature fractions (boiling points: 300–700, 700–750, 750–800, 800–850, or >850 EF); chemical fractions of the 750–800 EF temperature fraction (aliphatics and olefins, neutral PAH, nitrogen-containing polycyclic aromatic compounds, hydroxy-PAH); 25 µg benzo[a]pyrene; 5 mg crude coal tar +25 µg benzo[a]pyrene; coal tar temperature fractions +25 µg benzo[a]pyrene; chemical fractions +25 µg benzo[a]pyrene. The three lower temperature coal tar fractions did not contain benzo[a]pyrene, while the other two contributed 8.5 µg benzo[a]pyrene towards the total dose. Mice initiated with benzo[a]pyrene alone showed the greatest tumor response. Administration of the lowest boiling point coal tar fraction did not produce significantly more tumors than controls. Exposure to the crude coal tar or the 700–750 and 750–800 EF fractions produced a small, but significant increase in tumors compared with controls. The two highest temperature fractions showed substantial initiating activity. The aliphatic fraction did not have tumor initiating activity, the other chemical fractions had some activity, with that of the PAH fraction being the highest and similar to that of crude coal tar. Co-administration of benzo[a]pyrene and coal tar or coal tar fractions resulted in a decrease in the initiation of tumors compared with benzo[a]pyrene alone. The authors suggest that the reduction in benzo[a]pyrene tumor initiation by coal tar fractions may be caused

by altered rates or routes of metabolism of benzo[a]pyrene due to the presence of various components of the coal tar.

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

Seven groups of 30 female Sutter mice each were treated with 75 µL dimethylbenzanthracene (DMBA) and 25 µL coal tar creosote (undiluted creosote oil), alone and in combinations of the two to evaluate the carcinogenic, initiating, and promoting activity of coal tar creosote on mouse skin (Boutwell and Bosch 1958). Coal tar creosote alone, DMBA and coal tar creosote, and coal tar creosote with 25 µL croton oil (0.5% in benzene) all induced the development of papillomas and carcinomas. Tumors first appeared at 10–20 weeks of application. DMBA pretreatment shortened the latent period and increased the tumor yield of coal tar creosote treatment, but since a nearly maximal tumor induction response (i.e., percentage of mice with papillomas just below 100) was seen with coal tar creosote alone, tumor-promoting activity of coal tar creosote could not be definitely proven. The initiating activity of coal tar creosote was demonstrated by its ability to induce tumors when applied prior to croton oil treatment (croton oil alone was without effect). Coal tar creosote alone or in combination with DMBA or croton oil induced papilloma formation more slowly, and carcinomas appeared by 14 weeks and accumulated more rapidly than in the DMBA plus croton oil group. Thus, this study demonstrated the carcinogenic and tumor-initiating activity of coal tar creosote on Sutter mouse skin.

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

Three-month-old Charles River CD-1 male mice (30 per group) were treated with a variety of coal derived complex mixtures in an initiation/promotion assay (Mahlum 1983). The backs of the mice were shaved and the skin was treated with 50 µL of the various test materials. Groups of animals initiated with DMBA or benzo[a]pyrene served as positive controls, negative controls received 50 µL acetone. Two weeks after initiation, the animals were promoted with twice-weekly applications of 50 µL of phorbol myristate acetate (PMA) (also known as 12-O-tetradecanoylphorbol-13-acetate or TPA) for 6 months. Tumors were identified visually and were not characterized further by histopathology. The time of tumor appearance, the number of mice with tumors, and the number of tumors per mouse were recorded as measures of response. The following coal distillates were used as initiators: heavy distillate (HD) boiling point range 550–850 EF; 300–700 EF boiling point range fraction, and an 800–850 EF boiling point range fraction. In addition the following chemical fractions were prepared from HD: basic (BF), basic tar (BTF), neutral tar (NTF), and polynuclear aromatic (PNA) fractions. The promoting activity of middle distillate (MD), boiling point range 380–550 EF, was tested by initiating with 50 µg DMBA, followed 2 weeks later, by twice weekly applications of a 50% solution (w/v) of MD in acetone. Animals that received no DMBA, but were treated twice weekly with MD, were used as controls. DMBA was a more potent initiator than benzo[a]pyrene. Initiation with HD resulted in about the same incidence of tumors as benzo[a]pyrene. NTF was almost as active an initiator as HD, while BTF was only slightly less active. BF and PNA were considerably less active initiators. The 800–850 EF fraction showed a low degree of initiating activity, while the response of the 300–700 EF group was the same as the acetone controls. MD showed a low level of promotion in animals initiated with DMBA. No uninitiated mice showed tumors after 12 months, 17% of initiated mice had tumors at 6 months, and incidence increased to 52% by 12 months.

The carcinogenic activity of two high-temperature-derived coal tar creosote oils ("light" and "blended") was studied by Poel and Kammer (1957). The principal components of light oil are benzene, toluene, xylene, and solvent naphtha. Blended oil is a mixture of creosote oil, anthracene oil and the oil drained from the naphthalene recovery operation. Its principal components are methylated naphthalenes, acenaphthene, fluorene, phenanthrene, anthracene, and carbazole. The blended or light oils were applied by drops to the skin of mice at concentrations of 20 or 80% (blended oil) or 50% (light oil) 3 times/week for life. Both oils induced skin tumors in every exposure group by 26 weeks of application. Seven of the eight mice exposed to each concentration of blended oil had tumors that progressed to malignancy. One tumor regressed before the death of a mouse in the 80% group and one mouse in the 20% group had a papilloma that had not become malignant by the end of the experimental period. There was no evidence of tumor regression in the tests with light oil. Several mice exhibited metastases to the lungs or regional lymph nodes. The fractions tested did not contain benzo[a]pyrene (limit of detection=0.03% benzo[a]pyrene), so the authors concluded that the carcinogenic activity of the coal tar creosote oil used in the experiment was not due to benzo[a]pyrene.

Crude coal tar (10, 25, and 100%) in petrolatum was applied to the ear of male Australian albino rabbits (3 per group) 3 times/week for 15 weeks (Kligman and Kligman 1994). Crude coal tar was both comedogenic and carcinogenic at all doses tested (10, 25, or 100%). Tumors developed as early as 1–2 weeks after 3 weeks of treatment with 10% coal tar. The tumors were classified as papillomas, squamous cell carcinomas, keratoacanthomas, and cutaneous horns, and became extremely numerous with longer treatment.

Standard Reference Material (SRM) 1597 obtained from the National Institute of Standards and Technology, was tested in an assay of tumor initiation in female SENCAR mice (Marston et al. 2001). SRM 1597 is a mixture derived from a medium crude coke oven coal tar dissolved in toluene. Certified values have been published for selected PAH components of this mixture including B[a]P. Dibenzo[a,l]pyrene (DB[a,l]P) is not a component of SRM 1597. SRM 1597 (1 mg per 125 µL, which contains 10.4 µg B[a]P) was painted onto the shaved skin of 6–7-week-old mice over a period of 2 weeks (the number of applications was not reported) and in some cases, treatment with SRM 1597 was followed 5 minutes later with B[a]P or DB[a,l]P). The treatment groups were as follows: 10 mice with 200 µL toluene as a control; 30 mice with 1 mg SRM 1597; 35 mice with 200 nm (50.4 µg) B[a]P in 100 µL toluene; 35 mice with 1 mg SRM 1597 plus 200 nm (50.4 µg) B[a]P in 100 µL toluene; 35 mice with 2 nmol (0.6 µg) DB[a,l]P; and 35 mice with 1 mg SRM 1597 plus 2 nmol DB[a,l]P. Two weeks after initiation, twice-weekly promotion was begun with 12-O-tetradecanoyl-phorbol-13-acetate (TPA) at

1 µg/200µL acetone per mouse for 25 weeks. Mice were examined weekly for papillomas and at 25 weeks, tumors were confirmed histologically at necropsy. In the test of SRM 1597 and B[a]P, no papillomas were found in the control group, SRM 1597 initiated 5.3 tumors per tumor-bearing animal, B[a]P initiated 8.9 tumors per tumor-bearing animal and B[a]P plus SRM 1597 produced 8.8 tumors per tumor-bearing animal. Results of statistical analysis of mice treated with SRM 1597 compared with controls were not reported. Compared with B[a]P, cotreatment with SRM 1597 did not significantly change tumor incidence, either over time, or specifically at 25 weeks. In contrast, in the test of SRM 1597 and DB[a,l]P, 1 papilloma was found on one mouse in the control group, SRM 1597 initiated 4.1 tumors per tumor-bearing animal, DB[a,l]P initiated 8.1 tumors per tumor-bearing animal, and DB[a,l]P plus SRM 1597 produced 5.2 tumors per tumor-bearing animal. There were significant differences in the number of tumors per tumor-bearing animal for all three treated groups and, compared with DB[a,l]P alone, cotreatment with SRM 1597 significantly reduced the number of tumors per tumor-bearing animal. This reduction may be due to decreased metabolism of DB[a,l]P with consequent reduction in DB[a,l]P metabolite-DNA adduct formation in the presence of SRM 1597 (see Section 3.3).

In conclusion, the results of these studies indicate that coal tar creosote and several of its fractions can be carcinogenic when applied to the skin of mice or rabbits. Dermally applied coal tar creosote can also act as a tumor-initiating agent. Thus, it is likely that individuals whose skin comes into contact chronically with coal tar creosote would be at higher risk for skin cancer, particularly when exposure to other carcinogenic substances also occurs, as is a possible scenario in areas surrounding hazardous waste sites.

3.3 Genotoxicity

Creosote Bush. No studies were located regarding genotoxic effects of the creosote bush in humans or animals.

Wood Creosote. Zeiger et al. (1992) tested beechwood creosote in the Ames assay using *Salmonella typhimurium* strains TA 97, TA98, TA100, TA102, TA104, TA1535, TA1537, and TA 1538, with and without metabolic activation, and found it to be nonmutagenic.

Coal Tar Products. Studies of workers exposed to coal tar, bitumen fumes, coal tar pitch, or coal tar pitch volatiles have shown an association between exposure to these mixtures and significant increases in genotoxic effects; however, it must be noted that a recurrent limitation of these studies is the lack of precise exposure data. Significant increases in the frequency of chromosomal abnormalities and sister

chromatid exchanges (SCE) were observed in the peripheral blood lymphocytes (PBL) of 49 workers exposed to coal tar for 6–10 years compared with 50 age-matched, non-exposed individuals (Yadav and Seth 1998). There were similar findings in a study of 30 steelworkers occupationally exposed to coal tar pitch volatiles (Bender et al. 1988). Burgaz et al. (1998) reported an elevated incidence of SCE and micronuclei (MN) in PBL of 28 workers exposed to bitumen fumes during paving operations. A study of 24 workers exposed to coal tar pitch for 7–32 years showed a significant increase in SCE and serum P21 (the protein product of the *ras* oncogene) compared to 10 non-exposed individuals (Wu et al. 1998). Urine samples taken from 19 individuals occupationally exposed to coke oven emissions in a steel mill and 31 controls (De Meo et al. 1987) and urine samples from 30 coke oven workers and 26 controls (Mielzynska and Snit 1992) showed an association between exposure and increased mutagenic activity in the Ames *Salmonella typhimurium* test. However, an examination of the mutagenic activity of urine from only three workers exposed to coal tar creosote vapors at a wood preserving factory (Bos and Jongeneelen 1988; Bos et al. 1984a, 1984c) reported no mutagenic activity in 10-day urine samples. The absence of mutagens in these urine samples was ascribed by the study authors to a relatively low level of exposure, improper timing for urine sample collection, and the insensitivity of the assay.

Some studies have also documented increases in the number of DNA adducts in the blood of patients undergoing dermal coal tar therapy. For instance, Santella et al. (1995) reported increases in benzo[a]pyrene (B[a]P) DNA adducts in blood of psoriasis patients treated with 20–100 g tar per day. However, Pavanello and Levis (1994) found that there were no differences between the number of PAH-DNA adducts formed *in vivo*, determined by the ^{32}P-postlabeling method, in the PBL of psoriatic patients treated with 50% coal tar paste for up to 8 days and adduct levels in healthy individuals not treated with coal tar. Moreover, the levels of PAH-DNA adducts detected in patients before, during, and 16 days after coal tar therapy were statistically unchanged. In a previous study, Pavanello and Levis (1992) had examined the effect of coal tar treatment on DNA adduct formation *in vitro* in human lymphocytes taken from four male psoriatic patients 25–70 years old treated for 4–10 days with a paste containing 50% coal tar and nine healthy individuals who did not take any medication. No significant difference was detected in the total amount of B[a]P-DNA adducts in blood lymphocytes from patients or controls or between patients before and after treatment. In contrast, patients treated with a 50% coal tar paste, a 2% coal tar ointment, or a combination of pure coal tar and 2% ointment for 3–17 days had *in vivo* B[a]P-DNA adduct levels, determined by ELISA technique, that were higher during therapy than 2–5 months after therapy termination (Pavanello and Levis 1994). A study by Sarto et al. (1989) showed an association between the frequency of chromosomal aberrations and SCE in blood lymphocytes and the level of

exposure to coal tar of patients undergoing therapy for psoriasis with topical applications of pure coal tar or 4% coal tar-containing ointment.

Increases in the number of DNA adducts in skin biopsy samples have been observed in patients undergoing coal tar therapy with ointments containing 3–5% coal tar for at least 7 days (Zhang et al. 1990) and in patients treated for an average of 21 days with an ointment containing as much as 10% coal tar (Godschalk et al. 2001). Schoket et al. (1990) observed elevated levels of adducts in skin biopsy samples taken from psoriasis patients receiving coal tar and juniper tar (cade oil) therapy. Sarto et al. (1989) examined the mutagenicity of urine samples taken from patients treated for psoriasis with topical applications of pure coal tar or 4% coal tar-containing ointment. The results suggest that urinary mutagen levels were related to the levels of exposure to coal tar. Similar findings of mutagenicity of urine collected from psoriatic patients treated with coal tar were reported in other studies (Clonfero et al. 1990; Gabbani et al. 1999; Granella and Clonfero 1992).

There is some indication that genetic polymorphisms may play a role in the manifestation of genotoxic effects in individuals exposed to coal tar products. A study of 15 patients treated with a 2% coal tar ointment for at least 3 days showed that urinary mutagenicity, determined by *S. typhimurium* strains TA98 and YG1024 in the presence of microsomal enzyme, was associated with glutathione S-transferase M1 (GSTM1) genotype (Gabbani et al. 1999). The mean value of urinary mutagenicity of subjects with genotype GSTM1-null was double that of GSTM1-positive subjects and the difference was significant. In a study of 10 patients being treated for atopic eczema with an ointment containing up to 10% coal tar for an average of 21 days, Godschalk et al. (2001) showed that aromatic DNA adduct levels in skin biopsies of coal tar-treated patients were 2-fold higher in GSTM1(-/-) individuals compared to GSTM1(+) individuals, but the difference was not statistically significant. Significantly (10-fold) higher levels of p53 were found in the basal layer of GSTM1(-/-) individuals compared with GSTM1(+) patients. Analyses of skin biopsies of atopic dermatitis patients treated with 3–10% coal tar for 1 week revealed that the presence of a mutant myeloperoxidase genotype was associated with a reduction in the formation of B[a]P-adducts (Rojas et al. 2001). Adduct levels in patients without the mutant gene were 14.2 and 18.4 adducts per 10^8 nucleotides, while in patients with the mutant gene adduct, levels were 2.2 and 5.0 adducts per 10^8 nucleotides.

Several *in vivo* studies have shown increased DNA adduct formation in animals following oral administration of coal tar or coal tar waste. Dose-related increases in DNA adduct levels were observed in B6C3F_1 mice fed up to 1,750 mg coal tar/kg/day for 28 days (Culp and Beland 1994; Culp et al. 1996a). DNA adducts were detected in liver, lung, and forestomach. Weyand et al. (1991) reported dose-

related increases in DNA adduct formation in the lung of $B6C3F_1$ mice fed up to 1% coal tar waste for 15 days but these increases were not correlated with the total PAH content of the coal tar. $B6C3F_1$ mice fed 0.05, 0.25, or 0.50% coal tar waste for 94 or 185 days showed dose-related increases in DNA adduct formation in both lung and forestomach tissue (Weyand et al. 1994). Numerous other studies have also documented the formation of DNA adducts in animals fed coal tar waste from manufactured gas plants (Bordelon et al. 2000; Goldstein et al. 1998; Koganti et al. 2000). Some studies suggest that lungs are more sensitive than forestomach tissue to DNA adduct formation in mice (Weyand and Wu 1995; Weyand et al. 1994). The results of additional *in vivo* studies are summarized in Table 3-6.

The role of PAHs other than B[a]P in the mutagenicity of coal tar is still not clearly understood. Oral administration of 636 mg/kg/day MGP residue to mice for 14 days produced a range of lung and forestomach DNA adducts with three major components. Two of the adducts were identified as produced by B[a]P (10% of the lung adducts and 47% of forestomach adducts) or benzo[b]fluoranthene (13% of the lung adducts). The identity of the third adduct (41% of lung adducts, 32% of forestomach adducts) was unknown (Weyand and Wu 1995). Culp et al. (2000) and Culp and Beland (1994) reported that DNA adduct formation was higher in mice fed coal tar than in those fed B[a]P and Koganti et al. (2000) proposed that *7H*-benzo[c]fluorene, not B[a]P, was responsible for the formation of DNA adducts in lungs of mice fed coal tar. Genotoxic effects have been observed in several tissues after dermal application of coal tar products. For instance, DNA adducts were detected in mouse skin after dermal application of coal tar fractions (Marston et al. 2001; Springer et al. 1989) and in skin, lungs, and lymphocytes of rats after dermal application of bitumen fume condensates (Genevois et al. 1996). Dermal application of 250 mg/kg creosote in olive oil to rats for 24 hours resulted in the excretion of mutagens in urine (Bos et al. 1984c).

Various *in vitro* studies using the Ames *S. typhimurium* test (Bos et al. 1984a, 1984c) or the mouse lymphoma assay (Mitchell and Tajiri 1978) have demonstrated the genotoxicity of several coal tar products, including samples from creosote-treated wood. Using a modified Ames assay with *S. typhimurium*, Machado et al. (1993) found that coal tar pitch was more strongly mutagenic than asphalt fume condensates. The temperature at which the fumes were collected was positively correlated with mutagenicity. Bos et al. (1987) showed that creosote contains mutagens that are volatile at 37 EC. Simmon and Shepherd (1978) demonstrated that the genetic mode of action of creosote is induction of a frame-shift mutation. The results of additional *in vitro* studies are summarized in Table 3-7.

Table 3-6. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vivo*

Species (test system)	End point	Results	Reference
	CREOSOTE		
Mammalian systems:			
Rat/liver	DNA adducts	+	Chadwick et al. 1995
Mouse/lung, forestomach, spleen	DNA adducts	+	Weyand et al. 1991
	COAL TAR		
Non-mammalian systems: Perch/liver	DNA adducts	+	Ericson et al. 1998, 1999
Mammalian systems:			
Human/lymphocytes	Chromosomal aberrations/sister chromatid exchange	+	Sarto et al. 1989
Human/lymphocytes	Sister chromatid exchange	+	Wu et al. 1998
Human/lymphocytes	Chromosomal aberrations/sister chromatid exchange	+	Yadav and Seth 1998
Human/skin	DNA adducts	–	Schoket et al. 1990
Human/skin	DNA adducts	+	Zhang et al. 1990
Human/skin	DNA adducts	+	Rojas et al. 2001
Human/skin, blood cells	DNA adducts	+	Godschalk et al. 1998
Human/lymphocytes	DNA adducts	–	Pavanello and Levis 1992
Human/lymphocytes	DNA adducts	+	Pavanello and Levis 1994
Human/blood	DNA adducts	+	Santella et al. 1995
Rat/liver, lung, forestomach	DNA adducts	+	Culp and Beland 1994
Rat/lymphocytes, lung, skin	DNA adducts	+	Genevois et al. 1996
Rat/lung, liver, forestomach	DNA adducts	+	Goldstein et al. 1998
Rat/lung, liver	DNA adducts	+	Bordelon et al. 2000
Mouse/forestomach, small intestine	DNA adducts	+	Goldstein et al. 1998

Table 3-6. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vivo* (*continued*)

Species (test system)	End point	Results	Reference
	COAL TAR (cont'd)		
Mammalian systems (*cont'd*): Mouse/forestomach, small intestine	DNA adducts	+	Culp et al. 1996a
Mouse/lung, forestomach	DNA adducts	+	Weyand and Wu 1995
Mouse/lung, forestomach	DNA adducts	+	Weyand et al. 1994
Mouse/skin, lung, liver, kidney heart	DNA adducts	+	Randerath et al. 1996
Mouse/forestomach, lung, liver, intestine	DNA adducts	+	Culp et al. 2000
Mouse/lung	DNA adducts	+	Koganti et al. 2000
Mouse/lung	DNA adducts	+	Koganti et al. 2001
Mouse/skin	DNA adducts	+	Hughes et al. 1993
Mouse/skin	DNA adducts	+	Phillips and Alldrick 1994
Mouse/skin	DNA synthesis	+	Walter et al. 1978
Mouse/skin	Gene mutation	+	Vogel et al. 2001
	COAL TAR PITCH AND BITUMEN VOLATILES		
Mammalian systems:			
Human blood cells	Chromosomal aberrations	+	Bender et al. 1988
Human/white blood cells	DNA adducts	+	Lewtas et al. 1997
Human/lymphocytes	sister chromatid exchange (SCE)/high frequency SCE	(+/–)	Burgaz et al. 1998
Human/lymphocytes	Micronuclei	+	Burgaz et al. 1998
Rat/lung	DNA adducts	+	Lewtas et al. 1997

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

Table 3-7. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vitro*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Calf thymus DNA	DNA adducts	+	No data	Akkineni et al. 2001
Calf thymus DNA	DNA adducts	+	No data	Koganti et al. 2000
Calf thymus DNA	DNA adducts	+	No data	Reddy et al. 1997
Salmon testes DNA	DNA adducts	+	–	Genevois et al. 1998
Prokaryotic organisms:				
Salmonella typhimurium (histidine auxotrophs)	Gene mutation	+	–	Simmon and Shepherd 1978[a]
S. typhimurium	Gene mutation	+	+	Agurell and Stensman 1992
S. typhimurium	Gene mutation	+	No data	Reeves et al. 2001
S. typhimurium	Gene mutation	+	–	Baranski et al. 1992
S. typhimurium	Gene mutation	+	–	Bos et al. 1983, 1984b, 1984c, 1985, 1987
S. typhimurium	Gene mutation	+	–	Donnelly et al. 1993, 1996
S. typhimurium	Gene mutation	+	+	Kesik and Janik-Spiechowicz 1997
S. typhimurium	Gene mutation	+	–	Mayura et al. 1999
S. typhimurium	Gene mutation			Machado et al. 1993
S. typhimurium (taped-plate assay; vapor exposure)	Gene mutation	+	–	Bos et al. 1985, 1987
Escherichia coli WP2 (TK=/–), (tryptophan auxotroph)	Gene mutation	–	–	Simmon and Shepherd 1978[a]
Mammalian cells:				
Human mammary epithelial cells	DNA adducts	No data	+	Leadon et al. 1995
Mouse lymphoma cells	Gene mutation	+	–	Mitchell and Tajiri 1978
V79	Gene mutation	–	–	U.S. Department of Energy 1994
V79	Sister chromatid exchange	+	+	U.S. Department of Energy 1994

Table 3-7. Genotoxicity of Coal Tar Creosote, Coal Tar, Coal Tar Pitch, or Coal Tar Pitch Volatiles *In Vitro (continued)*

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

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

+ = positive results; – = negative results; DNA=deoxyribonucleic acid

3.4 TOXICOKINETICS

Specific information regarding the toxicokinetics of creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles is limited. Several compounds have been detected in coal tar creosote, yet there are no definitive data on which of these compounds people are exposed to in wood-treatment plants or at hazardous waste sites. Analyses have revealed that PAHs are the major components of the coal tar creosote mixture (TOMA 1981). Hence, pharmacokinetic studies on PAHs can be used as surrogates for coal tar creosote. However, this information is only speculative given the possible toxicokinetic interactions that occur among the PAHs and other components in the coal tar creosote mixture, and will be used only when data on coal tar creosote are not available. For more information on the toxicokinetics of PAHs, please refer to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (Agency for Toxic Substances and Disease Registry 1995). Phenols and cresols are also components of coal tar products. For more information on the toxicokinetics of these chemicals, please refer to the ATSDR *Toxicological Profile for Phenol* (Agency for Toxic Substances and Disease Registry 1998) and the ATSDR *Toxicological Profile for Cresols* (Agency for Toxic Substances and Disease Registry 1992).

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

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

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

Measurements were carried out in a creosote impregnation plant where six men volunteered to participate in the study (Elovaara et al. 1995). Personal breathing zone air samples were taken on 5 consecutive days followed by a work-free period of 64 hours. All workers wore leather protective gloves and cotton overalls. Two employees worked overtime (until 6:30 a.m.) on Monday, which was an exception to the regular 8-hour schedule. Particulate PAHs were collected during the whole shift and analyzed within 7 weeks. Workers were asked to collect all urine passed within the 24 hour period into divided samples for the designated periods. Results showed that the geometric mean (range) air concentrations were 4.77 (1.2–13.7) mg/m^3 (n=30) for total particulate PAHs (including pyrene) and 1,254 (370–4,200) mg/m^3 (n=30) for naphthalene. The PAH profile was similar in all samples. 1-Hydroxypyrene was found in the urine samples.

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

Four rotation crews of about 29 workers and one day crew of 22 workers worked in a 5-day shift, 8 hours/day in the potrooms (Ny et al. 1993). All workers wore disposable respirators that were renewed 4–5 times/day, thick cotton working clothes with long sleeves, safety shoes, safety glasses, gloves, and helmets. Other groups that worked occasionally in the potrooms were also included in this study. Some employees who worked in dusty environments also wore facial protective clothing. Personal breathing zone air samples taken randomly from 38 workers were sampled once. Measurements were done on 3 out of 5 working days for the rotation crews and on 4 days in 2 work weeks for the day crew. The filter holders and the XAD-2 tubes used in sampling were analyzed. Urine samples were collected from 33 of

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

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

Tumor-susceptible ICR CF-1 and tumor-resistant CAF1-JAX mice were exposed to 10 mg/m^3 coal tar aerosol-BTX mixture continuously, or for 90 days, or intermittently for 18 months (MacEwen et al. 1977). Coal tar used to generate the aerosol was of various samples from multiple coke ovens blended together with a 20% by volume amount of BTX fraction of the coke oven distillate. The coal tar-BTX mixture was comparable to the material inhaled by topside coke oven workers. Mice were serially sacrificed during the exposure period for the determination of coal tar lung burden and the time to tumor induction. Control animals were held in a vivarium. All animals were examined daily during the exposure and postexposure periods. Coal tar fluorescence retained in mouse lung and skin tissues (n=4) were measured. The amount of coal tar found on mouse skin did not change to any great degree after the first week of exposure. Lung tissue accumulated coal tar aerosol at a fairly steady rate during 18 months of intermittent exposure as compared to a high increased rate (from graph) during the 90 days of continuous exposure. The coal tar lung burden in mice was approximately equal for both exposure modes for the 180-day exposure period.

PAHs extracted from coal fly ash were intratracheally administered to pregnant Wistar rats at a dose of 20 mg/kg, once/day, on gestational days 18 and 19 (Srivastava et al. 1986). The presence of the PAHs in

both the maternal and fetal lungs and livers on gestational day 20 indicated that pulmonary absorption occurred following intratracheal administration, but inhalation exposure was not examined.

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

3.4.1.2 Oral Exposure

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

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

Coal Tar Products. The presence of coal tar creosote metabolites in the urine of humans and rabbits receiving calcium creosote (a calcium salt of creosote) tablets was evidence that this salt of creosote was absorbed following ingestion (Fellows 1937, 1939b). Furthermore, evidence exists that certain PAHs found in coal tar creosote such as anthracene (Rahman et al. 1986), benzo[a]pyrene (Hecht et al. 1979; Rahman et al. 1986; Rees et al. 1971; Yamazaki et al. 1987), chrysene (Chang 1943; Modica et al. 1983), and phenanthrene (Rahman et al. 1986) are absorbed following oral administration in animals.

Male B6C3F$_1$ mice were given 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar/day in feed for 28 days (Culp and Beland 1994). At the end of the feeding period, DNA adduct formation was quantified in the liver, lungs, and forestomach by ^{32}P-post-labeling. The adduct levels were then compared with those obtained by feeding benzo[a]pyrene to mice for 3 weeks at concentrations corresponding to the amount of benzo[a]pyrene in the coal tar doses. DNA adduct formation was found to increase as a function of dose in each tissue with both coal tar and benzo[a]pyrene, indicating absorption after oral exposure. Five groups of B6C3F$_1$ mice (24 males, 24 females) were fed a control gel diet containing 0.05, 0.25, or 0.50% MGP (Weyand et al. 1994). The urinary excretion of 1-hydroxypyrene by male

mice (12 per group) treated with 0.25 and 0.50% MGP was evaluated throughout the 185 days of diet administration. 1-Hydroxypyrene was detected in the urine, indicating absorption of MGP components.

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

3.4.1.3 Dermal Exposure

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

Coal Tar Products. No studies were located in humans or animals regarding the direct analysis of the extent or rate of coal tar creosote, coal tar, or coal tar pitch absorption following dermal exposure. However, reports of workers who developed cancer subsequent to dermal exposure suggested that coal tar creosote was absorbed through the skin (Cookson 1924; Henry 1946, 1947; Lenson 1956). Human exposure studies also demonstrate that coal tar creosote or its components are absorbed dermally in humans, based on excretion of metabolites after dermal exposure (Bickers and Kappas 1978; Bos and Jongeneelen 1988; Cernikova et al. 1983; Clonfero et al. 1989; Hansen et al. 1993; Jongeneelen et al. 1985; Santella et al. 1994; Sarto et al. 1989; Van Rooij et al. 1993a, 1993b; van Schooten et al. 1994; Viau and Vyskocil 1995). Van Rooij et al. (1993a) examined differences in the absorption of PAH between anatomical sites and individuals following dermal exposure of volunteers to 10% coal tar in a vehicle of zinc oxide paste. The surface disappearance of PAH and the excretion of urinary 1-hydroxypyrene after coal tar application were used to assess dermal absorption following controlled exposures. Surface disappearance measurements show low but significant differences in dermal PAH absorption between anatomical sites: shoulder > forehead; forearm, groin > ankle, hand (palmar site). Differences between individuals in PAH absorption are small (7%) in comparison with differences between anatomical sites (69%). Urinary excretion of 1-hydroxypyrene verified that the coal tar creosote and its components were absorbed through the skin, but the site of application had no effect on the excreted amount of 1-hydroxypyrene although the time to excrete half of the total metabolite varied between 8.2 and 18.9 hours.

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

Another indication that coal tar components are absorbed transdermally was reported by Paleologa et al. (1992). In particular, these investigators evaluated the occurrence of B[a]PDE-DNA adducts in white blood cells of 23 psoriatic patients undergoing clinical coal tar therapy. Two to 5 months after therapy, 10 of the patients were reanalyzed. The actual dose levels varied among the treated individuals because the application ranged from pure coal tar to 4% coal tar-based paste or ointment. No relationship appeared to exist between exposure level and concentration of B[a]PDE-DNA adducts. The results show that the mean adduct level during the treatment period was 0.26±0.16 fmole benzo[a]pyrene/g DNA (7.7±4.9 adducts/10^8 nucleotides), while 2–5 months later, the mean adduct level had decreased significantly to 0.11±0.08 fmole benzo[a]pyrene/g DNA (3.3±2.4 adducts/10^8 nucleotides).

A coal tar solution (crude coal tar diluted to 20% with ethanol and polysorbate 80) was applied to clinically unaffected skin of three patients with severe atopic dermatitis and six patients with generalized psoriasis (Bickers and Kappas 1978). Another skin area at least 10 cm away was not treated or was treated with 100 mL of the vehicle alone. Twenty-four hours later, a 6-mm punch biopsy was obtained from coal tar treated and control areas and the effect on AHH activity was determined. Application of coal tar to the skin caused induction of cutaneous AHH activity that varied from 2.4- to 5.4-fold over the enzyme activity in untreated skin areas, suggesting absorption after topical application.

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

Twenty-eight patients that required coal tar treatment on an area larger than two-thirds of the body surface were studied (Cernikova et al. 1983). Tar paste (10 and 20%) was used for treatment; in one application, approximately 1–6 g of coal tar containing 0.6% acridine was spread on the patient's skin. Urine analysis was performed by TLC to obtain information on polyaromatic and heterocyclic substances excreted in the urine. Further identification of the substance was performed by GC/mass spectrometry (GC/MS). The presence of acridine in urine after the coal tar application was identified by MS. The detection of acridine in urine provided proof of the absorption of a coal tar component through the skin. However, without additional information, no statements can be made regarding the dermal absorption of other coal tar components or whether acridine was preferentially absorbed through the skin.

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

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

It can also be concluded that dermal absorption occurred as evidenced by the development of skin tumors (Boutwell and Bosch 1958; Lijinsky et al. 1957; Poel and Kammer 1957; Roe et al. 1958) and lung

tumors (Roe et al. 1958) in mice following the dermal application of coal tar creosote (see Section 3.2.3.7). Other studies in animals support absorption of coal tar products after dermal application. Coal tar solution (0.05 mL of a 20% solution) was applied to the skin of six neonatal rats (4–6 days of age) and 24 hours later AHH activity was measured in the skin and liver (Bickers and Kappas 1978). There was greater than a 10-fold induction of skin AHH activity (298±13 versus 26.3±19 pmol hydroxy-benzo[a]pyrene/mg protein/hour in controls) and marked increased hepatic AHH activity (16,300±899 versus 750±35 pmol hydroxy-benzo[a]pyrene/mg protein/hour in controls) after topical application of the coal tar solution.

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

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

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

Coal Tar Products. No studies were located in humans regarding the distribution of coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following inhalation exposure. Because coal tar products are composed of hydrocarbons, they are likely to distribute to lipid-rich tissues (Agency for Toxic Substances and Disease Registry 1995). PAHs and their metabolites are known to cross the placenta (Agency for Toxic Substances and Disease Registry 1995). PAHs have also been detected in human breast milk (Madhavan and Naiduka 1995). Individuals concerned with the potential exposure of breast-feeding infants to PAHs should consult their doctor. Coal tar creosote is also likely to distribute to the liver as evidenced by the presence of metabolites in the urine, indicating microsomal enzyme induction.

Tumor-susceptible ICR CF-1 and tumor-resistant CAF1-JAX mice were exposed to 10 mg/m^3 coal tar aerosol-BTX mixture continuously, or for 90 days, or intermittently for 18 months (MacEwen et al. 1977). The coal tar-BTX mixture was comparable to the material inhaled by topside coke oven workers. Mice were serially sacrificed during the exposure period for the determination of coal tar lung burden and the time to tumor induction. Control animals were held in a vivarium. All animals were examined daily during the exposure and postexposure periods. Coal tar fluorescence retained in mouse lung and skin tissues were measured. The amount of coal tar found on mouse skin did not change to any great degree after the first week of exposure. Lung tissue accumulated coal tar aerosol at a fairly steady rate during 18 months of intermittent exposure as compared to a high increased rate (from graph) during the 90 days of continuous exposure. The coal tar lung burden in mice was approximately equal for both exposure modes around the 180-day exposure period.

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

Intratracheal administration of [^{3}H]-benzo[a]pyrene, along with the benzene extract of coal fly ash, to pregnant rats (20 mg/kg/day) on days 18 and 19 of gestation resulted in their distribution to the maternal lung and liver (Srivastava et al. 1986). The amount of radioactivity found in the maternal liver was

approximately 68% of the amount of radioactivity found in the maternal lung. The amounts of radioactivity found in the placenta, fetal lung, and fetal liver were approximately 4, 1.9, and 1.4%, respectively, of the amount of radioactivity found in the maternal lung. Much of the radioactivity was attributable to metabolites. These results in rats suggest that components of coal tar creosote and their metabolites can pass through the placenta and distribute to fetal tissue.

3.4.2.2 Oral Exposure

No studies were located in humans or animals regarding the distribution of, coal tar creosote, or coal tar pitch volatiles following ingestion. Based on chemical structure, it is likely that PAHs would have a strong affinity for adipose tissue. For example, benz[a]anthracene, chrysene, and triphenylene distributed to all tissues following oral administration (22.8 mg/kg) to female rats, but its greatest distribution was to adipose tissue. In this study, benz[a]anthracene concentrations were 10 times higher in adipose than in other tissues (Bartosek et al. 1984).

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

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

Coal Tar Products. Culp and Beland (1994) fed male B6C3F_1 mice 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar/day in feed for 28 days. A second group of mice was fed benzo[a]pyrene for 21 days at levels corresponding to those found in the coal tar-containing feed mixtures. At the end of the feeding period, DNA adduct formation was quantified in the liver, lungs, and forestomach by ^{32}P-post-labeling. The adduct levels were then compared with those obtained from the mice fed benzo[a]pyrene.

DNA adduct formation was found to increase as a function of dose in each tissue with both coal tar and benzo[a]pyrene. DNA adduct levels were in the order forestomach > liver > lung at lower dose groups, while the order changed to liver > forestomach > lung at the highest dose group. Total DNA binding was greater in the coal tar fed mice than in the benzo[a]pyrene fed animals (. 10- to 30-fold greater in the liver and forestomach, and over 90-fold greater in the lungs at the lower doses).

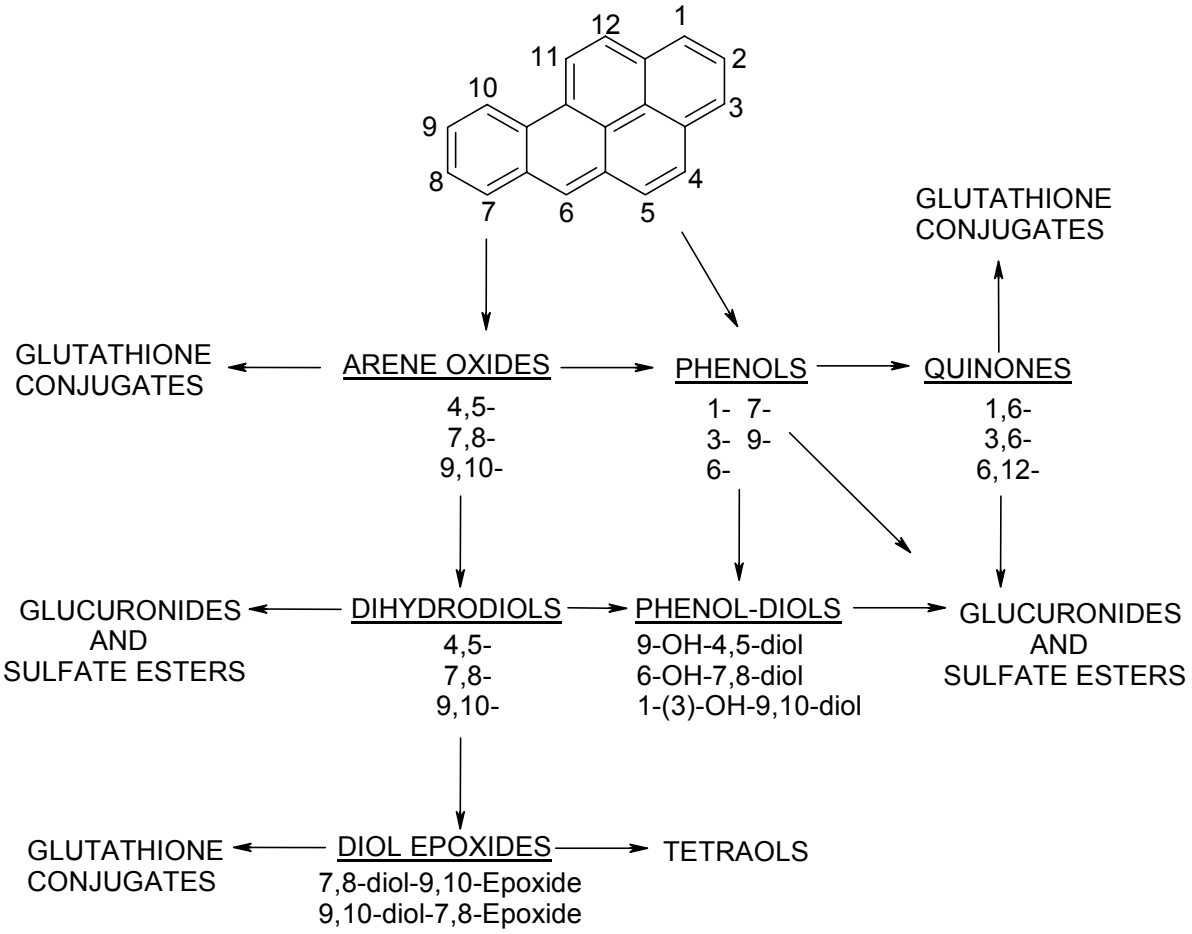
3.4.2.3 Dermal Exposure

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

3.4.3 Metabolism

Generally, the PAH components of wood creosote, coal tar creosote, coal tar, and coal tar pitch are metabolized by oxidative enzymes in the liver and lungs to generate active metabolites that can bind to macromolecules. The metabolic profiles vary among species and compounds, but the components follow the same major reaction pathways. Hence, the metabolites are structurally very similar. The proposed metabolic scheme for a representative PAH, benzo[a]pyrene, is presented in Figure 3-4. The principal

Figure 3-4. Proposed Metabolic Scheme for Benzo[a]pyrene



products include phenols, dihydrodiols, quinones, anhydrides, and conjugates of these products (Autrup and Seremet 1986; Dahl et al. 1985; Fellows 1939b; Geddie et al. 1987; Hopkins et al. 1962; Jongeneelen et al. 1985, 1986, 1988; Ogata et al. 1995; Petridou-Fischer et al. 1988; Povey et al. 1987; Rice et al. 1986; Santella et al. 1994; Weyand and Bevan 1987).

Metabolic studies of wood or coal tar creosote have generally been confined to measurements of metabolites in the blood or urine (Bieniek 1997; Bowman et al. 1997; Chadwick et al. 1995; Fellows 1939b; Grimmer et al. 1997; Heikkila et al. 1997; Jongeneelen et al. 1985, 1986, 1988; Malkin et al. 1996; Ogata et al. 1995; Santella et al. 1994; Weston et al. 1994). However, a number of studies have examined the role of individual enzymes in the metabolism of coal tar products. Experiments by Bickers and Kappas (1978), Li et al. (1995), Luukanen et al. (1997), Genevois et al. (1998), and Fielden et al. (2000) assessed metabolic induction and activity of AHH, glucuronosyltransferase, and cytochrome P450 in response to coal tar.

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

Dermal treatment of healthy volunteers with 10% coal tar for 4 days produced an 18-fold induction of CYP1A1 mRNA levels in coal-tar-treated skin (Li et al. 1995). *In vitro* incubation of DNA with coal tar fume concentrates in the presence of mouse and yeast microsomes expressing various cytochrome P450 isoforms or the aryl hydrocarbon hydroxylase receptor (AHR) demonstrated that coal tar fume condensates require metabolic activation to produce DNA adducts (Genevois et al. 1998). Both the AHR and CYP1A were involved in the metabolism of coal tar fume condensate. It was also shown that the reactive metabolites formed by CYP1A are substrates for microsomal epoxide hydrolase.

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

3.4.3.1 Inhalation Exposure

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

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

A similar study was carried out in a coke plant in Zabrze, Poland (Bieniek 1997). The concentrations of 1-naphthol and 2-naphthol in the urine of 102 workers from the coke plant were compared with those of 36 controls not occupationally exposed to coal tar volatiles. Significant differences were found between the concentrations of 1- and 2-naphthols in the urine of exposed and unexposed workers ($P<0.05$). The correlation between the concentrations of naphthols in urine and napthalene in air were statistically significant ($P<0.001$).

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

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

3.4.3.2 Oral Exposure

Wood Creosote. Eight healthy male volunteers were orally administered a single dose of 133 mg wood creosote by capsule with 200 mL water after a light breakfast (Ogata et al. 1995). Peripheral venous blood and urine samples were collected at various time intervals. The metabolites in the serum started to rise 15 minutes after the oral dose, reaching the maximum 30 minutes after dosing. The maximum serum concentrations (Cmax) of glucuronides were 0.18±0.07, 0.91±0.38, 0.33±0.18, and 0.47±0.23 mg/L, and of sulfates were 0.16±0.06, 0.22±0.09, 0.17±0.07, and <0.04 mg/L for phenol, guaiacol, *p*-cresol, and cresol, respectively. The Cmax for unconjugated phenols were 0.06±0.01, 0.05±0.01, 0.12±0.05, and <0.04 mg/L for phenol, guaiacol, *p*-cresol and cresol, respectively. Rats receiving a single dose of either 0.0002, 0.002, 0.02, 0.2, or 2.0 mg pyrene/kg by gavage in olive oil excreted 1-hydroxypyrene in the urine in a dose-dependent manner (Jongeneelen et al. 1986). This metabolite could be detected up to 96 hours after administration. No unchanged pyrene was excreted.

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

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

of V_{max}/K_m for 1-hydroxypyrene UGT by 18-fold and for *p*-nitrophenol 2–3-fold. These results suggest that a highly efficient form of glucuronosyltransferase was selectively induced by creosote.

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

Induction of CYP1A1 and CYP2B10 in liver microsomes from ovariectomized mature and immature DBA/2 mice and ICR mice gavaged with 10, 50, or 100 mg/kg creosote in sesame oil once a day for 4 days was compared with that in microsomes derived from control animals that received only sesame oil (Fielden et al. 2000). CYP1A1 and CYP2B10 activities were assessed based on EROD (ethoxyresorufin-O-deethylase) and PROD (pentoxyresorufin-O-dependentylase) activities, respectively. Creosote treatment significantly increased the activity of CYP1A1 and CYP2B10 in both immature and mature mice, but the CYP1A1 increase was age-dependant, with immature mice showing a 5.9-fold increase in EROD activity after treatment with 100 mg/kg/day creosote while mature mice treated similarly had an 11.4-fold increase in liver EROD activity. No age-dependent difference was seen in induction of CYP2B10 since PROD activity was increased by creosote treatment 1.6–2.2-fold in both mature and immature mice.

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

3.4.3.3 Dermal Exposure

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

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

Similar results were obtained in another study of psoriasis patients (43 patients and 39 untreated controls) being treated with a coal tar ointment (Weston et al. 1994). The benzo[a]pyrene metabolite, r7,t8,t9,c10-tetrahydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene, was detected in urine of 18 psoriasis patients (42%) and 4 untreated subjects (10%). There was a significant difference in the levels of r7,t8,t9,c10-tetrahydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene in patients and untreated individuals with levels varying from undetectable to 330 fmol/mL for patients and from undetectable to 40 fmol/mL for untreated individuals. A second metabolite 1-hydroxypyrene-glucuronidide was found in all urine samples, but levels were significantly higher in psoriasis patients than in untreated controls, ranging from 180 to 50,000 fmol/mL in patients and 36–650 fmol/mL in untreated individuals.

Patients with psoriasis (57) and healthy volunteers (53) with no reported exposures to coal tar shampoos or ointments, self-applied either an ointment or a gel-based coal tar product, or both, to the entire body surface at least once a day, followed by UV-B treatment (Santella et al. 1994). The estimated exposure was 20–100 g of tar/day. Twenty-four hour urine samples were collected from all subjects. Urinary 1-hydroxypyrene was analyzed by HPLC. Urinary PAH metabolites measured by PAH-ELISA were

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

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

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

Coal tar solution (0.05 mL of a 20% solution) was applied to the skin of six neonatal rats (4–6 days of age), and 24 hours later, AHH activity was measured in the skin and liver (Bickers and Kappas 1978). There was greater than a 10-fold induction of skin AHH activity (298±13 versus 26.3±19 pmol hydroxy benzopyrene/mg protein/hour in controls) and marked increased hepatic AHH activity (16,300±899 versus 750±35 pmol hydroxy benzopyrene/mg protein/hour in controls) after topical application of the coal tar solution.

Cytochrome P4501A1 (CYP1A1) expression was increased in healthy volunteers treated dermally with 10% coal tar for 4 days producing an 18-fold induction of CYP1A1 mRNA levels in coal-tar-treated skin (Li et al. 1995). *In vitro* incubation of DNA with coal tar fume concentrates in the presence of mouse and yeast microsomes expressing various cytochrome P450 isoforms or the AHR demonstrated that coal tar fume condensates require metabolic activation to produce DNA adducts (Genevois et al. 1998). Both the AHR and CYP1A were involved in the metabolism of coal tar fume condensate, but neither was absolutely required. The role of microsomal epoxide hydrolase was also tested, and it was shown that the reactive metabolites formed by CYP1A are substrates for epoxide hydrolase. Addition of epoxide hydrolase to the microsome preparations caused an 80% reduction in the relative level of DNA adducts produced from coal tar fume condensates by CYP1A1.

3.4.4 Elimination and Excretion

Coal Tar Products. Excretion of the PAH compounds of coal tar creosote is controlled by their rate of metabolism. Excretion of these metabolites or any remaining parent compound is primarily in the urine, bile, and feces. Weyand and Bevan (1987) demonstrated this by cannulating the bile ducts of rats that received [^{3}H]-benzo[a]pyrene intratracheally. Those rats with the biliary cannulas had significantly lower levels of activity in their intestines, intestinal contents, and stomach than rats without biliary cannulas. Sanders et al. (1986) showed that PAHs were primarily removed in the feces after dermal administration of [^{14}C]-benzo[a]pyrene and [^{14}C]-7,12-dimethylbenz[a]-anthracene, suggesting hepatobiliary excretion. Urinary excretion of PAH metabolites also occurs, but to a lesser extent than by the other routes. Excretion of the major portion of experimental doses of PAHs suggests half-lives in hours to days, with inhalation exposure yielding the fastest elimination, followed by oral exposure and dermal exposure (Agency for Toxic Substances and Disease Registry 1995). It is known that PAHs and their metabolites cross the placenta (Agency for Toxic Substances and Disease Registry 1995) and have been detected in human breast milk (Madhavan and Naiduka 1995). Individuals concerned with the potential exposure of breast-feeding infants to PAHs should consult their doctor.

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

3.4.4.1 Inhalation Exposure

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

Coal Tar Products. Measurements were carried out in a creosote impregnation plant where 6 men volunteered to participate in the study (Elovaara et al. 1995). Personal breathing zone air samples were taken on 5 consecutive days followed by a work free period of 64 hours. All workers wore leather protective gloves and cotton overalls. Two employees worked overtime (until 6:30 a.m.) on Monday, which was an exception to the regular 8-hour schedule. Particulate PAHs were collected during the whole shift and analyzed within 7 weeks. Workers were asked to collect all urine passed within the 24-hour period into divided samples for the designated periods. Results showed that the geometric mean (range) air concentration of total particulate PAHs (including pyrene) was 4.77 (1.2–13.7) mg/m^3 and that of naphthalene was 1,254 (370–4,200) mg/m^3. The PAH profile was similar in all samples. The lowest concentrations of 1-hydroxypyrene in creosote workers were found in the Monday morning urine samples after 64 hours off work. The highest concentrations were consistently found in the evening samples (6–9 hours after work) but lower at the end of the shift. The urinary 1-hydroxypyrene levels on Monday morning before work ranged from 4 to 22 mmol/mol creatinine; levels on Tuesday morning to Saturday morning ranged from 16 to 120 mmol/mol creatinine; and levels at end of shift ranged from 19 to 85 mmol/mol creatinine. The evening after work (taken on Monday, Wednesday, and Friday) urinary levels of 1-hydroxypyrene ranged from 27 to 122 mmol/mol creatinine.

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

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

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

Urine samples collected from two reference groups of nonoccupationally exposed individuals and four groups of workers were measured for urinary excretion of 1-hydroxypyrene (Viau et al. 1995). The study groups are described as follows: reference group 1 (12 males, 9 females) was workers with no occupational exposure to PAH (single spot urine sample collected during the day); reference group 2

(7 males) was administrative workers in a silicon carbide plant (urine samples obtained Monday morning upon arrival at work); the silicon carbide group (83 males) worked in a silicon carbide plant involved in various occupations (urine samples collected at the beginning and end of work shift on a Monday and Friday); the creosote group (19 males) was workers exposed to creosote in a wood treatment plant (one urine sample collected towards the end of the work week and another sample obtained after at least 64 hours of exposure); the decontamination group (29 males) was workers in various occupations related to the removal of soil contaminated with PAH from the pyrolysis of used tires after a major fire at a dump (single urine sample collected at beginning of shift); and the brushwood cutting group (10 males) was workers responsible for the clearing of brushwood under electricity power lines (single urine sample collected at end of shift). Urine samples from reference group 1, creosote, decontamination, and brushwood cutting groups were analyzed by high performance chromatography; samples from reference group 2 and silicon carbide group were analyzed by GC/MS. Results showed that the creosote group was largely exposed to pyrene. Even after >64 hours without exposure, the mean (geometric) excretion of 1-hydroxypyrene was higher for the creosote group (0.53 mmol/mol creatinine) than for the reference groups 1 (0.08 mmol/mol creatinine) and 2 (0.10 mmol/mol creatinine). The mean (geometric) excretion in creosote workers during their working week was 1.63 (0.18–10.47) mmol/mol creatinine. The brushwood cutting workers excreted more 1-hydroxypyrene than the referents. These results were pooled with those of the nonoccupationally exposed reference groups yielding a total of 140 individuals having a mean (geometric) excretion of 0.08 mmol/mol creatinine and the 5th, 50th, and 95th percentiles of 0.02, 0.09, and 0.32 mmol/mol creatinine, respectively. The mean (geometric) excretion in the 95 nonsmokers and 45 smokers of this pool were 0.07 and 0.12 mmol/mol creatinine, respectively.

3.4.4.2 Oral Exposure

Wood Creosote. Eight healthy male volunteers were orally administered a single dose of 133 mg wood creosote by capsule with 200 mL water after a light breakfast (Ogata et al. 1995). Urine samples were collected at various time intervals. Phenols in urine were analyzed by HPLC. Wood creosote used in this study as determined by GC contained 11.3% phenol, 24.3% guaiacol, 13.7% *p*-cresol, and 18.2% cresol (w/w). The urinary recoveries of the sum of the conjugated and unconjugated forms of each phenolic compound were 75±35, 45±36, 103±51, and 74±36% for phenol, guaiacol, *p*-cresol, and cresol, respectively.

Coal Tar Products. No studies were located regarding the excretion of coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following oral exposure in humans.

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

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

5 weeks peaked after 3 weeks and then declined by 33% after 5 weeks of treatment. Low levels of mutagenic metabolites were also found in the urine of animals treated with creosote alone.

3.4.4.3 Dermal Exposure

No studies were located regarding the excretion of wood creosote following dermal exposure in humans or animals.

Coal Tar Products. Human exposure studies demonstrate that coal tar creosote or its components are absorbed dermally in humans, based on excretion of metabolites after dermal exposure (Bickers and Kappas 1978; Bos and Jongeneelen 1988; Cernikova et al. 1983; Clonfero et al. 1989; Diette et al. 1983; Hansen et al. 1993; Jongeneelen et al. 1985; Santella et al. 1994; Sarto et al. 1989; Van Rooij et al. 1993a, 1993b; van Schooten et al. 1994; Viau and Vyskocil 1995). Van Rooij et al. (1993a) examined differences in absorption of PAH between anatomical sites and individuals following dermal exposure of volunteers to 10% coal tar in a vehicle of zinc oxide paste. Differences between individuals in PAH absorption are small (7%) in comparison with differences between anatomical sites (69%). Urinary excretion of 1-hydroxypyrene verified that the coal tar creosote and its components were absorbed through the skin, but the site of application had no effect on the excreted amount of 1-hydroxypyrene although the time to excrete half of the total metabolite varied between 8.2 and 18.9 hours. Another study of excretion after dermal absorption was conducted by Van Rooij et al. (1993b) in a wood preserving plant in the Netherlands in October 1991. Volunteers for this study were workers who worked near the impregnation cylinders (three subjects) and the assembly hall (seven subjects). Exposure measurements were performed in 2 consecutive weeks on a Monday after a weekend off. On one Monday, the workers wore protective clothing over their clothes and on the other Monday, no protective clothing was used. PAH contamination on the skin and PAH concentration was measured on the two Mondays on all workers. Urine samples were collected from Sunday morning through Tuesday morning for the assessment of the internal exposure to PAH. The excreted amount of 1-hydroxypyrene in urine decreased significantly from 6.6 to 3.2 mg (30.2–14.7 nmol).

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

Five female patients (two nonsmokers, three smokers) suffering from eczematous dermatitis on the arms and legs were treated for several days with an ointment containing 10% *pix lithanthracis dermata* (coal tar), representing 16.7 mg/g pyrene and 7.0 mg/g benzo[a]pyrene (Bos and Jongeneelen 1988). During treatment, the ointment was removed daily and a fresh dose of approximately 40 g was rubbed in. Urine samples were collected, one before application and two during the day for the first 3 days of treatment. High concentrations of toxic compounds in the urine samples were found and mutagenicity tests were not successful. One out of two nonsmoking patients excreted a large amount of thioether products during the beginning of the treatment: 19.6 mmol thioether (SH)/mol creatinine was measured in the evening urine sample of the first day of treatment and 24.5 mmol SH/mol creatinine in the morning urine sample of the second day of treatment. The concentrations were within the normal range in urine samples measured on the evening of the second day (5.4 mmol SH/mol creatinine) and on the morning of the third day (3.3 mmol SH/mol creatinine). No similar increase in thioether excretion during coal tar treatment was found for other patients, whose values were within or slightly above the normal range. The concentration of 1-hydroxypyrene rose rapidly to 100 times the control value after the beginning of the treatment of these patients reaching 50–500 μmol/mol creatinine. Pretreatment urine samples of the smoker patients contained somewhat higher levels of 1-hydroxypyrene than those for a separate group of control smokers.

Twenty-eight patients who required coal tar treatment on an area larger than two-thirds of the body surface were selected for this study (Cernikova et al. 1983). Tar paste (10 and 20%) was used for treatment; in one application approximately 1–6 g of coal tar containing 0.6% acridine was spread on the patient's skin. Urine analysis was performed by TLC to obtain information on polyaromatic and heterocyclic substances excreted in the urine. Further identification of the substance was performed by GC/MS. The presence of acridine in urine after the coal tar application was identified by MS. Acridine was not quantified.

Sixteen urine samples were collected from four male, nonsmoking psoriatic patients undergoing treatment with the Goeckerman regimen (cutaneous application of coal tar based ointment, followed by exposure to UV irradiation) in the Dermatology Clinic of the University of Padua (Clonfero et al. 1989). Patient A was treated with pure coal tar for 1 day; patients B, C, and D were treated with 4% coal tar based ointment for 2, 8, and 13 days, respectively. Body surface involved by psoriasis was 30, 40, 35, and 60% for patients A, B, C, and D, respectively. Total PAH (and pyrene) content of the two coal tar preparations was 28,800 (3,100) and 470 (104) ppm, respectively. The samples were collected at different times after the beginning of therapy (from 12 hours after the first application of coal tar to 72 hours after the last application). Levels of 1-hydroxypyrene ranged from 25.4 mg/g creatinine to 1,565 mg/g creatinine. Total PAH content in urine ranged from 6.4 mg/g creatinine to 64.2 mg/g creatinine. Baseline levels of

total PAH and mutagenic activity were determined in evening urinary samples of 5 healthy, nonsmoking subjects, not exposed to PAHs. The control group for the determination of 1-hydroxypyrene levels consisted of 52 nonsmokers who exhibited values of 1.3 mg/g creatinine. Results showed levels of 1-hydroxypyrene are 20 and 1,000 times higher in the exposed group than in controls; total PAHs were 3.5–20 times higher in the exposed group than in controls. In 5 of 15 cases, the urinary mutagenicity of the exposed group was not significantly higher than that of the controls, while in one case it was not evaluated due to toxic effects. The mutagenic activity of the urinary extracts of the exposed subjects was at most 8 times greater than the average mutagenicity of the controls.

Patients with psoriasis (57) and healthy volunteers (53) with no reported exposures to coal tar shampoos or ointments, self-applied either an ointment or a gel-based coal tar product, or both, to the entire body surface at least once a day, followed by UV-B treatment (Santella et al. 1994). The estimated exposure was 20–100 g/tar/day. Twenty-four-hour urine samples were collected from all subjects. Urinary 1-hydroxypyrene was analyzed by HPLC. Urinary PAH metabolites measured by the PAH-ELISA were elevated in patients (mean 730±1,370 mmol) as compared to untreated volunteers (110±90 mmol equivalents of B[a]P/mol creatinine). Urinary levels of 1-hydroxypyrene were also elevated in patients (mean 547±928 mmol/mol creatinine) compared with untreated volunteers (mean 0.14±0.17 mmol).

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

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

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

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al.

1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

The pharmacokinetics of wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles have not been defined because of their chemical complexity. Creosotes vary tremendously in composition and hence, mechanisms of action most likely differ among individual samples of creosotes.

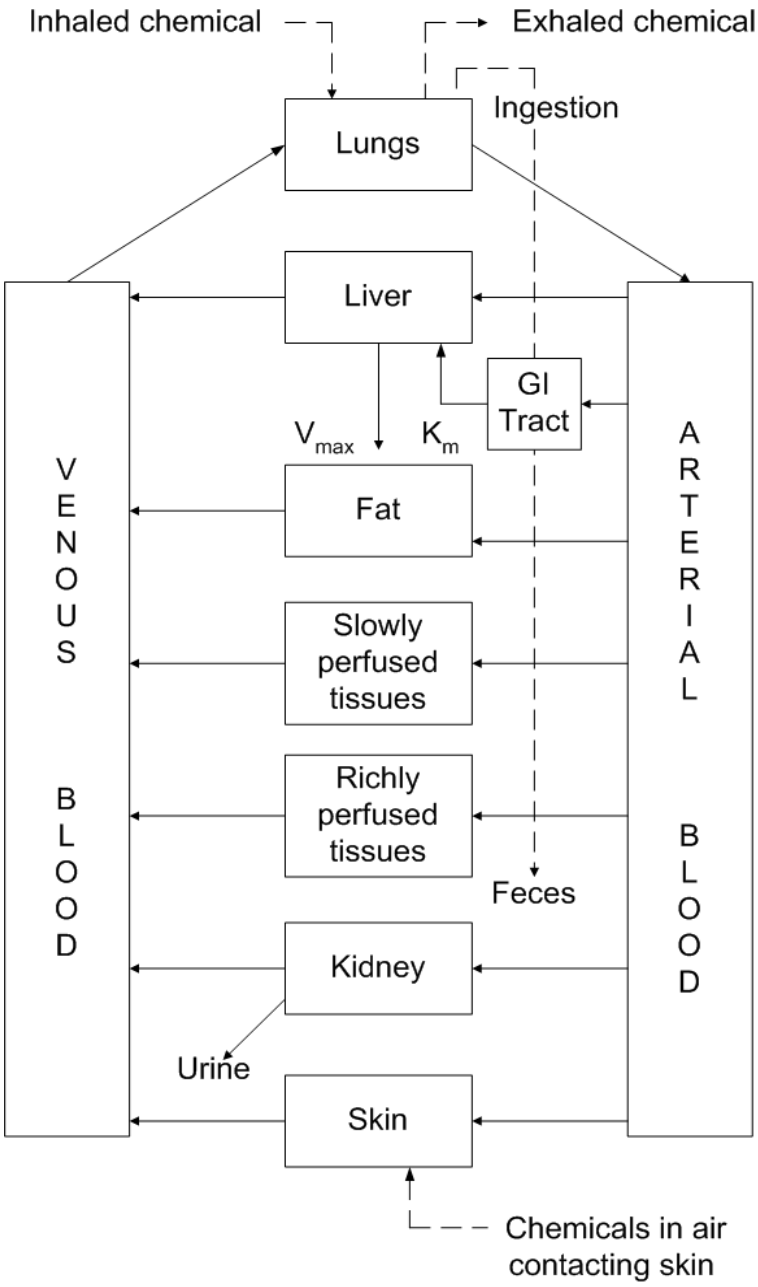
Information on individual components is not adequate to define the properties of the whole mixture and for this reason no PBPK models have been proposed for creosote.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. No studies were located in humans or animals regarding the direct analysis of absorption of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles via the inhalation, oral, or dermal routes. Studies of humans exposed to coal tar creosote have measured increased levels of urinary metabolites of various components of coal tar creosote suggesting that at least some components of coal tar creosote are absorbed by all routes. However, these studies do not provide any information as to the mechanism of absorption. PAHs are lipophilic compounds that are probably absorbed by passive diffusion, but no information was located for mechanism of absorption of other components of creosote. From data on individual PAHs (Agency for Toxic Substances and Disease Registry 1995), gastro-intestinal absorption of the PAH components of coal tar creosote may be increased by the presence of oils and fats in the stomach and bile in the intestines, while dermal absorption is affected by the anatomical site to which it is applied. Dermal absorption of PAHs may also be increased when they are solubilized in a fat or oil mixture prior to application or conversely may be reduced by binding and/or metabolism in the skin. However, due to the variable composition of coal tar creosote, coal tar pitch, and coal tar, the predictive value of studies carried out on single PAHs is limited. For further information on PAHs please refer to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (Agency for Toxic Substances and Disease Registry 1995).

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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

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

Metabolism. No studies were located in humans or animals that specifically addressed the metabolism of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following inhalation, oral, or dermal exposure. The PAH components of creosote are metabolized by oxidative enzymes in the liver and lungs to generate active metabolites that can bind to macromolecules. The metabolic profiles of these substances vary among species and compounds, but the components follow the same reaction pathways and so the metabolites are structurally similar. The major products include phenols, dihydrodiols, quinones, anhydrides, and conjugates of these products. Enzymes involved in the metabolism of PAHs vary depending on tissue and the particular PAH, but can include various isoforms of cytochrome P450 (predominantly CYP1A1, but also CYP1A2, CYP1B1, or CYP2C) (Genevois et al. 1998), epoxide hydrolase, glutathione-S-transferases, glucuronidases, and AHH (Agency for Toxic Substances and Disease Registry 1995). For more information on the metabolism of PAHs the reader is referred to the ATSDR *Toxicological Profile on Polycyclic Aromatic Hydrocarbons* (Agency for Toxic Substances and Disease Registry 1995). Phenol is metabolized via three pathways in mammals; P450 catalyzed hydroxylation, sulphate conjugation, or glucuronide conjugation. The two conjugation pathways can be considered competitive pathways in most species of mammal. Thus, the relative amounts of each product formed depend on dose level as well as the relative abundance and kinetic

parameters of the two enzyme systems. For further information on the metabolism of phenol the reader is referred to the ATSDR *Toxicological Profile on Phenol* (Agency for Toxic Substances and Disease Registry 1998).

Excretion. No studies were located in humans or animals regarding the excretion of wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles following inhalation, oral, or dermal exposure. Phenol is a normal constituent of human urine and phenol administered via all routes of absorption is rapidly eliminated in the urine and the bile (Agency for Toxic Substances and Disease Registry 1998). PAHs are lipophilic compounds that could remain indefinitely within fatty tissues, but metabolism of PAHs renders them more water soluble and more excretable. Excretion of the metabolites of PAHs is primarily in the urine, bile, and feces. Experimental data suggests half-lives of hours to days with elimination being fastest after inhalation exposure followed by oral and dermal exposure (Agency for Toxic Substances and Disease Registry 1995). PAHs have been detected in human breast milk (Madhavan and Naiduka 1995).

3.5.2 Mechanisms of Toxicity

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

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

study indicated that (1) low doses of noncarcinogenic PAHs could have an impact on the carcinogenic potential of B[a]P in mixtures, (2) the carcinogenic activity of coal tar cannot be accounted for by the level of B[a]P present, and (3) certain noncarcinogenic components of coal tar can have their carcinogenic potential altered by the presence of other aliphatic compounds.

Individual components of creosote are also metabolized by several different enzyme systems including cytochrome P450, epoxide hydrolase, glutathione-S-transferases, glucuronidases, AHH, phenol sulfotransferase, and glucuronyltransferase. Human polymorphisms are known to exist for many of these enzymes and are likely to affect the relative toxicity of creosote for these individuals. The relative activity of metabolic enzymes may also vary with the age of the individual, which will again affect the relative toxicity of particular components of creosote for old or young individuals (for further discussion of age-related effects, the reader is referred to Section 3.7). Therefore, for creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles, it is not presently possible to define mechanisms of transport, distribution, or the precise chemical or physiological events that lead to toxic damage or carcinogenicity in the biological system.

3.5.3 Animal-to-Human Extrapolations

Animal-to-human extrapolations of the toxicity of creosote are complicated by the inherent chemical variety of these substances. Creosotes are complex mixtures of variable composition and the individual components are likely to show interspecies variation in toxicity. Only one study was located that treated more than one species of animal with the same sample of creosote (Miyazato et al. 1981), and although this study suggested that mice were more susceptible to the acute effects of beechwood creosote than rats, the differential susceptibility observed with this particular sample cannot be applied to creosotes of different composition. In general, the adverse effects observed in animals are similar to those reported for humans with cancer being the most serious, but it is not possible at present to assess whether the doses required to produce adverse effects in animal systems are similar to those required to produce similar effects in humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors.* In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans after exposure to wood creosote, coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles.

Wood Creosote. Effects of wood creosote on the endocrine organs are confined to changes in testis and adrenal gland weights without any accompanying histological alterations. Miyazato et al. (1981) reported that oral exposure of rats to beechwood creosote in the diet for 3 months increased relative weight of the testis. However, there were no accompanying histological changes in the testis and no changes in ovary

weights. No change in testis or ovary weight was observed for mice exposed to beechwood creosote for up to 96 weeks (Miyazato et al. 1981, 1984a, 1984b). Oral exposure of male rats to 313 mg/kg/day beechwood creosote for 96 weeks produced a significant increase in the relative weight of the adrenal glands of male rats (Miyazato et al. 1984b). However, another study of beechwood creosote found no effect on the adrenal glands (Miyazato et al. 1981).

Coal Tar Products. An excess of breast cancer cases in St. Louis Park, Minnesota, was tentatively associated with coal tar contamination of the water supply (Dean et al. 1988). However, in a subsequent analysis of these data, the Minnesota Department of Health (1985) concluded that this study did not provide adequate evidence to associate breast-cancer with coal tar creosote-contaminated water (for a detailed discussion of these data, see Section 3.2.2.7 Cancer). No adverse effects on sperm characteristics were reported in male workers exposed to coal tar pitch volatiles in an industrial setting (Ward 1988). In addition, no adverse reproductive outcomes were detected in a survey of inhabitants of a housing development built on an abandoned creosote factory site, which was known to be contaminated with creosote (Agency for Toxic Substances and Disease Registry 1994). A retrospective study of dermal exposure to coal tar found no increased risk of spontaneous abortion associated with exposure to coal tar during pregnancy, but this was a small study and was unlikely to have sufficient resolution to detect a modest increase in risk (Franssen et al. 1999).

Coal tar creosote was tested for estrogenic activity using both *in vivo* and *in vitro* assays with inconclusive results (Fielden et al. 2000). Results from the *in vitro* tests showed that creosote binds both the estrogen receptor (ER) and the human sex hormone-binding globulin (SHBG), and can induce ER-mediated gene expression. However, *in vivo* assays using ovariectomized DBA/2 mice and ICR mice gavaged with 0, 10, 50, or 100 mg/kg creosote in sesame oil or 0.1 mg/kg 17α-ethynylestradiol (positive control) once a day for 4 days were negative. Treatment with 17α-ethynylestradiol produced a significant increase in uterine weight and vaginal cell cornification compared with animals receiving only sesame oil, but no significant increase in uterine weight or vaginal cell cornification was observed in animals treated with creosote. The study authors also tested the ability of creosote to induce gene expression via the AhR in Hepa 1c1c7 cells, to induce CYP1A1 and CYP2B10 in liver microsomes, and to interact with the estrogen-inducible/dioxin-suppressible pS2-Luc reporter gene. Creosote induced gene expression via the AhR and increased the activity of CYP1A1 and CYP2B10, but although treatment of cells expressing the pS2-Luc reporter gene with increasing concentrations of creosote produced a dose-dependent increase in activity, no consistent inhibition of E2-induced activity in these cells was noted. The AhR in DBA/2 mice is known to be much less responsive to PAHs than that of ICR mice; however, estrogenic effects of creosote were not observed in either strain and the authors concluded that although creosote has the

potential to interact with the endocrine system, it does not appear to be sufficiently potent to produce an effect in this assay.

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

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

Adverse effects in other endocrine organs are limited to a few reports of weight changes in the adrenal glands. An increase in adrenal weight was observed in rats gavaged on gestational days 12–16 with 90 mg/kg/day coal tar (Hackett et al. 1984). However, other studies of coal tar creosote have shown no effect on the adrenal glands (Iyer et al. 1993; Springer et al. 1986b, 1987; Zangar et al. 1989).

There is some evidence that certain PAHs, (e.g., benzo[a]pyrene) may act as endocrine disruptors (Agency for Toxic Substances and Disease Registry 1995); however, without data regarding possible synergistic or antagonistic effects, it is not known whether these individual compounds have similar effects when incorporated into a complex mixture such as coal tar creosote. For more information on the health effects of these compounds, the reader can refer to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (Agency for Toxic Substances and Disease Registry 1995).

3.7 CHILDREN'S SUSCEPTIBILITY

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

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth

and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

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

The effects of creosote have not been thoroughly studied in children, but they would likely experience the same health effects seen in adults exposed to creosote. The pharmacokinetics of wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles have not been defined because of their chemical complexity. Creosotes vary tremendously in composition and hence, mechanisms of action most likely differ among individual samples of creosotes. Information on individual components is not adequate to define the properties of the whole mixture and for this reason no PBPK models have been developed for creosote. Individual components of creosote are metabolized by several different enzyme systems including phase I (cytochrome P450 isozymes, AHH, epoxide hydrolase) and phase II (glutathione-S-transferases, glucuronidases, phenol sulfotransferase, and glucuronyltransferase). Human polymorphisms are known to exist for many of these enzymes and are likely to affect the relative toxicity of creosote for these individuals. The relative activity of metabolic enzymes may also vary with the age of the individual, which will again affect the relative toxicity of particular components of creosote for old or young individuals. For instance, several cytochrome P450 isozymes are known to be absent or expressed at very low levels in the developing human fetus while glucuronyl transferases and sulphotransferases do not reach adult levels until 1–3 years of age (Leeder and Kearns 1997).

Creosote Bush. No information was located pertaining to adverse health effects in children or young animals from the creosote bush. There are very few data on human exposure to the creosote bush. Case

reports of people who drank chaparral tea indicate kidney damage as a likely outcome (Gordon et al. 1995), while dermal exposure to the creosote bush may cause skin irritation (Leonforte 1986; Smith 1937).

Wood Creosote. No information was located pertaining to adverse health effects in children or young animals from wood creosote. There are very few data on human exposure to wood creosote. Ingestion of beechwood creosote exacerbates chronic nephrosis in rats (Miyazato et al. 1984b), and dermal exposure to beechwood creosote may cause skin irritation (Attalla 1968). These studies suggest that dermal contact with creosote from toxic waste sites could cause skin irritation.

No reports of adverse developmental effects on humans or animals after exposure to wood creosote were found in the literature.

Coal Tar Products. Only one study was located that examined effects of exposure to coal tar creosote in children (Agency for Toxic Substances and Disease Registry 1994). This was a survey of inhabitants of a housing development that had been built on part of an abandoned creosote wood treatment plant. In this study, increased incidence of skin rashes compared to unexposed controls was the only health effect reported in children (less than 11 years of age) exposed to coal tar creosote. The incidence of rashes in different age groups varied, but did not show any definite trend.

Data from studies of adult humans occupationally exposed to coal tar creosote indicate that cancer is likely to be the most severe adverse effect of coal tar exposure, although there is also evidence of skin and eye irritation (see Chapter 2 and Section 3.2 for more details). Studies of animals after inhalation, oral, or dermal exposure to coal tar creosote confirm cancer as a likely outcome of coal tar exposure and suggest that there may also be adverse effects to the lungs, liver, spleen, thymus, skin, and eyes (see Chapter 2 and Section 3.2 for more details). However, the concentrations of coal tar used in animal studies are higher than could be expected from proximity to a hazardous waste site and so it is not clear how relevant some of these systemic effects are to children. Children exposed to creosote will probably have a longer potential latency period and may therefore be at greater risk of developing cancer from these substances than individuals exposed as adults.

No reports of adverse developmental effects on humans after exposure to coal tar were found in the literature. No adverse developmental outcomes were detected in a survey of inhabitants of a housing development built on an abandoned creosote factory site, which was known to be contaminated with creosote (Agency for Toxic Substances and Disease Registry 1994). A retrospective study of dermal

exposure to coal tar found no increased risk of birth defects associated with exposure to coal tar during pregnancy, but this was a small study and was unlikely to have sufficient resolution to detect a modest increase in risk (Franssen et al. 1999).

A series of studies (Hackett et al. 1984; Springer et al.1982, 1986a; Zangar et al. 1989) have demonstrated serious developmental toxicity for rats and mice exposed to coal tar. However, some evidence of maternal toxicity in the form of reduced body weight gain and changes in organ weights was also observed for animals treated with doses of coal tar producing developmental toxicity (Hackett et al. 1984; Iyer et al. 1993; Springer et al. 1986a). Treatment of pregnant rats with coal tar by all routes of exposure produces reduced growth (reduced crown-rump length and delayed ossification) of the offspring, and an increase in the incidence of cleft palates and small lungs (Hackett et al. 1984; Springer et al. 1982, 1986a; Zangar et al. 1989). Dermal exposure of pregnant mice to coal tar produces an increase in the incidence of cleft palates dilated ureters and renal pelvic cavitation (Zangar et al. 1989). Zangar et al. (1989) carried out a comparison of the doses producing significant developmental effects in rats (Hackett et al. 1984; Springer et al. 1982; Zangar et al. 1989) and concluded that inhalation may be the most effective route for induction of developmental toxicity, followed by the oral and dermal routes, in that order. However, the authors noted that inhalation dosimetry is more difficult to calculate accurately due to unknown contributions from the oral and dermal routes.

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

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

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

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

Coal tar is composed of hydrocarbons, which are lipophilic substances and are therefore likely to distribute to lipid-rich tissues (Agency for Toxic Substances and Disease Registry 1995). For instance, PAHs and their metabolites are known to cross the placenta (Agency for Toxic Substances and Disease Registry 1995) and have been detected in human breast milk (Madhavan and Naiduka 1995). A study of the distribution of intratracheally administered radioactive benzo[a]pyrene mixed with a benzene extract of coal fly ash in pregnant rats found that a small proportion of the radioactivity was distributed to the fetal lung and liver and to the placenta (respectively 1.9, 1.4, and 4% of the amount in maternal lung).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to creosote are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by creosote are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations That Are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Creosote

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

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

PAHs form DNA adducts that can be measured in body tissues or blood following exposure to creosote that contains PAHs (Culp and Beland 1994; Pavanello and Levis 1994; Schoket et al. 1990; Zhang et al.

1990). These PAH-DNA adducts are not specific for coal tar creosote, and the adducts measured could have been from exposure to other sources of PAHs.

3.8.2 Biomarkers Used to Characterize Effects Caused by Creosote

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

For more information on biomarkers for renal and hepatic effects of chemicals, see Agency for Toxic Substances and Disease Registry/Centers for Disease Control and Prevention (1990) and for information on biomarkers for neurological effects, see OTA (1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

Coal Tar Products. The primary interactions known to occur between coal tar creosote and other substances involve the induction of cancer. Coal tar creosote is a complex mixture of organic substances consisting predominantly of liquid and solid aromatic hydrocarbons. Several of these components of coal tar creosote are known animal carcinogens as well as cocarcinogens, initiators, promoters, potentiators, or

inhibitors of carcinogenesis. Pretreatment of male Fischer 344 rats with orally administered coal tar creosote resulted in urinary excretion of mutagenic metabolites of creosote, and increased the bioactivation of orally administered 2,6-DNT to mutagenic metabolites, as measured in the Ames assay. Urinary excretion of mutagenic metabolites from rats pretreated with creosote and dosed with DNT at 1, 3, and 5 weeks peaked after 3 weeks and then declined by 33% after 5 weeks of treatment. The increase in urinary excretion of mutagenic metabolites was significantly greater than in rats that received only DNT at weeks 1 and 3, but not at week 5 (Chadwick et al. 1995).

As discussed in Section 3.2.3.7, coal tar creosote and several of its fractions are carcinogenic when applied to the skin of mice. Dermally applied creosote can also act as a tumor-initiating agent when applied prior to croton oil treatment, and can enhance and accelerate tumor induction by B[a]P. Thus, the risk of cancer following dermal exposure to creosote is likely to be enhanced when concurrent exposure to other potential co-carcinogens, tumor promoters, initiators, and potentiators occurs. Due to the ubiquitous nature of PAHs and other carcinogenic substances in the environment, particularly at hazardous waste sites, the likelihood that these types of synergistic interactions with creosote will occur could be important in assessing potential hazards.

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

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

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to creosote than will most persons exposed to the same level of creosote in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of creosote, or compromised function of organs affected by creosote. Populations who are at greater risk due to their unusually high exposure to creosote are discussed in Section 6.7, Populations With Potentially High Exposures.

Coal Tar Products. Data indicate that some populations may be at increased risk of developing skin cancer following prolonged dermal exposure to industrial grade coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles. The results of earlier occupational studies (Henry 1946, 1947), case reports (Cookson 1924; Lenson 1956; O'Donovan 1920), and experimental animal studies (Boutwell and Bosch 1958; Poel and Kammer 1957; Roe et al. 1958) indicate that prolonged dermal exposure to coal tar creosote may increase the risk of developing skin cancer. This risk may be increased for people with skin damaged from excessive sun exposure, disease, or exposure to other substances that potentiate the carcinogenic effect of coal tar creosote (Lenson 1956; Lijinsky et al. 1957; Sall and Shear 1940; TOMA 1979, 1981).

There is limited evidence, based on animal studies and the known health effects of the PAH constituents of coal tar creosote, that additional subsections of the population may be susceptible to the toxic effects of creosote. These include people with pre-existing respiratory, kidney, or liver disease. People with deficient immune systems may also be at high risk of developing adverse health effects due to exposure to carcinogens, such as PAHs (Stjernsward 1966, 1969; Szakal and Hanna 1972). Another potentially susceptible group are those individuals with the genetic trait of inducible AHH, one of the mixed function oxidases. When this enzyme is induced, the rate at which aryl compounds, such as PAHs, are biotransformed into toxic intermediates is increased, rendering these individuals at higher risk. It has been proposed that genetically expressed AHH inducibility is related to the development of bronchogenic carcinoma in persons exposed to PAHs contained in tobacco smoke. Approximately 45% of the general population are considered to be at high risk, and 9% of the 45% are considered to be at very high risk of developing bronchogenic carcinoma following exposure to PAHs (Calabrese 1978). These percentages were estimated from the population frequency of genetically controlled AHH induction (Calabrese 1978). Individual components of creosote are metabolized by several different enzyme systems including phase I (cytochrome P450 isozymes, AHH, epoxide hydrolase) and phase II (glutathione-S-transferases, glucuronidases, phenol sulfotransferase, and glucuronyltransferase) enzymes. Human polymorphisms are known to exist for many of these enzymes and are likely to affect the relative toxicity of creosote for these individuals. These enzymes are also known to have age-dependant expression and susceptibility may therefore vary with the age of the individual. However, no studies were located that addressed differential susceptibility of children to the effects of creosote. A detailed discussion of children's susceptibility can be found in Section 3.7.

Coal tar exposure produces developmental toxicity in rats and mice, and may also do so in pigs. However, the developmental risk to humans of exposure to coal tar is less clear. The doses that produced developmental toxicity in animals were relatively high and are unlikely to be attained through

environmental exposure in the vicinity of toxic waste sites. However, some evidence for species sensitivity exists and the possibility of developmental toxicity in humans due to coal tar exposure cannot be discounted and the human fetus may be another susceptible population.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to creosote. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to creosote. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to creosote:

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

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

Viccellio P, Bania T, Brent J, et al., eds. 1998. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to creosotes and coal tar mixtures generally means an exposure to a combination of large molecular toxins (including PAHs) and more immediately chemically reactive phenolic chemicals. The phenolic components act as direct caustic agents to skin, mucosa, and cornea, causing burns and scarring. The tars are photosensitizers and potential DNA-combining agents with different and latent clinical consequences, including cancer. Exposure to these compounds may occur via ingestion and direct liquid application. Although relatively nonvolatile, tar absorption following inhalation exposure to mists can occur through mucocilliary trapping and transport followed by gastrointestinal absorption.

The suggested emergency management of direct cutaneous exposure to creosote is prompt and comprehensive decontamination (Haddad et al. 1998). Treatment commonly includes removal of all contaminated clothing and washing of the skin, hair, and nails with large volumes of soapy water. It is recommended that those administering the treatment wear rubber gloves for their own protection. In order to reduce dermal irritation from creosote-contaminated soil and water, limited exposure, through the

wearing of protective clothing, and immediate washing of exposed skin were the recommendations of the Texas Department of Health to residents of a housing development built on an abandoned creosote factory site (Agency for Toxic Substances and Disease Registry 1994).

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

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

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

3.11.2 Reducing Body Burden

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

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

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

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

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

3.12 ADEQUACY OF THE DATABASE

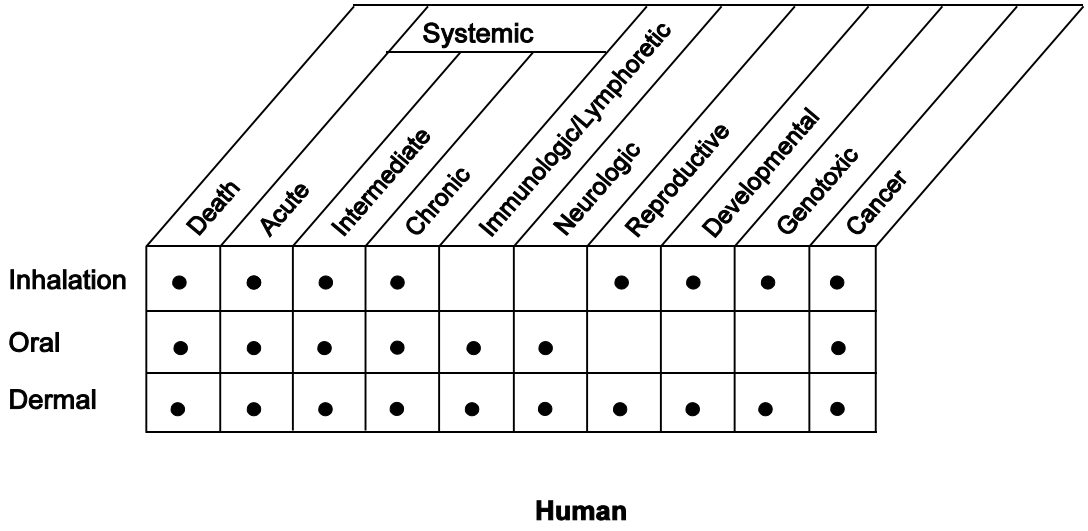
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of creosote is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of creosote.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

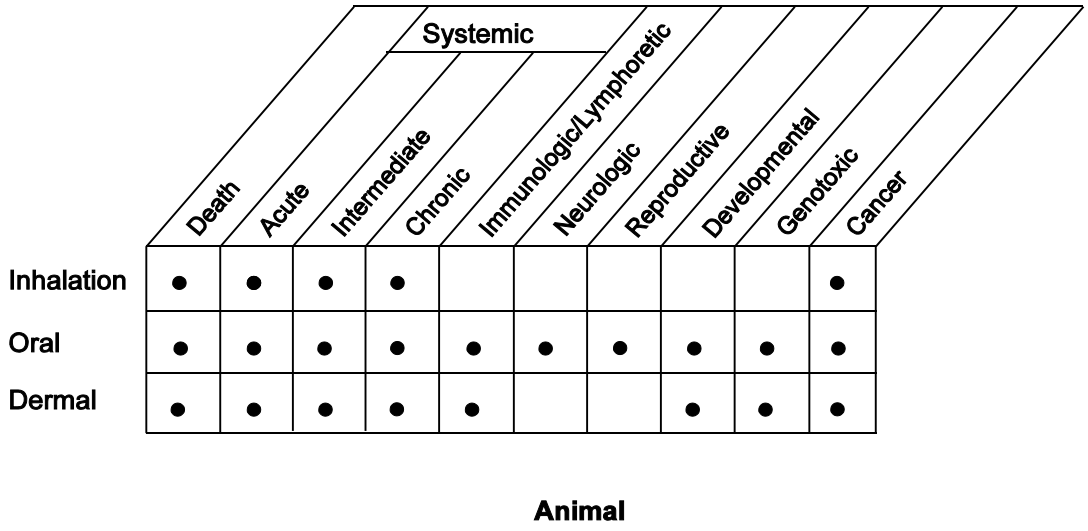
3.12.1 Existing Information on Health Effects of Creosote

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to creosote are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of creosote. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989c), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

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



Human



Animal

● Existing Studies

The database for the health effects of both wood creosote and coal tar products in experimental animals is inadequate, and consists primarily of acute lethality studies or early animal studies that would be considered inadequate by current standards. The systemic effects of ingested creosote have only been well described for beechwood creosote, although some studies exist for coal tar products. Little information is available on the effects of coal tar creosote following inhalation exposure. However, dermal exposure of mice to coal tar creosote and other coal tar products has been shown in numerous studies to induce skin tumors and, in two cases, lung tumors, while oral exposure has induced tumors in the lung, liver, and forestomach. Since coal tar creosote is a complex mixture consisting primarily of PAHs, the toxic effects of coal tar creosote may be inferred from available information on these constituents. However, given the fact that many of these constituents are known cocarcinogens, initiators, promoters, and potentiators of carcinogenesis, the possibility for the occurrence of synergistic interactions in creosote cannot be ruled out. Thus, information on the toxicity of the various components of coal tar creosote cannot take the place of sound data on the toxic effects of the creosote mixture itself. This can also be assumed to be true for the other coal tar products. An additional factor to be considered when reviewing the database for creosote is the effect of weathering. When creosote is released into the environment, weathering produces rapid changes in chemical composition (see Section 6.3). Thus, although data on toxic effects of unweathered creosote would be useful for individuals who are occupationally exposed to creosote, it is not clear how useful such data will be for individuals undergoing environmental exposure to weathered creosote.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Information is available on the effects of oral and dermal acute-duration exposures to wood creosotes (Miyazato et al. 1981; Ogata et al. 1993, 1999) and coal tar products (Hackett et al. 1984; Iyer et al. 1993; Mahlum 1983; Pfitzer et al. 1965; Springer et al. 1986a, 1989; Wrench and Britten 1975; Zangar et al. 1989) in humans and animals. However, there are few well-conducted animal or human studies describing health effects following inhalation exposure (Emmett 1986; Springer et al. 1982). The type of information available includes primarily LD_{50} values and data on acute toxicity in animals (coal tar products and beechwood creosote), and acute toxicity following accidental or intentional ingestion or dermal exposure in humans (coal tar creosote and other coal tar products). Coal tar creosote exerts its acute toxic effects primarily via dermal exposure, causing architectural damage to the tissues with which it comes in contact, such as the skin and eyes. Acute ingestion of coal tar creosote appears to affect primarily the kidney and liver. Thus, the toxic effects of coal tar creosote on the skin following single-dose dermal exposure in humans are well characterized, but little else is known regarding the systemic effects of this form of creosote in either humans or animals.

The available information is insufficient to derive either an acute oral or inhalation MRL for coal tar creosote or other coal tar products because human reports that identified target organs lacked exposure information, and no short-term animal studies exist that describe effects other than death or developmental defects. Identification of target organs from short-term animal studies following oral and dermal exposure would be useful in assessing the risk associated with the acute ingestion or skin contact with coal tar creosote-contaminated water or soils by humans. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., damage to the skin following dermal contact), it is impossible to predict effects following exposure by one route based on effects observed following exposure by another route.

Intermediate-Duration Exposure. Information is available on the effects of intermediate-duration dermal exposures to coal tar in humans (Franssen et al. 1999; Jones et al.1985; Menter and Cram 1983; Torinuki and Tagami 1988) and the effects of intermediate-duration exposures to beechwood creosote (oral) (Miyazato et al. 1981) and coal tar creosote (oral and dermal) in animals (Boutwell and Bosch 1958; Chadwick et al. 1995; Culp and Beland 1994; Kligman and Kligman 1994; Wallcave et al. 1971; Weyand et al. 1991, 1994, 1995). However, there are few well-conducted animal studies describing the health effects of inhalation exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles (Heinrich et al. 1994a, 1994b; MacEwen et al. 1977; Sasser et al. 1989; Springer et al. 1986b, 1987). The exact duration and level of exposure in the human studies generally cannot be quantified because the information is derived from anecdotal case reports rather than controlled epidemiological studies. The animal studies with beechwood creosote describe predominantly hepatic and renal end points, and those conducted with coal tar creosote describe dermal, hepatic, renal, hematological, and respiratory end points. Little or no in depth information on respiratory, cardiovascular, gastrointestinal, hematological, or musculoskeletal effects in animals is available. The available information is insufficient to derive either an intermediate oral or inhalation MRL for coal tar creosote or other coal tar products because no intermediate-duration human or animal studies exist that describe adverse effects other than on the skin. Given the widespread use of coal tar creosote as a wood preservative, and the fact that beechwood creosote is rarely used today, more information on the systemic effects of intermediate-duration exposures to coal tar creosote and other coal tar products by the oral and dermal routes (by conducting 90-day intermediate toxicity studies) would be useful to identify target organs in animals in order to assess the risk associated with the intermediate-duration ingestion of, or skin contact with, coal tar creosote-contaminated water or soils by humans. Since coal tar products give off volatile components, studies of inhalation exposure to these compounds would also be useful. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different

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

Chronic-Duration Exposure and Cancer. Some information is available on the effects of chronic-duration dermal exposures to coal tar creosote and other coal tar products in humans (Cookson 1924; Goulden and Stallard 1933; Henry 1946, 1947; Lenson 1956; Mackenzie 1898; O'Donovan 1920; Shambaugh 1935; Shimauchi et al. 2000) and the effects of chronic-duration exposures to beechwood creosote (oral) (Miyazato et al. 1984b) and coal tar creosote (dermal) in animals (Niemeier et al. 1988; Poel and Kammer 1957). However, there are few well-conducted animal studies describing the health effects of chronic oral or inhalation exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles (Culp et al. 1996a, 1996b, 1998; Heinrich et al. 1994a, 1994b; MacEwen et al. 1977). The exact duration and level of exposure in the human studies generally cannot be quantified because the information is derived from anecdotal case reports rather than controlled epidemiological studies. The animal studies with beechwood creosote describe predominantly hepatic and renal end points, and those conducted with coal tar creosote describe dermal, but very rarely other systemic effects. Little or no reliable information on respiratory, cardiovascular, gastrointestinal, hematological, or musculoskeletal effects in animals is available. The available information is insufficient to derive either a chronic oral or inhalation MRL for coal tar creosote because no chronic-duration human or animal studies exist that describe effects other than on the skin. Given the widespread use of coal tar creosote as a wood preservative, and the fact that beechwood creosote is rarely used today, more information on the systemic effects of chronic-duration exposures to coal tar creosote by the oral and dermal routes would be useful to identify target organs in animals in order to assess the risk associated with the chronic-duration ingestion of, or skin contact with, coal tar creosote-contaminated water or soils by humans. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., damage to the skin following dermal contact), it may not be possible to predict effects following exposure by one route based on effects observed following exposure by another route.

Various case reports and the results of cross-sectional occupational surveys associate chronic occupational creosote exposure with the development of skin cancer (Cookson 1924; Goulden and Stallard 1933; Henry 1947; Lenson 1956; Mackenzie 1898; O'Donovan 1920; Shambaugh 1935; Shimauchi et al. 2000). More recent cancer epidemiological studies and surveys of the literature help to fill in data gaps, but are retrospective, and often fail to provide exact information concerning exposure (Franssen et al. 1999; Liu et al. 1997; Pittelkow et al. 1981; TOMA 1982). Several skin painting studies

have been conducted in animals using coal tar creosote and its various fractions (Cabot et al. 1940; Deelman 1962; Emmett et al. 1981; Hueper and Payne 1960; Lijinsky et al. 1957; Mahlum 1983; Niemeier et al. 1988; Wallcave et al. 1971; Watson and Mellanby 1930). Although some of these studies would be considered inadequate by current standards, the results nevertheless indicate that coal tar creosote and its constituents can induce skin tumors as well as act as tumor initiators and promoters. Carcinogenicity studies conducted with beechwood creosote by the oral route, found no evidence of cancer in mice (Miyazato et al. 1984a, 1984b). However, oral cancer bioassays with coal tar in mice found a significant incidence of liver, lung, and forestomach tumors (Culp et al. 1996a, 1998; Weyand et al. 1995). More information on the carcinogenic potential of chronically ingested coal tar creosote (e.g., an oral bioassay in rats) would be useful. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since creosote appears to cause route-of-entry adverse effects (e.g., skin tumors following dermal contact), it may not be possible to predict effects following exposure by one route based on effects observed following exposure by another route.

Genotoxicity. The genotoxic potential of coal tar creosote has been investigated almost exclusively using *in vitro* assays (Agurell and Stensman 1992; Baranski et al. 1992; Bos et al. 1983, 1984b, 1984c, 1985, 1987; Donelly et al. 1993, 1996; Kesik and Janik-Spiechowicz 1997; Machado et al. 1993; Mayura et al. 1999; Reeves et al. 2001; Simmon and Shepherd 1978) and animal tissues (Chadwick et al. 1995; Ericson et al. 1998, 1999; Weyand et al. 1991) although some evaluations of chromosomal aberrations in peripheral lymphocytes and DNA adducts in skin and other tissues have been conducted in humans (Pavanello and Levis 1992, 1994; Yadav and Seth 1998; Zhang et al. 1990). The limited genotoxicity tests that have been conducted on urine obtained from humans exposed to creosote had varied results. The available data indicate that creosote is an indirect mutagen and induces gene mutation in bacteria and mouse lymphoma cells. However, a substantial database exists on the genotoxic effects of the PAHs found in the creosote mixture. More *in vivo* assays using human tissues with coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles, or specific components of these mixtures, would be useful to more completely characterize the genotoxic potential of these mixtures.

Reproductive Toxicity. Little information on the reproductive effects of coal tar creosote in humans or animals is available. One epidemiological study in humans indicates no reproductive hazard from exposure through environmental contamination (Agency for Toxic Substances and Disease Registry 1994) and another indicated no increased risk of spontaneous abortion from the use of coal tar as a dermal treatment for psoriasis during pregnancy (Franssen et al. 1999). However, animal studies have shown that exposure to coal tar causes increased resorptions, decreased ovary weights (with a loss of luteal tissue),

and increased testis weights in mice and rats (Hackett et al. 1984; Springer et al. 1982, 1986b, 1987). An increase in relative testis weight was also observed in rats administered beechwood creosote in the diet for 3 months (Miyazato et al. 1981). There were no accompanying gross or histopathological lesions of the testes in these animals, so the toxicological significance of this change is not known. Given the widespread potential for exposure to coal tar creosote, and industrial exposure to other coal tar products, and the indication from animal studies that creosote may be a reproductive toxicant, multi-generation reproductive toxicity studies should be conducted by the oral and dermal routes of exposure. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since coal tar has been shown to produce reproductive toxicity in animals by the oral, dermal, and inhalation routes, it appears that reproductive toxicity may not be route-dependent.

Developmental Toxicity. Information on the developmental effects of creosote in humans was not found. Studies have demonstrated serious developmental toxicity for rats and mice exposed to coal tar by all routes, including reductions in fetal ossification, crown-rump length, fetal weight, fetal lung weight, and placental weights (Springer et al. 1982), a significant increase in the incidence of cleft palate (Hackett et al. 1984), increased early mortality in pups of treated dams (Springer et al. 1986a), and significant increases in prenatal mortality in exposed rat and mouse fetuses (Zangar et al. 1989).
In many of these studies, it is not possible to exclude the potential role of maternal toxicity in the development of adverse fetal effects. It would be useful to carry out studies to explicitly evaluate the role of maternal toxicity in the development of creosote-induced adverse developmental effects. The pharmacokinetic data on coal tar creosote are insufficient to determine whether similar effects may be expected to occur across different routes of exposure. However, since coal tar has been shown to produce developmental toxicity in animals by the oral, dermal, and inhalation routes, it appears that developmental toxicity may not be route-dependent.

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

Neurotoxicity. The available information about the possible neurotoxic effects of creosote is very limited, but some signs of neurological involvement in humans and animals following exposure to beechwood creosote and creosote bush (Gordon et al. 1995; Miyazato et al. 1981) and coal tar (Hanlon 1938; NIOSH 1980b) have been described. These effects were generally excitatory in nature (e.g., convulsions). No reliable data are available on the short-term neurotoxic effects of coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatile exposure by the inhalation, oral, or dermal routes, or long-term neurotoxic effects of low-level exposure to coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatiles by the inhalation, oral, or dermal routes in humans or animals. Reports of individuals exposed to creosote suggest that neurotoxicity (e.g., dizziness, altered vision, etc.) may be an early sign of toxic exposure to creosote. Short-term and long-term neurotoxicity studies in animals, using sensitive functional and neuropathological tests, and exposure by the inhalation, oral and dermal routes would be useful in determining if coal tar creosote is a neurotoxic agent.

Epidemiological and Human Dosimetry Studies. Few controlled epidemiological studies have been conducted in humans on the effects of exposure to coal tar creosote. In particular, epidemiological studies of workers in creosote treatment plants accompanied by accurate occupational exposure data would be useful to more fully assess the risk of inhalation and dermal exposure to coal tar creosote. Most of the available information on the effects of coal tar creosote in humans comes from occupational studies in the wood-preserving and construction industries (Armstrong et al. 1994; Bertrand et al. 1987; Bolt and Golka 1993; Costantino et al. 1995; Gibbs and Horowitz 1979; Karlehagen et al. 1992; Kerr et al. 2000; Lloyd 1971; Lloyd et al. 1970; Martin et al. 2000; Mazumdar et al. 1975; Park and Mirer 1996; Persson et al. 1989; Redmond 1976; Redmond et al. 1972, 1976; Rockette and Arena 1983; Rönneberg and Andersen 1995; Sakabe et al. 1975; Spinelli et al. 1991; Stern et al. 2000; TOMA 1982; Tremblay et al. 1995). Limitations inherent in these studies include unknown exposure concentrations and durations, as well as concomitant exposure to other potentially toxic substances. The few available industrial surveys and epidemiological studies are limited in their usefulness because of small sample size, short follow up periods, and brief exposure periods. Despite their inadequacies, studies in humans suggest that coal tar creosote is a dermal irritant and a carcinogen following dermal exposure. Only one epidemiological study of people living in close proximity to a coal tar creosote-contaminated area was found in the literature (Agency for Toxic Substances and Disease Registry 1994). Additional well-controlled epidemiological studies of people with documented exposure to creosote, living in close proximity to areas where coal tar creosote has been detected in surface and ground water, or near hazardous waste sites, and of people occupationally exposed to creosote could add to and clarify the existing database on creosote-induced human health effects. Particular health effects that should be examined in future studies include cancer,

developmental, reproductive, immunotoxic, and neurotoxic effects as well as adverse noncancer dermal effects.

Biomarkers of Exposure and Effect.

Exposure. No method is currently available to measure the parent creosote mixture in human tissues or fluids. However, 1-hydroxypyrene, the metabolite of pyrene, a component of the creosote mixture, can be measured in the urine of exposed individuals following relatively high-level exposures of acute and chronic duration (Bos and Jongeneelen 1988; Jongeneelen et al. 1985, 1988). The identification of PAH metabolites in urine could potentially serve as a method of biological monitoring of exposed workers and possibly individuals living in the vicinity of hazardous waste sites where creosote has been detected. However, because of the ubiquitous nature of PAHs in the environment, detection of PAH metabolites in the body tissues or fluids cannot always be attributed to creosote exposure. PAHs form DNA adducts that can be measured in body tissues or blood following exposure to creosote containing PAHs. Again, these PAH-DNA adducts are not specific for coal tar creosote, and the adducts measured could have been from exposure to other sources of PAHs. Therefore, a biomarker of exposure specific to creosote would be useful to monitor exposure to this mixture.

Effect. The formation of benzo[a]pyrene-DNA adducts has been demonstrated (Pavanello and Levis 1992; Zhang et al. 1990) and may also serve as a biomarker of PAH-induced carcinogenicity. However, these adducts are not specific for coal tar creosote exposure, as exposure to benzo[a]pyrene from sources other than coal tar creosote can occur. Studies to identify and measure effects more diagnostic of coal tar creosote-specific injury would be useful. Also, increasing the sensitivity of these tests would be valuable in evaluating the health status of individuals who have been exposed to low levels of creosote.

Absorption, Distribution, Metabolism, and Excretion. Studies monitoring the pharmacokinetics of the coal tar creosote mixture are limited. Much of the information regarding the disposition of creosote is based on indirect evidence or the pharmacokinetic information available on a single class of creosote components, the PAHs. For more information on the toxicokinetics of PAHs, please refer to the ATSDR *Toxicological Profile for Polycyclic Aromatic Hydrocarbons* (Agency for Toxic Substances and Disease Registry 1995).

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

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

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

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

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

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

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

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

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

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

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

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

3.12.3 Ongoing Studies

Creosote is currently subject to an EPA Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) registration standard and data call-in, and the Creosote Council II is currently conducting a research program that includes testing in intermediate inhalation, intermediate dermal, developmental, and reproductive toxicity. The Federal Research in Progress database (FEDRIP 2000) listed ongoing studies of CYP1A1 as a biomarker of exposure and susceptibility to creosote, the effect of wood creosote on diarrhea in rats, and modifiers of PAH carcinogenesis.