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

3.1 TOXICOKINETICS

Specific information regarding the toxicokinetics of creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles is limited. Several compounds have been detected in coal tar creosote, yet there are no definitive data on which of these compounds people are exposed to in wood-treatment plants or at hazardous waste sites. No method is currently available to measure the parent creosote mixture in human tissues or fluids. Toxicokinetics of the major constituents of creosote can be predicted from studies of the individual constituents and structural analogs; however, due to the variable composition of creosote compounds, the predictive value of studies conducted using these individual constituents is limited and should therefore be used with caution when drawing any conclusions. This information is provided in various ATSDR toxicological profiles, including cresols (ATSDR 2008a), naphthalene (ATSDR 2005), PAHs (ATSDR 1995), phenol (ATSDR 2008b), and xylene (ATSDR 2007).

3.1.1 Absorption

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

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

No studies in humans or animals were located regarding the direct analysis of the extent or rate of coal tar creosote, coal tar, coal tar pitch, or coal tar pitch volatile absorption following inhalation exposure. However, there is evidence to suggest that inhalation absorption of coal tar products may occur. Employees of a coal tar creosote wood-impregnating plant, employees in a coal tar plant, and coke oven workers excreted 1-hydroxypyrene, a metabolite of pyrene, a creosote component, in their urine (Bos and

Jongeneelen 1988; Jongeneelen et al. 1985, 1988). Similarly, workers asphalting roads with coal tar excreted 1-hydroxypyrene in their urine (Bos and Jongeneelen 1988; Jongeneelen et al. 1988). Increased levels of 1-hydroxypyrene were observed over the course of the workday for all groups of workers, indicating an accumulation of pyrene during the exposure period (Bos and Jongeneelen 1988). The presence of this metabolite in the urine suggested that coal tar creosote components were absorbed and metabolized following inhalation exposure. However, it is possible that some dermal exposure may have occurred as well.

Measurements were carried out in a creosote impregnation plant where six men volunteered to participate in the study (Elovaara et al. 1995). Personal breathing zone air samples were taken on 5 consecutive days followed by a work-free period of 64 hours. Particulate PAHs were collected using a filter during the whole shift (from 6:00 am to 2:00 pm) and analyzed within 7 weeks (total of 30 samples). All workers wore leather protective gloves and cotton overalls. Two employees worked overtime on Monday, which was an exception to the regular 8-hour schedule, reducing their 64-hour work-free period. Workers were asked to collect all urine passed within the 24-hour period into divided samples for the designated periods. Results showed that the geometric mean (range) air concentrations were 4.77 (1.2–13.7) mg/m^3 (n=30) for total particulate PAHs (including pyrene) and 1,254 (370–4,200) mg/m^3 (n=30) for naphthalene. The PAH profile was similar in all samples. 1-Hydroxypyrene was found in the urine samples.

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

inhaled pyrene measured for the chiseler was 1.2 mmol/shift. Excretion of urinary 1-hydroxypyrene was detected for all participants.

Four rotation shift crews (working hours rotated between 12:00 am–8:00 am, 8:00 am–4:00 pm, and 4:00 pm–12:00 am) of about 29 workers and one day crew (working hours 8:00 am–4:30 pm) of 22 workers worked in a 5-day shift, 8 hours/day in the potrooms (Ny et al. 1993). All workers wore disposable respirators that were renewed 4–5 times/day, thick cotton working clothes with long sleeves, safety shoes, safety glasses, gloves, and helmets. Other groups that worked occasionally in the potrooms were also included in this study. Some employees who worked in dusty environments also wore facial protective clothing. Personal breathing zone air samples taken randomly from 38 workers were sampled once. Measurements were done on 3 out of 5 working days for the rotation crews and on 4 days in 2 work weeks for the day crew. The filter holders and the XAD-2 tubes used in sampling were analyzed. Urine samples were collected from 33 of 38 workers before and after the 5-day work week. Control urine samples were taken from 10 guards not exposed to coal tar pitch volatiles. 1-Hydroxypyrene in urine was determined by liquid chromatography (LC). Results showed that field blanks were not contaminated with coal tar pitch volatiles. No benzo[a]pyrene was found on XAD-tubes. Vapor-phase measurement, which would have detected only volatile and semi-volatile constituents, showed 48% pyrene and 24% total PAHs. The highest filter sample (particulate) concentration of pyrene was 170 mg/m^3, and the highest sorbent tube (vapor) concentration of pyrene was 94 mg/m^3. The correlation between these two variables was 0.70. Individuals who worked continuously in the potrooms were exposed to variable concentrations of coal tar pitch volatiles, ranging from 10 to 2,710 mg/m^3. Multiple regression analysis of increased urinary 1-hydroxypyrene was strongly related to the environmental PAH exposure. Increased urinary 1-hydroxypyrene was greater among those using facial protective clothing under their respirators; this was probably caused by poor fitting or by facial coverings becoming contaminated by PAH. The predicted limit value of change in urinary 1-hydroxypyrene, using the model for coal tar pitch volatiles, was 4.3 mmol/mol creatinine. The predicted limit value of change in urinary 1-hydroxypyrene, using the model for benzo[a]pyrene, was 4.3 mmol/mol creatinine.

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

Tumor-susceptible ICR CF-1 and tumor-resistant CAF1-JAX mice were exposed to 10 mg/m^3 coal tar aerosol-BTX mixture continuously, or for 90 days, or intermittently for 18 months (MacEwen et al.

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

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

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

Wood creosote. Constituents of wood creosote have been detected in plasma and urine following oral dosing with wood creosote (Kuge et al. 2003; Ogata et al. 1995). Eight healthy male volunteers were orally administered a single dose of a 133 mg wood creosote capsule and 200 mL water after a light breakfast (Ogata et al. 1995). Peripheral venous blood and urine samples were collected at various time intervals. Absorption appeared to be substantial based on the high percentage of the dose of creosote phenols recovered in urine over a 24-hour period following dosing (group mean): 103% for p-cresol, 75% for phenol, 74% for cresol, and 45% for guaiacol. Kuge et al. (2003a, 2003b) administered single oral doses of wood creosote (45–225 mg) to 30 adults and followed the kinetics of appearance and elimination of creosol, o-cresol, 4-ethyguaicol, and guaiacol from plasma. The time for maximum plasma levels ranged from 0.46 to 1.08 hours and did not appear to be affected by the creosote dose level.

Coal tar products. Based on data on PAHs, absorption of PAH components of coal tar products after oral exposure may be positively influenced by the presence of oils and fats in the stomach, and bile in the intestines (ATSDR 1995). Due to relative water insolubility of PAHs, absorption is enhanced by

solubilization in an intermediate phase that can be metabolized during the process of lipid digestion and absorption. Excretion after oral exposure may be detected hours to days after exposure. Due to the variable composition of coal tar creosote, coal tar, and coal tar pitch, the predictive value of oral absorption studies conducted with pure PAHs is limited.

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

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

Male B6C3F1 mice were given 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar/day in feed for 28 days (Culp and Beland 1994). At the end of the feeding period, DNA adduct formation was quantified in the liver, lungs, and forestomach by ^{32}P-post-labeling. The adduct levels were then compared with those obtained by feeding benzo[a]pyrene to mice for 3 weeks at concentrations corresponding to the amount of benzo[a]pyrene in the coal tar doses. DNA adduct formation was found to increase as a function of dose in each tissue with both coal tar and benzo[a]pyrene, indicating absorption after oral exposure. Five groups of B6C3F1 mice (24 males, 24 females) were fed a control gel diet containing 0.05, 0.25, or 0.50% MGP (Weyand et al. 1994). The urinary excretion of 1-hydroxypyrene by male mice (12 per group) treated with 0.25 and 0.50% MGP was evaluated throughout the 185 days of diet administration. 1-Hydroxypyrene was detected in the urine, indicating absorption of MGP components.

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

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

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

Another study of dermal absorption was conducted by Van Rooij et al. (1993b) in a wood preserving plant in the Netherlands in October 1991. Volunteers for this study worked near the impregnation cylinders (three subjects) and the assembly hall (seven subjects). Exposure measurements were

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

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

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

Five female patients (two nonsmokers, three smokers) suffering from eczematous dermatitis on the arms and legs were treated for several days with an ointment containing 10% *pix lithanthracis dermata* (coal

tar), representing 16.7 mg/g pyrene and 7.0 mg/g benzo[a]pyrene (Bos and Jongeneelen 1988). During treatment, the ointment was removed daily and a fresh dose of approximately 40 g was rubbed in. Urine samples were collected, one before application and two during the day for the first 3 days of treatment. 1-Hydroxypyrene was detected in the urine of all patients, indicating absorption of a component of the coal tar.

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

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

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

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

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

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

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

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

3.1.2 Distribution

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

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

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

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

Intratracheal administration of [^{3}H]-benzo[a]pyrene, along with the benzene extract of coal fly ash, to pregnant rats (20 mg/kg/day) on GDs 18 and 19 resulted in their distribution to the maternal lung and liver (Srivastava et al. 1986). The amount of radioactivity found in the maternal liver was approximately 68% of the amount of radioactivity found in the maternal lung. The amounts of radioactivity found in the placenta, fetal lung, and fetal liver were approximately 4, 1.9, and 1.4%, respectively, of the amount of

radioactivity found in the maternal lung. Much of the radioactivity was attributable to metabolites. These results in rats suggest that components of coal tar creosote and their metabolites can pass through the placenta and distribute to fetal tissue.

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

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

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

Coal tar products. Culp and Beland (1994) fed male B6C3F1 mice 0, 197, 410, 693, 1,067, and 1,750 mg/kg/day coal tar/day in feed for 28 days. A second group of mice was fed benzo[a]pyrene for 21 days at levels corresponding to those found in the coal tar-containing feed mixtures. At the end of the feeding period, DNA adduct formation was quantified in the liver, lungs, and forestomach by ^{32}P-post-labeling. The adduct levels were then compared with those obtained from the mice fed benzo[a]pyrene. DNA adduct formation was found to increase as a function of dose in each tissue with both coal tar and benzo[a]pyrene. DNA adduct levels were in the order forestomach > liver > lung at lower dose groups,

while the order changed to liver > forestomach > lung at the highest dose group. Total DNA binding was greater in the coal tar fed mice than in the benzo[a]pyrene fed animals (≈10- to 30-fold greater in the liver and forestomach, and >90-fold greater in the lungs at the lower doses).

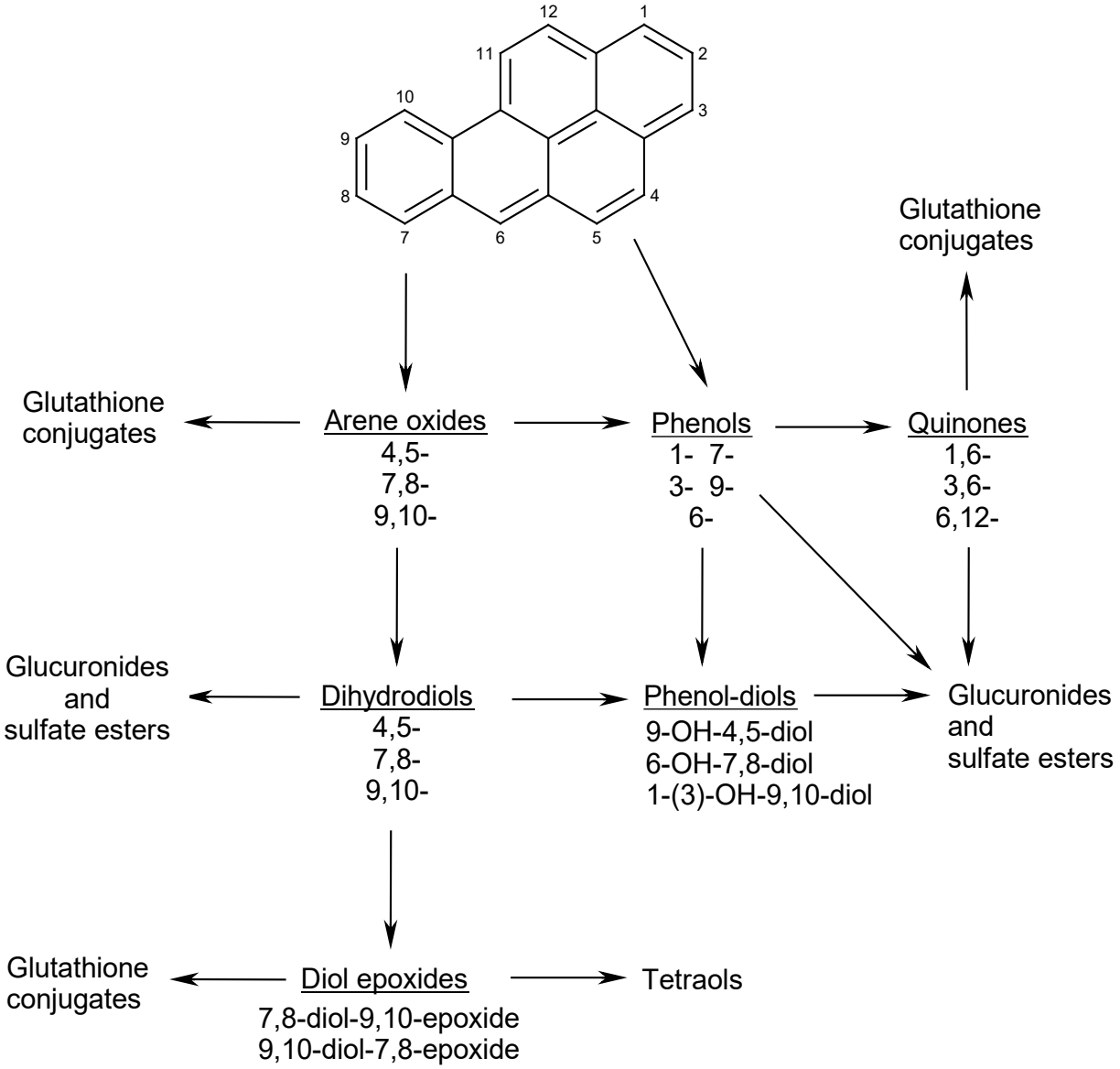
Dermal Exposure. No studies in humans or animals were located regarding the distribution of wood creosote, coal tar creosote, coal tar, or coal tar pitch following dermal exposure. Distribution of creosotes or coal tar products in humans following dermal exposure is expected to be qualitatively similar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

3.1.3 Metabolism

Metabolism of major constituents of creosote can be predicted from studies of the individual constituents and structural analogs. This information is provided in various ATSDR toxicological profiles, including cresols (ATSDR 2008a), naphthalene (ATSDR 2005), PAHs (ATSDR 1995), phenol (ATSDR 2008b), and xylene (ATSDR 2007). Generally, the PAH components of wood creosote, coal tar creosote, coal tar, and coal tar pitch are metabolized by oxidative enzymes in the liver and lungs to generate active metabolites that can bind to macromolecules. The metabolic profiles vary among species and compounds, but the components follow the same major reaction pathways. Hence, the metabolites are structurally very similar. The proposed metabolic scheme for a representative PAH, benzo[a]pyrene, is presented in Figure 3-1. The principal products include phenols, phenol diols (including catechols), dihydrodiols, quinones, anhydrides, and conjugates of these products (Autrup and Seremet 1986; Dahl et al. 1985; Fellows 1939b; Geddie et al. 1987; Hopkins et al. 1962; Jongeneelen et al. 1985, 1986, 1988; Ogata et al. 1995; Petridou-Fischer et al. 1988; Povey et al. 1987; Rice et al. 1986; Santella et al. 1994; Weyand and Bevan 1987).

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

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



Coal tar products induce AHH and a variety of metabolic enzymes. Application of coal tar to skin of human adults induced activities of the following enzymes in skin at the site of application: CYP1A1, CYP1A2, CYP1B1, CYP2C18, quinone reductase, glutathione S-transferase (GSTP1), glutamyl cysteine synthetase, glutathione peroxidase-1, cyclooxygenase-2 and heme oxygenase-1 (Smith et al. 2003, 2006). Application of coal tar for 24 hours to the healthy skin of psoriasis and dermatitis patients caused a 2–5-fold induction of AHH activity compared to untreated skin from the same individuals (Bickers and Kappas 1978). In this same study, incubation of human skin with coal tar solution *in vitro* also caused induction of AHH, which reached a maximum after 24 hours; and application of coal tar to the skin of rats

produced significant induction of AHH both in skin (10-fold) and in liver (>20-fold). Dermal treatment of healthy volunteers with 10% coal tar for 4 days produced an 18-fold induction of CYP1A1 messenger ribonucleic acid (mRNA) levels in coal-tar-treated skin (Li et al. 1995). Pretreatment of mice with gavage doses resulted in induction of hepatic glucuronidation of 1-hydroxypyrene (18-fold) and *p*-nitrophenol (2–3-fold) (Luukkanen et al. 1997). Nordihydroguaiaretic acid, a constituent of wood creosote, was shown to inhibit CYP1A2, CYP3A, CYP2B, and CYP2C11 in *in vitro* preparations of rat liver microsomes (Billinsky et al. 2012).

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

Inhalation Exposure

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

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

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

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

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

Oral Exposure

Wood creosote. Eight healthy male volunteers were orally administered a single dose of 133 mg wood creosote by capsule with 200 mL water after a light breakfast (Ogata et al. 1995). Peripheral venous blood and urine samples were collected at various time intervals. The metabolites in the serum started to rise 15 minutes after the oral dose, reaching the maximum 30 minutes after dosing. The maximum serum concentrations (Cmax) of glucuronides were 0.18±0.07, 0.91±0.38, 0.33±0.18, and 0.47±0.23 mg/L, and of sulfates were 0.16±0.06, 0.22±0.09, 0.17±0.07, and <0.04 mg/L for phenol, guaiacol, *p*-cresol, and cresol, respectively. The Cmax values for unconjugated phenols were 0.06±0.01, 0.05±0.01, 0.12±0.05, and <0.04 mg/L for phenol, guaiacol, *p*-cresol and cresol, respectively. Rats receiving a single dose of

either 0.0002, 0.002, 0.02, 0.2, or 2.0 mg pyrene/kg by gavage in olive oil excreted 1-hydroxypyrene in the urine in a dose-dependent manner (Jongeneelen et al. 1986). This metabolite could be detected up to 96 hours after administration. No unchanged pyrene was excreted.

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

Induction of glucuronosyltransferase activity in liver microsomes from male Wister rats treated with coal tar creosote (200 mg/4 mL olive oil/kg) by gavage 72 and 24 hours before death was compared with activity in microsomes from untreated control animals (Luukkanen et al. 1997). Microsome preparations from the livers of these rats were used to assay the activities of 1-hydroxypyrene uridine 5'-diphospho-glucuronosyltransferase (UGT) and *p*-nitrophenol UGT and estimate the kinetic parameters of the two enzymes. Pretreatment with creosote lowered the apparent K_m value for 1-hydroxypyrene UGT and significantly increased the estimated maximum velocity V_{max} over 4-fold. The apparent K_m values of *p*-nitrophenol UGT were higher and the V_{max} values lower than the ones for 1-hydroxypyrene UGT, but again, treatment with creosote lowered the apparent K_m value and increased the estimated maximum velocity V_{max}. Pretreatment with creosote increased the ratio of V_{max}/K_m for 1-hydroxypyrene UGT by 18-fold and for *p*-nitrophenol by 2–3-fold. These results suggest that a highly efficient form of glucuronosyltransferase was selectively induced by creosote.

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

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

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

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

Dermal Exposure

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

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

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

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

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

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

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

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

3.1.4 Excretion

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

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

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

Coal tar products. Elevated urinary levels of PAHs were observed in workers in a creosote impregnation plant (Elovaara et al. 1995). The geometric mean (range) workplace air concentration of total particulate PAHs (including pyrene) was 4.77 (1.2–13.7) mg/m^3 and that of naphthalene was 1,254 (370–4,200) mg/m^3. Urinary PAH levels were higher 6–9 hours following the work shift and lower following absence from work for 64 hours. Urinary levels of PAH were measured in assemblers who handled creosote-impregnated wood or who chiseled coal tar pitch insulation (Heikkilä et al. 1995). The total air concentrations of PAHs and of 4–6 aromatic ring-containing PAHs when chiseling was 440 mg/m^3 (50-fold higher than assemblers) and 290 mg/m^3 (200-fold higher than assemblers), respectively. Excretion of urinary 1-hydroxypyrene was higher in chiselers compared to assemblers. Workers in potrooms had elevated levels of 1-hydroxypyrene in urine (Ny et al. 1993). Those who worked continuously in the potrooms were exposed to variable concentrations of coal tar pitch volatiles, ranging

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

Weyand et al. (1991) fed male mice 0.25% MGP residue, a form of coal tar, in feed for 15 days. The coal tar mixtures were of five different compositions. Analysis of urine collected on the first and last day of exposure indicated that 1-hydroxypyrene was the major metabolite excreted by all groups. Urinary levels of 1-hydroxypyrene were greater on day 15 of ingestion compared to day 1 of ingestion. 1-Naphthol, 1-hydroxyphenanthrene, and 2-hydroxyphenanthrene were also detected in the urine. In another study by Weyand et al. (1994), five groups of B6C3F1 mice (24 males, 24 females) were fed a control gel diet containing 0.05, 0.25, or 0.50% MGP residue, a type of coal tar formed as a byproduct of coal gasification, for a period of 185 days. The total amount of 1-hydroxypyrene excreted reached a maximum of 5–6 mg within 34 days of diet administration.

Numerous studies conducted in humans have demonstrated that, following dermal exposures, metabolites of constituents of coal tar creosote (e.g., PAHs) are excreted in urine (Bickers and Kappas 1978; Bos and Jongeneelen 1988; Cernikova et al. 1983; Clonfero et al. 1989; Diette et al. 1983; Hansen 1993; Jongeneelen et al. 1985; Santella et al. 1994; Sarto et al. 1989; Van Rooij et al. 1993a, 1993b; van Schooten et al. 1994; Viau and Vyskocil 1995).

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

Five female patients (two nonsmokers, three smokers) suffering from eczematous dermatitis on the arms and legs were treated for several days with an ointment containing 10% *pix lithanthracis dermata* (coal tar), representing 16.7 mg/g pyrene and 7.0 mg/g benzo[a]pyrene (Bos and Jongeneelen 1988). During treatment, the ointment was removed daily and a fresh dose of approximately 40 g was rubbed in. Urine samples were collected, one before application and two during the day for the first 3 days of treatment. The concentration of 1-hydroxypyrene rose rapidly to 100 times the control value after the beginning of the treatment of these patients reaching 50–500 µmol/mol creatinine.

Clonfero et al. (1989) measured urinary PAHs in four male nonsmoking psoriatic patients undergoing treatment with the Goeckerman regimen (cutaneous application of coal tar-based ointment, followed by exposure to UV irradiation). Patient A was treated with pure coal tar for 1 day; patients B, C, and D were treated with 4% coal tar-based ointment for 2, 8, and 13 days, respectively. Body surface involved by psoriasis was 30, 40, 35, and 60% for patients A, B, C, and D, respectively. Total PAH (and pyrene) content of the two coal tar preparations was 28,800 (3,100) and 470 (104) ppm, respectively. A control group consisted of 52 nonsmokers who exhibited values of 1.3 mg/g creatinine. Levels of 1-hydroxypyrene were 20 and 1,000 times higher in the exposed group than in controls; total PAHs were 3.5–20 times higher in the exposed group than in controls.

In a study of 57 patients with psoriasis (57) and healthy volunteers (53) with no reported exposures to coal tar shampoos or ointments, patients' self-applied either an ointment or a gel-based coal tar product, or both, to the entire body surface at least once a day, followed by UV-B treatment (Santella et al. 1994). The estimated exposure was 20–100 g/tar/day. Urinary PAH metabolites were approximately 7 times higher in patients compared to controls. Urinary levels of 1-hydroxypyrene were also elevated in patients compared with controls.

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

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

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

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 endpoints.

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

3.1.6 Animal-to-Human Extrapolations

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

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic

makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

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

The effects of creosote as a mixture have not been thoroughly studied in children, although information may be available on some of the individual components (see Section 3.1). The pharmacokinetics of wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles have not been defined because of their chemical complexity. Creosotes vary tremendously in composition and hence, mechanisms of action most likely differ among individual samples of creosotes. Individual components of creosote are metabolized by several different enzyme systems including phase I (cytochrome P450 isozymes, AHH, epoxide hydrolase) and phase II (glutathione-S-transferases, glucuronidases, phenol sulfotransferase, and glucuronyltransferase). Human polymorphisms are known to exist for many of these enzymes and are likely to affect the relative toxicity of creosote for these individuals. The relative activity of metabolic enzymes may also vary with the age of the individual, which will again affect the relative toxicity of particular components of creosote for old or young individuals. For instance, several cytochrome P450 isozymes are known to be absent or expressed at very low levels in the developing human fetus while glucuronyl transferases and sulphotransferases do not reach adult levels until 1–3 years of age (Leeder and Kearns 1997).

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

No reports of adverse developmental effects on humans after exposure to wood creosote or coal tar products were found in the literature. No adverse developmental outcomes were detected in a survey of inhabitants of a housing development built on an abandoned creosote factory site, which was known to be contaminated with creosote (ATSDR 1994). A retrospective study of dermal exposure to coal tar found no increased risk of birth defects associated with exposure to coal tar during pregnancy, but this was a

small study and was unlikely to have sufficient resolution to detect a modest increase in risk (Franssen et al. 1999). Coal tar exposure produces developmental toxicity in rats and mice (Hackett et al. 1984; Springer et al. 1982, 1986a; Zangar et al. 1989). However, the developmental risk to humans of exposure to coal tar is less clear. The doses that produced developmental toxicity in animals were relatively high and are unlikely to be attained through environmental exposure in the vicinity of toxic waste sites. However, some evidence for species sensitivity exists and the possibility of developmental toxicity in humans from coal tar exposure cannot be discounted.

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

Pre-existing Conditions, Diseases, and Exposure to Other Substances. Data indicate that some populations may be at increased risk of developing skin cancer following prolonged dermal exposure to industrial grade coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles. The results of earlier occupational studies (Henry 1946, 1947), case reports (Cookson 1924; Lenson 1956; O'Donovan 1920), and experimental animal studies (Boutwell and Bosch 1958; Poel and Kammer 1957; Roe et al. 1958) indicate that prolonged dermal exposure to coal tar creosote may increase the risk of developing skin cancer. This risk may be increased for people with skin damaged from excessive sun exposure, disease, or exposure to other substances that potentiate the carcinogenic effect of coal tar creosote (Koppers Company 1979, 1981; Lenson 1956; Lijinsky et al. 1957; Sall and Shear 1940). There is limited evidence, based on animal studies and the known health effects of the PAH constituents of coal tar creosote, that additional subsections of the population may be susceptible to the toxic effects of creosote. These include people with pre-existing cardiovascular, respiratory, kidney, or liver disease. People with

deficient immune systems may also be at high risk of developing adverse health effects due to exposure to carcinogens, such as PAHs (Stjernsward 1966, 1969; Szakal and Hanna 1972).

Genetic Polymorphisms. Another potentially susceptible group are those individuals with the genetic trait of inducible AHH, one of the mixed function oxidases. When this enzyme is induced, the rate at which aryl compounds, such as PAHs, are biotransformed into toxic intermediates is increased, rendering these individuals at higher risk. Genetically expressed AHH inducibility may be related to the development of bronchogenic carcinoma in persons exposed to PAHs contained in tobacco smoke. Approximately 45% of the general population are considered to be at high risk, and 9% of the 45% are considered to be at very high risk of developing bronchogenic carcinoma following exposure to PAHs (Calabrese 1978). These percentages were estimated from the population frequency of genetically controlled AHH induction (Calabrese 1978). Individual components of creosote are metabolized by several different enzyme systems including phase I (cytochrome P450 isozymes, AHH, epoxide hydrolase) and phase II (glutathione-S-transferases, glucuronidases, phenol sulfotransferase, and glucuronyltransferase) enzymes. Human polymorphisms are known to exist for many of these enzymes and are likely to affect the relative toxicity of creosote for these individuals. These enzymes are also known to have age-dependent expression and susceptibility may therefore vary with the age of the individual. However, no studies were located that addressed differential susceptibility of children to the effects of creosote. Theoretically, combinations of polymorphisms many enhance or reduce susceptibility to creosote.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to creosote are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/

exposurereport/). If available, biomonitoring data for creosote from this report are discussed in Section 5.6, General Population Exposure.

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 effect caused by creosote are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Coal Tar Products. No method is currently available to measure the parent creosote mixture and other coal tar products in human tissues or fluids. However, individual components of the mixture can be measured. Urinary naphthols have been shown to be accurate biomarkers of naphthalene exposure during tar distillation or impregnation of wood with coal tar creosote (Bieniek 1997; Heikkilä et al. 1997; Preuss et al. 2005). PAH components of the creosote mixture and their metabolites can also be measured in the urine of exposed individuals (Bickers and Kappas 1978; Borak et al. 2002; Bos and Jongeneelen 1988; Bowman et al. 1997; Cernikova et al. 1983; Clonfero et al. 1989; Diette et al. 1983; Elovaara et al. 1995; Grimmer et al. 1997; Hansen 1993; Hecht et al. 2010; Heikkilä et al. 1995; Jongeneelen et al. 1985, 1988; Malkin et al. 1996; McClean et al. 2007; Ny et al. 1993; Persoons et al. 2020; Raulf-Heimsoth et al. 2008; Santella et al. 1994; Sarto et al. 1989; Van Rooij et al. 1993a, 1993b; van Schooten et al. 1994; Viau and Vyskocil 1995; Viau et al. 1995; Weston et al. 1994). For example, Jongeneelen et al. (1985) found a metabolite of pyrene (which is a constituent of coal tar creosote), 1-hydroxypyrene, in concentrations of 1–40 μg/g creatinine in urine samples taken from workers who handled approximately 2,400 g creosote/day. The amount of 1-hydroxypyrene detected in urine samples taken during the weekend was

less than that detected during the weekdays, when the exposure was presumably higher than on the weekends. No correlation was found between occupational exposure levels and urine levels, so it is not known whether urine metabolites specific to creosote could be detected following exposure to low levels of creosote. However, in another study, workers exposed to coal tar while asphalting roads with coal tar excreted 1-hydroxypyrene in their urine (Jongeneelen et al. 1988). In these workers, occupational exposure appeared to be related to the amount of 1-hydroxypyrene in the urine. Urinary 1-hydroxypyrene was also detected in study of 21 coal tar sealant workers (McCormick et al. 2022). The identification of 1-hydroxypyrene in the urine could serve as a method of biological monitoring of exposed workers, and possibly individuals living in the vicinity of hazardous waste sites where creosote has been detected following both short-and long-term exposure. However, because PAHs are ubiquitous in the environment, detection of PAH metabolites in the body tissues or fluids is not specific for exposure to creosote. PAH exposure can occur from a variety of sources, and there is no way to determine if creosote was the source.

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

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

3.3.2 Biomarkers of Effect

Coal Tar Products. The available genotoxicity data derived by *in vitro* techniques indicate that coal tar products such as coal tar creosote and coal tar pitch are indirect mutagens (i.e., requiring the presence of an exogenous mammalian metabolic system) and induce gene mutation in bacteria and mouse lymphoma cells. The mutagenicity of creosote and coal tar pitch observed in the conventional *S. typhimurium* assay is at least partially contributed to by the PAHs such as benzo[a]pyrene and benzanthracene. However, because these results are exclusively from *in vitro* tests and the limited genotoxicity tests conducted on urine obtained from humans exposed to creosote have been negative, or have been positive in instances

where exposure to other mutagens may have occurred, these changes cannot be considered specific biomarkers of effect caused by creosote, nor is it possible to determine whether the genotoxic effects result from either acute- or chronic-duration exposure to either low or high levels of coal tar creosote because all of the data were from *in vitro* studies. The same can be said for determination of chromosomal aberrations in peripheral lymphocytes from exposed humans (Bender et al. 1988; Sarto et al. 1989). Furthermore, because the mutagenicity of coal tar creosote is at least partially due to its PAH components, exposure to PAHs from other sources could produce the same results. Coal tar creosote exerts its acute toxic effects primarily via dermal exposure, causing architectural damage to the tissues with which it comes in contact. Therefore, burns and irritation of the skin and eyes are the most frequent manifestations of coal tar creosote toxicity following acute-duration dermal exposure to high levels. However, damage to the skin is not specific to creosote, and can be seen with other corrosive or photosensitizing agents. No other biomarkers (specific or otherwise) have been identified following exposure to coal tar creosote.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Coal Tar Products. The primary interactions known to occur between coal tar creosote and other substances involve the induction of cancer. Coal tar creosote is a complex mixture of organic substances consisting predominantly of liquid and solid aromatic hydrocarbons. Several of these components of coal tar creosote are known animal carcinogens as well as cocarcinogens, initiators, promoters, potentiators, or inhibitors of carcinogenesis (Haverkos et al. 2017). Pretreatment of male Fischer 344 rats with orally administered coal tar creosote resulted in urinary excretion of mutagenic metabolites of creosote and increased the bioactivation of orally administered 2,6-DNT to mutagenic metabolites, as measured in the Ames assay. Urinary excretion of mutagenic metabolites from rats pretreated with creosote and dosed with DNT at 1, 3, and 5 weeks peaked after 3 weeks and then declined by 33% after 5 weeks of treatment. The increase in urinary excretion of mutagenic metabolites was significantly greater than in rats that received only DNT at weeks 1 and 3, but not at week 5 (Chadwick et al. 1995).

As discussed in Section 2.19, coal tar creosote and several of its fractions are carcinogenic when applied to the skin of mice. Dermally applied creosote can also act as a tumor-initiating agent when applied prior to croton oil treatment and can enhance and accelerate tumor induction by benzo[a]pyrene. Thus, the risk of cancer following dermal exposure to creosote is likely to be enhanced when concurrent exposure to other potential co-carcinogens, tumor promoters, initiators, and potentiators occurs. Due to the ubiquitous nature of PAHs and other carcinogenic substances in the environment, particularly at hazardous waste

sites, the likelihood that these types of synergistic interactions with creosote will occur could be important in assessing potential hazards.

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

Pentachlorophenol and arsenical compounds are also used in wood preserving. For this reason, it is likely that they will be found with creosote at hazardous waste sites. However, there is no information available on the potential interactions of creosote with pentachlorophenol or arsenical compounds. In addition, PAHs undergo a weathering process in soils and sediment (EPA 2006). No specific information was identified to define how weathering affects interactions with other chemicals.