DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR CREOSOTE

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

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Peer reviewers for the third pre-public comment draft of the Toxicological Profile for Creosote were:

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Comments provided by Reviewer #1

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1. Relevance to Public Health

QUESTION: Do you agree with those effects known to occur in humans as reported in the text? If not, please explain why and provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

COMMENT 1: Yes.

RESPONSE: *No response needed.*

QUESTION: Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

COMMENT 2: Because of the way these discussions are organized it is not obvious which effects are observed only in animals. There is no reason to think, however, that effects such as developmental toxicity reported in animals could not be observed in humans, if human studies were conducted. I realize that human epidemiologic studies on reproductive effects are generally very limited in scope and number.

RESPONSE: *Discussions in Section 1.2 provide an overview of effects observed in humans and effects observed in animals. It is specifically noted if observations were reported in studies in humans and in animals. ATSDR agrees that very limited information is available in epidemiological studies on reproductive effects.*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain.

COMMENT 3: Generally agree, but coal tar shampoos are still widely marketed for dandruff control, this comes up later in the full text but could be mentioned here.

RESPONSE: *In Section 1.1, the following sentence was revised to include shampoos used for dandruff control.*

> There are also over-the-counter medications and shampoos containing low-dose solutions of coal tar to treat certain skin conditions like dandruff, eczema, and seborrheic dermatitis.

Minimal Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation? Please explain.

COMMENT 4: Agree, data on actual composition of these materials is highly variable.

RESPONSE: *No response needed.*

QUESTION: Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT 5: No comment.

RESPONSE: *No response needed.*

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature? If not, please suggest appropriate changes.

COMMENT 6: I agree that "The epidemiological database of studies examining associations between occupational exposure to creosote compounds and cancer is extensive…" and that there are several thorough assessments of carcinogenicity by IARC, NTP, etc. I caution against saying that "associations between occupational exposures to creosote compounds and cancer is not in dispute…" however. I'm sure that in our litigious country, there are legal cases going on today in which the evidence for carcinogenicity is in dispute. I say this because I have found that even for agents such as asbestos and benzene, it is unwise to assume that associations between exposures and health effects are truly settled in law. I suggest there be some alternative language to the effect that the evidence has been extensively summarized and reviewed, and the associations between exposures and cancer have uniformly (or consistently) been supported (or something like that).

Also in the following sentence (lines 24–25), please clarify whether the determinations of which were the important studies were made by IARC, or the authors of the profile.

In section 2.19, a question about the statement "These populations are exposed to many different chemicals and environmental stressors (e.g., heat, electromagnetic fields), in addition to components of creosote, which may have contributed to the observed cancer outcomes." Is this the conclusion reached in the ATSDR review, or does it reflect the conclusions of the authors of the individual studies? For example while the subjects in some of these studies were certainly exposed to heat, did the authors conclude that heat was a contributing cause of cancer?

RESPONSE: *The first comment above pertains to the following sentence in Section 2.19. "*Furthermore, based on the carcinogenicity assessments of conducted by HHS (NTP 2021), IRIS (1988, 1989), and IARC (2010, 2012a), associations between occupational exposures to creosote compounds and cancer is not in dispute*." This statement was revised as follows:*

> Furthermore, the carcinogenicity of creosote has been extensively reviewed in assessments of conducted by HHS (NTP 2021), IRIS (1988, 1989), and IARC (2010, 2012a); these reviews provide evidence of associations between occupational exposures to creosote compounds and cancer.

*The second part of the comment refers to the following sentence in Section 2.19. "*Therefore, the discussion of the cancer epidemiology that follows includes a tabular summary of the important studies

included in the IARC (2010, 2012a) and discussion of newer studies. *The sentence in Section 2.19 was revised as shown below.*

> Therefore, the presentation of the cancer epidemiology data that follows includes a tabular summary of the important studies identified by IARC (2010, 2012a) and a discussion of newer studies.

*The third part of the Reviewer's comment is on the following sentence in Section 2.19, "*These populations are exposed to many different chemicals and environmental stressors (e.g., heat, electromagnetic fields), in addition to components of creosote, which may have contributed to the observed cancer outcomes.*" The sentence was revised to state:*

> These populations are likely to have been exposed to many different chemicals, including components of creosote, which may have contributed to the observed cancer outcomes.

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)?

COMMENT 7: Yes.

RESPONSE: *No response needed.*

QUESTION: Were the major study limitations sufficiently described in the text without going into lengthy discussions?

COMMENT 8: Yes.

RESPONSE: *No response needed.*

QUESTION: If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT 9: Para 2.1 lines 20–22 states "U.S. coal tar plants in which coal tar creosote and coal tar were the main treatments used (exposure not evaluated)…" I do not have access to the article cited (Koppers Company 1981) but I wonder are these the main products made at these facilities (as opposed to the treatments used?)

RESPONSE: *The Reviewer's comment regarding the statement in Section 2.10 is correct. Coal tar creosote and coal tar were the main products made at these facilities. The sentence was revised.*

> In an industrial health survey of employees in nine U.S. coal tar plants in which coal tar creosote and coal tar were the main products made (exposure not evaluated), renal effects, including protein and cells in the urine, were noted in the employees examined (Koppers Company 1981).

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT 10: The studies mentioned appear to be adequately designed.

RESPONSE: *No response needed.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT 11: I don't have an opinion on this.

RESPONSE: *No response needed.*

QUESTION: Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

COMMENT 12: On p 11 of the introduction, the text states "Due to the complex nature of the coal tar and creosote compounds and concurrent occupational exposures, the available occupational studies are presented qualitatively without discussion of exposure concentrations." Later throughout the text, however, exposure levels are quantified (for example p 84 lines 13–18 describing the study of aluminum smelter workers by Fritisci); also quantitative exposure levels are cited extensively in section 5.7. This seems inconsistent.

RESPONSE: *The sentence referred to in the comment above is in Section 2.1. In response to the Reviewer's comment, the sentence in Section 2.1 was revised as follows.*

> Due to the complex nature of the coal tar and creosote compounds and concurrent occupational exposures, most of the available occupational studies are presented qualitatively without discussion of exposure concentrations. However, if exposure concentrations were reported, they are included in the discussion.

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT 13: None I am aware of.

RESPONSE: *No response needed.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

COMMENT 14: None I am aware of.

RESPONSE: *No response needed.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT 15: Yes.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT 16: Yes.

RESPONSE: *No response needed.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT 17: Yes.

RESPONSE: *No response needed.*

QUESTION: Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.

COMMENT 18: The discussion of the overall database of human epi studies should be revised. I did not check all the human studies in detail, but among those I am most familiar with (the coke oven studies by Lloyd and subsequent coauthors), there is information on death from all causes, heart disease, etc, in addition to cancers. My point then is that the discussions of the cohort mortality studies should be reconsidered to include information on deaths from heart disease, CNS, and respiratory diseases where these are reported.

RESPONSE: *The Reviewer's comment refers to Section 2.2. In response, the studies by Lloyd et al. (Lloyd 1971; Lloyd et al. 1970) and Redmond et al. (1972) were added to Table 2-5 in Section 2.2. In addition, columns were added to Table 2-5 for all-cause mortality and mortality due to all cancer (combined for all sites). Text discussing mortality due to all cancer and all-cause mortality for specific studies was added throughout Section 2.2. In addition, the following revised text was added to the beginning of Section 2.2*

> In this section, mortality due to all cancers (combined), all-cause mortality (including cancer), and noncancer causes, including diseases of the respiratory, cardiovascular, renal, and neurological systems are reviewed and discussed below; these studies are summarized in Table 2-5. Studies evaluating mortality due to specific cancer types are discussed in Section 2.19.

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

Toxicokinetics

QUESTION: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

COMMENT 19: Please see my suggestion on discussing the semi-volatile nature of these compounds in air.

RESPONSE: *The following sentence was added to Section 3.1.1 to address the Reviewer's comment.*

> 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).

QUESTION: Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

COMMENT 20: They appear to be presented but this is not my area of expertise.

RESPONSE: *No response needed.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT 21: These discussions seem to be adequate.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Please provide any relevant references.

COMMENT 22: The discussion seems to be adequate, the only additional point that could be raised is that children at be at risk of exposures taken-home by adult workers

RESPONSE: *The focus of Section 3.2 is on the potential health effects from exposures, not on the sources of exposure. The potential for exposures of children taken home by adult workers is addressed in Section 5.6 as follows.*

> There is also potential for family members of workers in industries manufacturing or using coal tar or creosote products to be unintentionally exposed to the constituents of these mixtures from contaminated items such as clothing or footwear.

QUESTION: Is there a discussion of populations at higher risk of susceptibility? Do you agree with the choice of populations? Please explain and provide any additional relevant references.

COMMENT 23: The discussion seems to be adequate.

RESPONSE: *No response needed.*

Biomarkers of Exposure and Effect

QUESTION: Are the biomarkers of exposure specific for the substance? Please explain.

COMMENT 24: The discussion seems to the adequate, given that the exposures are to complex mixtures, not individual substances.

RESPONSE: *No response needed.*

QUESTION: Are the biomarkers of effect specific for the substance? Please explain.

COMMENT 25: The discussion seems to the adequate, given that the exposures are to complex mixtures, not individual substances.

RESPONSE: *No response needed.*

Interactions with Other Chemicals

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? Please explain and provide any additional references.

COMMENT 26: Interactions are addressed, however there appears to be limited information available.

RESPONSE: *ATSDR agrees with the Reviewer that limited information is available on interactions of creosotes with other chemicals.*

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

COMMENT 27: Interactions are addressed, however there appears to be limited information available.

RESPONSE: *No response needed.*

Chapter 4. Chemical and Physical Information

QUESTION: Are any of the values or information provided in the chemical and physical properties tables wrong or missing? Please explain and provide any additional references.

COMMENT 28: Please see comment below

RESPONSE: *This is addressed in response to the following comment (see response to comment 29).*

QUESTION: Is information provided on the various forms of the substance? Please explain.

COMMENT 29: The semi-volatile nature of the creosote/coal tar mixtures, and their chemical components needs to be discussed. Section 4.2 would be a good place to address this, but it should also be mentioned in Section 3 on toxicokinetics, and Section 5 on Potential for human exposure. For example in Section 5 p183 line 3, the fact that higher molecular weight compounds exist in the particulate phase is mentioned, but the significance of this to inhalation exposures is not discussed. The partitioning of these semi-volatile compounds (SVOCs) between the vapor and particulate phase is an important consideration in air sampling methods, also in the inhalation toxicity of these compounds. There is an extensive literature on this, a good start would be to discuss the findings reported in:

Partitioning theory for respiratory deposition of semivolatile aerosols. Volckens J, Leith D. Ann Occup Hyg. 2003 Mar;47(2):157-64. doi: 10.1093/annhyg/meg015.PMID: 12582000; and

Impact of gas/particle partitioning of semivolatile organic compounds on source apportionment with positive matrix factorization. Xie M, Hannigan MP, Barsanti KC. Environ Sci Technol. 2014 Aug 19;48(16):9053-60. doi: 10.1021/es5022262. Epub 2014 Aug 8. PMID: 25083820

RESPONSE 30: *In Section 4.1, ATSDR added the following sentence:*

> The partitioning behavior of PAHs and other semi-volatile substances between the vapor and particulate phase in air is well understood (Eisenreich et al. 1981; Xie et al. 2014). In general, several of the low molecular weight constituents are semi-volatile and exist in air in the vapor-phase, while larger PAHs are less volatile and tend to exist in the particulate phase; this affects atmospheric transport, degradation, and deposition into the lungs (Volkens and Leith 2003).

Chapter 5. Potential for Human Exposure

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete?

COMMENT 31: Yes.

RESPONSE: *No response needed.*

QUESTION: Please explain and provide any additional relevant references. Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population?

COMMENT 32: Yes.

RESPONSE: *No response needed.*

QUESTION: Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites?

COMMENT 33: Yes.

RESPONSE: *No response needed.*

QUESTION: Do you know of other relevant information? Please provide references for added information.

COMMENT 34: No.

RESPONSE: *No response needed.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT 35: Please refer to my comment on question 2 above on vapor/particle partitioning.

RESPONSE: *ATSDR has added additional text in Section 5.4.2 under transformation and degradation:*
Rates for constituents in the atmosphere with low vapor pressures may be slowed because they will exist in the particulate phase and, therefore, undergo atmospheric oxidation and direct photolysis at slower rates as compared to substances that exist primarily in the vapor phase.

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT 36: This would be a good place to discuss the semi-volatile nature of many of the compounds of interest. This is relevant to the discussion of atmospheric concentrations in sections 5.3.1. and 5.3.2, also on Levels in the environment (5.5). Current air sampling methods for SVOCs such as EPA Methods TO-4A & TO-13A and NIOSH Method 5506 use two-stage sampling media that includes a filter to collect particles, and a sorbent material to collect vapors. Data collected historically that used only a filter, or a sorbent material undoubtedly underestimated actual atmospheric levels, and subsequent inhalation exposures.

RESPONSE: *In response to this comment, the following sentence was added to Section 5.1.*
Current air sampling methods for semi-volatile substances employ two-stage sampling media, which includes a filter to collect particles, and a sorbent material to collect vapors. Data collected historically using only a filter or a sorbent material most likely underestimated actual atmospheric levels and subsequent inhalation exposures.

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT 37: Yes, however as mentioned previously the possibility of take-home exposures to family members of workers in highly exposed workplaces should be mentioned.

RESPONSE: *ATSDR has added the following sentence to the discussion of general population exposure (Section 5.6).*

> There is also potential for family members of workers in industries manufacturing or using coal tar or creosote products to be unintentionally exposed to the constituents of these mixtures from contaminated items such as clothing or footwear.

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap? Please provide any relevant references.

COMMENT 38: No,

RESPONSE: *No response needed.*

QUESTION: Do you agree with the identified data needs? Please explain.

COMMENT 39: In the sections on Exposure Levels in Environmental Media, in terms of airborne levels of creosotes and constituents, the need for data that captures both the particulate, as well as the vapor fractions is needed. As mentioned earlier, historical ambient air and inhalation exposure levels usually measured one, but not both of these fractions (sorbent tubes collect vapors, filters collect particles), resulting in underestimates of actual exposures. Also, please see comment below.

RESPONSE: *In response to this comment, a statement was added to Section 6.2.*

> There is a data need to capture airborne levels of individual constituents of these mixtures and report the levels in both the vapor and particulate phases.

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion? Please note any bias in the text.

COMMENT 40: A point not so much on bias but on accuracy; the section Epidemiology and Human Dosimetry Studies states (P 205 L 5-6) that "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…" then a number of studies are cited. I'm not familiar with all these studies, but I know the citations to Bertrand, Lloyd, Mazumdar and Redmond are all studies of coke oven workers.

Later in this paragraph, are the statements "The few available industrial surveys and epidemiological studies are limited in their usefulness because of small sample size, short followup 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." This needs to be reconsidered, as at least the studies of coke oven workers (Lloyd, Mazumdar and Redmond) do not suffer from these limitations. Finally, these studies do not support the statement that "…coal tar creosote is a dermal irritant and a carcinogen following dermal exposure." as the exposures among the coke oven workers included both dermal and inhalation exposures.

RESPONSE: *In response to the first part of the comment regarding a sentence in Section 6.2, the sentence was revised to delete references to occupational studies that are not on populations in the wood-preserving or construction industries.*

> Most of the available information on the effects of coal tar creosote in humans comes from occupational studies in the wood-preserving and construction industries (Karlehagen et al. 1992; Kerr et al. 2000; Persson et al. 1989; Stern et al. 2000)

The second part of the comment refers to a sentence in Section 6.2. This specific sentence refers to workers in the in the wood-preserving and construction industries. Therefore, studies on coke oven workers (e.g., Lloyd, Mazumdar and Redmond) or other workers were not added to this sentence.

Chapter 7. Regulations and Guidelines

QUESTION: Are you aware of any additional regulations or guidelines that should be included? Please provide citations.

COMMENT 41: Table 7 1. Regulations and Guidelines Applicable to Coal Tar Creosote, Coal Tar, Coal Tar Pitch, and Coal Tar Pitch Volatiles seems incomplete. Among the occupational standards and guidelines, the ACGIH threshold limit values should be included. OSHA has organized this information nicely at https://www.osha.gov/annotated-pels/table-z-1

RESPONSE: *The website included in the comment above was reviewed. It presents permissible exposure limits (PELs) for coal tar pitch volatiles, but does not include any on coal tar creosote, coal tar, or coal tar pitch. The PEL for coal tar pitch volatiles is already included in Table 7-1. ATSDR does not include the threshold limit values (TLVs) if there are Occupational Safety and Health Administration (OSHA) or National Institute for Occupational Safety and Health (NIOSH) values. This is in accordance with ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov).*

Appendices

QUESTION: Please provide any comments on the content, presentation, etc. of the included appendices.

COMMENT 42: No comments

RESPONSE: *No response needed.*

Annotated Comments

The Reviewer provided annotated comments on the toxicological profile. Many of these comments are identical or nearly identical to specific comments above. This section focuses on comments not previously addressed.

COMMENT 43: (Section 1.1, page 2, line 17) I'm not sure that combustion is the right term to use here, consider using the term pyrolysis to describe the process of heating coal in an oxygen-deficient environment

RESPONSE: *The comment above refers to the following sentence in Section 1.1. "*In addition, the composition of each, although referred to by specific name (e.g., coal tar creosote), is not consistent, and

the components and properties of the mixture depend on the temperature of the destructive distillation (carbonization) and on the nature of the carbon-containing material used as a feedstock for combustion.*"* *In response, the word combustion was replaced by pyrolysis.*

> In addition, the composition of each, although referred to by specific name (e.g., coal tar creosote), is not consistent, and the components and properties of the mixture depend on the temperature of the destructive distillation (carbonization) and on the nature of the carbon-containing material used as a feedstock for pyrolysis.

COMMENT 44: (Section 2.1, page 10, line 24) Same comment as before on calling this combustion, this term is usually applied to processes that involve oxidation

RESPONSE: *The comment above pertains to the following sentence in Section 2.1. "*Another factor to consider when evaluating health effect data for creosote mixtures is that the composition of a particular creosote mixture, although referred to by specific name (e.g., wood creosote or coal tar creosote), is not consistent because the components and properties of the mixture depend on the temperature of the destructive distillation (carbonization) and on the nature of the carbon-containing material used as a feedstock for combustion*." The sentence was revised to change combustion to pyrolysis.*

> Another factor to consider when evaluating health effect data for creosote mixtures is that the composition of a particular creosote mixture, although referred to by specific name (e.g., wood creosote or coal tar creosote), is not consistent because the components and properties of the mixture depend on the temperature of the destructive distillation (carbonization) and on the nature of the carbon-containing material used as a feedstock for pyrolysis.

COMMENT 45: (Section 2.2, page 65, line 6) Reconsider, this isn't exactly correct. Look for example at Lloyd 1970, there were 69 deaths observed from malignant neoplasms among coke plant workers, while these coke plant workers had 73 deaths observed due to heart disease.

RESPONSE: *The comment above pertains to the following sentence in Section 2.2. "*Increased mortality observed in occupational studies has been primarily linked to cancer; these studies are discussed in Section 2.19. *The discussion of mortality in Section 2.2 was revised to include all cancer mortality and all-cause mortality. Columns were added to Table 2-5 for all-cause mortality and mortality due to all cancer (combined for all sites) and text discussing mortality due to all cancer and all-cause mortality for specific studies was added throughout Section 2.2. In addition, the specific sentence noted in the Reviewer's comment was deleted and the following revision was made.*

> In this section, mortality due to all cancers (combined), all-cause mortality (including cancer), and noncancer causes, including diseases of the respiratory, cardiovascular, renal, and neurological systems are reviewed and discussed below; these studies are summarized in Table 2-5. Studies evaluating mortality due to specific cancer types are discussed in Section 2.19.

COMMENT 46: (Section 2.2, page 65, line 6) I don't quite follow the point here, a lot of the studies discussed include information on death from all causes, in addition to specific causes like CVS, cancer, etc.

RESPONSE: *The Reviewer's comment is in reference to the sentence in Section 2.2:* "Several studies also evaluated associations from occupational exposure and death from all causes, but because cancer

mortality is a major contributor to all-cause mortality, these studies are not discussed." *This sentence was deleted from Section 2.2 and the following text was added.*

> In this section, mortality due to all cancers (combined), all-cause mortality (including cancer), and noncancer causes, including diseases of the respiratory, cardiovascular, renal, and neurological systems are reviewed and discussed below; these studies are summarized in Table 2-5. Studies evaluating mortality due to specific cancer types are discussed in Section 2.19.

COMMENT 47: (Section 2.2, page 67, line 5) Lloyd?

RESPONSE: *The comment above pertains to the following sentence in Section 2.2. "*However, studies examining 888 Norwegian coke workers (Bye et al. 1998) and 5,321 coke oven workers in Pennsylvania (Constantino et al. 1995) found no associations between exposure and cardiovascular or respiratory disease mortality.*" Per the Reviewer's comment, results of studies by Lloyd et al. (Lloyd 1971; Lloyd et al. 1970) and Redman et al. (1972) were added to this discussion as shown below.*

> However, studies examining 888 Norwegian coke workers (Bye et al. 1998) and up to 5,321 coke oven workers in the steel industry in Pennsylvania followed over a 30-year period (Constantino et al. 1995; Lloyd 1971; Lloyd et al. 1970; Redmond et al. 1972) found no associations between exposure and cardiovascular or respiratory disease mortality.

COMMENT 48: (Section 2.4, page 73, line 16) Discusses exposures quantitatively, contradicts earlier statement about qualitative exposure information.

RESPONSE: *The Reviewer's comment in Section 2.4 refers to the following sentence in Section 2.1: "*Due to the complex nature of the coal tar and creosote compounds and concurrent occupational exposures, the available occupational studies are presented qualitatively without discussion of exposure concentrations.*" In response to the Reviewer's comment, the sentence in Section 2.1 was revised as follows.*

> Due to the complex nature of the coal tar and creosote compounds and concurrent occupational exposures, most of the available occupational studies are presented qualitatively without discussion of exposure concentrations. However, if exposure concentrations were reported, they are included in the discussion.

COMMENT 49: (Section 2.19, page 101, line 25) Cancer epi limited to those studies cited by IARC, is it possible to at least mention any studies that were not included even if they are not comprehensively reviewed?

RESPONSE: The Reviewer's comment is on the sentence in Section 2.19, "Therefore, the discussion of the cancer epidemiology that follows includes a tabular summary of the important studies identified by IARC (2010, 2012a) and discussion of newer studies." The profile includes discussion of more recent cancer studies that were published after the IARC (2010, 2012a) assessments. These studies include Alicandro et al. (2016), Poynter et al. (2017), and Roelofzen et al. (2010).

COMMENT 50: (Section 3.1.1, page 122, line 14) Here and elsewhere some background about the semi-volatile nature of these compounds would be useful to the interpretation of these exposure measurements

RESPONSE: *This comment refers to the interpretation of the results of personal air monitoring of potroom workers (Ny et al. 1993) in Section 3.1.1. The summary of the Ny et al. (1993) study was revised to state that the vapor-phase measurements would detect only the volatile and semi-volatile constituents of the exposure material.*

> 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.

In addition, a sentence was added to the beginning of Section 3.1.1:

> 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).

COMMENT 51: (Section 3.3.1, page 147, line 15) The Reviewer commented "from".

RESPONSE: *The Reviewer's comment suggests that the word "form" should be replaced with the word "from" in the following sentence. "*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)*." The correct word is "form." Adducts form between PAHs and DNA.*

COMMENT 52: (Section 5.1, page 164, line 15) Clarify which century, since…?

RESPONSE: *The Reviewer requests clarification for the following sentence in Section 5.1. "*Coal tar creosote has been widely used as a wood-treatment pesticide since the turn of the century*." The sentence was revised to specify the 20th century.*

> Coal tar creosote has been widely used as a wood-treatment pesticide since the turn of the 20th century.

COMMENT 53: (Section 5.1, page 165, line 19) Is there anything in the literature about the possibility that children may exposed by compounds that adults take-home from their workplace, for example on work clothes?

RESPONSE: *In response to this comment, sentences were added to Sections 5.1 and 5.6.*

> *The following sentence addressing exposure to children was added to the bullet points at the beginning of Section 5.1.*
> Family members of workers in industries using these products could be potentially exposed from contaminated work clothing or footwear.
>
> *The following sentence addressing exposure to children was added to Section 5.6.*
> There is also potential for family members of workers in industries manufacturing or using coal tar or creosote products to be unintentionally exposed to the constituents of these mixtures from contaminated items such as clothing or footwear.

COMMENT 54: (Section 5.4.1, page 180, line 19) Elaborate here on the semi-volatile nature of these materials.

RESPONSE: *The Reviewer's comment pertains to the following sentence in Section 5.4.1. "*Coal tar creosote, coal tar, and coal tar pitch are more complex chemical mixtures." *This sentence was revised to add information on the semi-volatile nature of these mixtures.*

> Coal tar creosote, coal tar, and coal tar pitch are more complex chemical mixtures; however, the lower molecular weight substances are also semi-volatile and tend to exist in the vapor phase in the ambient atmosphere.

COMMENT 55: (Section 5.7, page 197, line 14) The Reviewer commented "creatinine".

RESPONSE: *The Reviewer's comment indicates that creatinine, not creatine, is the correct word to be used in the following sentence in Section 5.7. "*A urinary concentration of 2.3 µmol/mol creatine was equated with the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) of 0.2 mg/m^3 for coal tar pitch volatiles, and consequently with the relative risk for lung cancer of approximately 1.3 for a group of exposed workers.*" The Reviewer is correct; the sentence was revised to replace creatine with creatinine.*

> A urinary concentration of 2.3 µmol/mol creatinine was equated with the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) of 0.2 mg/m^3 for coal tar pitch volatiles, and consequently with the relative risk for lung cancer of approximately 1.3 for a group of exposed workers.

COMMENT 56: (Section 5.7, page 197, line 14) Consider rewording, this is a very long sentence

RESPONSE: *The sentence in Section 5.7 referred to in the comment above is, "*Although an empirical relationship between the biomarker, 1-hydroxypyrene, and relative cancer risk in an exposed group may be determined, because creosote constituents vary from source to source, and because the carcinogenic PAH fraction and the routes of exposure will also vary, the health risks related to exposure to coal tar creosote versus coal tar pitch volatiles versus coal tar will differ between exposed groups such as creosote and coke oven workers (Viau et al. 1995).*" The sentence was revised.*

> An empirical relationship between the biomarker, 1-hydroxypyrene, and relative cancer risk in an exposed group may be determined because creosote constituents vary from source to source. However, because the carcinogenic PAH fraction and the routes of exposure will also vary, the health risks related to exposure to coal tar creosote versus coal tar pitch volatiles versus coal tar will differ between exposed groups such as creosote and coke oven workers (Viau et al. 1995).

COMMENT 57: (Section 5.7, page 198, line 2) The Reviewer commented "creatinine".

RESPONSE: *The Reviewer's comment indicates the creatinine, not creatine, is the correct word to be used in the following sentence in Section 5.7. "*The respective pre- and postshift urinary excretion levels of 1-hydroxypyrene for coke oven workers were 0.89 and 2.47 µmol/mol creatine; for asphalt pavers, respective levels were 1.35 and 1.76 µmol/mol creatine.*" The Reviewer is correct; the sentence was revised to replace creatine with creatinine.*

> The respective pre- and postshift urinary excretion levels of 1-hydroxypyrene for coke oven workers were 0.89 and 2.47 µmol/mol creatinine; for asphalt pavers, respective levels were 1.35 and 1.76 µmol/mol creatinine.

COMMENT 58: (Section 6.2, page 198, line 15) I don't think the studies support this.

RESPONSE: *The comment above pertains to the following sentence in Section 6.2. "*Despite their inadequacies, studies in humans suggest that coal tar creosote is a dermal irritant and a carcinogen following dermal exposure.*" In response to this comment, the indicated sentence was deleted from the profile.*

Comments provided by Reviewer #2

GENERAL COMMENTS

COMMENT 1: This document presents a great many studies of the potential toxicity of creosote complex mixtures. A comprehensive survey of the tests of toxicity of creosote are presented for a wide spectrum of organs, life stages, biologic functions and diseases. An excellent job was done with this document. Some modest suggestions are made for improvement.

RESPONSE: *ATSDR appreciates the comment from the Reviewer.*

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1. Relevance to Public Health

QUESTION: Do you agree with those effects known to occur in humans as reported in the text?

COMMENT 2: Yes.

RESPONSE: *No response needed.*

QUESTION: Are the effects only observed in animals likely to be of concern to humans?

COMMENT 3: Yes, experimental animal studies are valuable in a variety ways. Cause and effect relationships can determined with randomized assortment of subjects to different treatment groups. Exact dose-effect functions can be determined in the absence of potentially confounding exposures. Mechanisms of toxicity can be more completely determined. And finally, human toxicity can be predicted before new chemicals are introduced.

RESPONSE: *No response needed.*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain.

COMMENT 4: Yes.

RESPONSE: *No response needed.*

Minimal Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation?

COMMENT 5: Deriving a MRL for creosote is quite difficult because not only is it a complex mixture of potential toxicants by the complex mixture differs in important ways across differ creosote examples.

RESPONSE: *No response needed.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor?

COMMENT 6: Agree

RESPONSE: *No response needed.*

QUESTION: Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT 7: (Section 1.2) Throughout, it is a mistake to dichotomize studies into those that do and do not fund significant effects. As statistics know truth does not begin or end at $p<0.05$. More formal meta-analyses are needed to incorporate over magnitude of effect and where statistical and biologically significant effects are seen in a body of research. Having some studies detect significant effects and others did not detect significant effects does not in itself constitute inconsistent findings. A modest effect can be intermittently detected a statistically significant. More formal meta-analysis can help resolve this. Also, it is important to determine the integrity of the control groups in the studies. When extraneous factors are not well controlled there can be large variability in the control group which if pronounced can greatly limit the ability to detect significant effects in exposed groups.

Overall, there is a need to document control means and variability and calculate deviation that would be required to detect a significant difference from controls.

More insight can be gained into the toxicity of creosote by accessing the considerable literature concerning the toxicity of the chemicals within this complex mixture. Comparing the toxicity of the known "bad actors" in the mixture with the toxicity of the mixture itself can help determine which additional chemicals may be driving the toxicity of the mixture.

RESPONSE: *ATSDR agrees with the Reviewer that statistical significance, determined by a selected type 1 error (e.g., p-value <0.05), does not equate with biological significance or causality. Many different factors must be considered in determining the power (affected by variance in control and treatment groups) and strengths of the study design. However, a detailed evaluation of each study or a* de novo *meta-analysis of these studies is beyond the scope of the ATSDR Toxicological Profile, which is intended to identify and summarize the most pertinent available literature on health effects of creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. This is in accordance with ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov).*

*Regarding the Reviewer's statement that "*more insight can be gained into the toxicity of creosote by accessing the considerable literature concerning the toxicity of the chemicals within this complex mixture,*" ATSDR agrees that this additional information would be informative.* ATSDR's approach to the evaluation and interpretation of the toxicology of the "whole" mixture includes any joint toxic actions of the chemicals in the mixture (e.g., additive or other interactions) and how they influence the overall toxicity of the mixture. Although 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, it is also understood that the toxicity of the individual components may not be representative of the actual toxicity

of the mixture, therefore the health effects of the individual components (e.g., PAHs, phenol, or others) are not discussed in detail in this profile, but are discussed in the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons. The intent of this profile is to discuss the creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. More information on ATSDR's approach to evaluation of chemical mixtures can be found in ATSDRs *Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors (Update) (cdc.gov)*. Additional information on the scope and development of toxicological profiles can be found in ATSDR's *Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov)*.

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature? If not, please suggest appropriate changes.

In response to this question, the Reviewer provided the following specific comments.

COMMENT 8: (Section 2.3, page 70, lines 6–7) Decreased body weight due to decreased food consumption should not be dismissed as not being a toxic effect. Toxicant effects on sensory systems and consummatory function helps define the mechanism of toxicity.

RESPONSE: *In the comment above, the Reviewer is referring to the following sentence in Section 2.3.* "Note that for dietary exposure studies, decreased body weight and body weight gain is frequently accompanied by decreased food consumption due to palatability; in these cases, effects on body weight are not considered to be an adverse effect of creosote compounds." *In the absence of data identifying the mechanism of decreased food consumption or specific effects of creosote on sensory systems, ATSDR considers decreased body weight gain accompanied by decreased food consumption to not be adverse (e.g., not considered to be a LOAEL) when palatability may be an issue, as is the case for creosote. Should data become available to identify the underlying cause for decreased consumption of food containing creosote, this would be included in the next update of the creosote profile. To provide additional clarity in the profile, the following sentence was added to the beginning of Section 2.3.*

> In the absence of information that decreased food consumption is due to a chemical-specific adverse effect rather than due to palatability alone, effects on body weight accompanied by decreased food consumption are not considered to be an adverse effect (e.g., not a LOAEL) of oral exposure to creosote compounds.

COMMENT 9: (Section 2.3, page 70, lines 11–12) The finding that with weight deficit there was no difference in extra-gestational body weight is concerning, because exposure did decrease the gestational body weight gain.

RESPONSE: *The Reviewer's comment is referring to the following sentence in Section 2.3:* "Decreased body weight (11% reduction) was observed in an acute-duration, gestational exposure study in female rats exposed to 660 mg/m^3 of a coal tar aerosol for 6 hours/day on GDs 12–16, but there was no difference in extragestational body weight (maternal body weight–gravid uterus/fetal weight) compared to controls (Springer et al. 1982)." *ATSDR agrees that decreased gestational body weight is "concerning." Per ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov),* a reduction in body weight (non-gravid, extragestational, and gestational) of 10-19% is classified as a LOAEL, with decreases of ≥20% classified as a serious LOAEL. Given this guidance, the decreased gestational weight gain is classified as a LOAEL. *The reduction in body weight gain for this Springer et al. (1982) study is listed as a LOAEL in the LSE table (Table 2-1).*

COMMENT 10: (Section 2.3, page 71, lines 4–5) Coal tar exposure induced decreases in food consumption is not a confound but a mechanism for the decreases in body weight.

RESPONSE: *The comment above refers to the following statement in Section 2.3:* "Dietary creosote studies examining body weight often have confounded results due to differences in food consumption by the animals, particularly at the higher coal tar doses." *This sentence was deleted from the profile. The following sentence was added to the beginning of Section 2.3.*

> In the absence of information that decreased food consumption is due to a chemical-specific adverse effect rather than due to palatability alone, effects on body weight accompanied by decreased food consumption are not considered to be an adverse effect (e.g., not a LOAEL) of oral exposure to creosote compounds.

COMMENT 11: (Section 2.3, page 71, lines 32–33) Effects of chemical exposures on sensory perception can indeed produce adverse effects as seen here with reduced weight.

RESPONSE: *The comment above pertains to the following sentence in Section 2.3: "*Body weight gain was decreased in rats given 163 (males) or 210 (females) mg/kg/day beechwood creosote, and in mice given 465 (males) or 134 (females) mg/kg/day beechwood creosote in feed for 3 months; however, this is not considered adverse because decreased food consumption due to palatability was also observed (Miyazato et al. 1981)." *The sentence was revised as follows:*

> Body weight gain was decreased in rats given 163 (males) or 210 (females) mg/kg/day beechwood creosote and in mice given 465 (males) or 134 (females) mg/kg/day beechwood creosote in feed for 3 months; however, as noted earlier in Section 2.3, this is not considered adverse because decreased food consumption, most likely due to palatability alone, was also observed (Miyazato et al. 1981).

As noted in an earlier comment, in the absence of data identifying the mechanism of decreased food consumption or specific effects of creosote on sensory systems, ATSDR considers decreased body weight gain to not be adverse (e.g., not a LOAEL) when palatability alone may be an issue, as is likely the case for creosote. The following sentence was added to the beginning of Section 2.3.

> In the absence of information that decreased food consumption is due to a chemical-specific adverse effect rather than due to palatability alone, effects on body weight accompanied by decreased food consumption are not considered to be an adverse effect (e.g., not a LOAEL) of oral exposure to creosote compounds.

COMMENT 12: (Section 2.4, page 73, lines 6–7) Was there any evidence for increased exposure to these other toxicants in the workers exposed to coal tar or is this just speculation?

RESPONSE: *The Reviewer commented on the following statement in Section 2.4: "*However, the relationship between exposure to coal tar and adverse respiratory effects is potentially confounded by the possibility that the subjects were also exposed to other chemicals and cigarette smoke (Koppers Company 1979)."

This text was revised for clarity as follows:

> However, the relationship between exposure to coal tar and adverse respiratory effects is uncertain due to potential confounders, including possible co-exposures to other chemicals and cigarette smoke (Koppers Company 1979).

COMMENT 13: (Section 2.4, page 73, lines 16–18) But these results were dose-related, just not in a linear fashion. Even in a linear dose-effect function the lowest exposure quartile would commonly be expected to have the least or no effect. As to the highest quartile, yes it would commonly be expected that it would show the greatest effect but there are reasons why it may not, including increased use of medical treatments in that group or increased days taken off of work or other pathological effect that could limit the expression of the functions measured. In any case it is important to know if there was a significant drop-off between the 3rd and 4th quartiles or was this just a case of variability due to uncontrolled factors having some quartiles be just above or below the threshold for significance.

RESPONSE: *The Reviewer's comment refers to the following sentences in Section 2.4: "*Stratification of exposure by quartiles (Q) showed an increased risk of wheeze in Q2 and Q3 and chest tightness in Q2 and Q3 at cumulative exposures of 0.007–0.017 (Q2) and 0.017–0.11 mg/m^3 years (Q3), respectively; however, these results do not display a dose-response trend, with effects dropping off at the highest quartile of exposure. No association was observed in the other two quartiles (Q1: <0.007 mg/m^3 years; Q4: >0.11 mg/m^3 years)." *The study report does not provide sufficient information to determine the reason for the drop off in response at the highest exposure quartile. For example, the number of workers included in each quartile is not reported. If there was a substantial decrease in the number of workers evaluated in Q4, the power to detect effects may have been decreased. Thus, it is not possible to determine if the drop-off between Q3 and Q4 was due to uncontrolled factors. The sentence noted above was revised to delete the statement that the results do not display a dose-response trend.*

> Stratification of exposure by quartiles (Q) showed an increased risk of wheeze in Q2 and Q3 and chest tightness in Q2 and Q3 at cumulative exposures of 0.007–0.017 (Q2) and 0.017–0.11 mg/m^3 years (Q3), respectively. No association was observed in the other two quartiles (Q1: <0.007 mg/m^3 years; Q4: >0.11 mg/m^3 years).

COMMENT 14: (Section 2.4, page 73, lines 28–29) It is the mechanism that is uncertain, not the toxicological significance.

RESPONSE: *The Reviewer commented on the following sentence in Section 2.4: "*A 19% increase in relative lung weight was reported for female rats exposed to 660 mg/m^3 of a coal tar aerosol on GDs 12–16, but histopathology was not conducted; therefore, the toxicological significance of this finding is uncertain (Springer et al. 1982)." *It is ATSDR's practice that to determine the toxicological significance of change in organ weights, additional assessments, such as histopathology or organ function, are needed. The sentence was revised as follows.*

> A 19% increase in relative lung weight was reported for female rats exposed to 660 mg/m^3 of a coal tar aerosol on GDs 12–16, but histopathology and pulmonary function were not assessed; therefore, insufficient information is available to determine the toxicological significance of this finding (Springer et al. 1982).

COMMENT 15: (Section 2.5, page 75, lines 4–7) Was there evidence that these employees were exposed to greater amounts of cigarette smoke and other chemicals than the reference group? Otherwise this is just speculation.

RESPONSE: *The Reviewer's comment pertains to the following sentence in Section 2.5:* "The ability to relate cardiovascular effects to coal tar exposure was potentially confounded by the possibility that the subjects were also exposed to other chemicals such as pentachlorophenol and cigarette smoke, and there was a lack of medical history (Koppers Company 1979)." *In response to this comment, the sentence was revised for clarity.*

The ability to relate cardiovascular effects to coal tar exposure is challenging due to the lack of information on smoking, medical history, and possible exposure to other chemicals in the workplace history (Koppers Company 1979).

COMMENT 16: (Section 2.6, page 76, lines 1–2) Were there any safety studies for approval of this pharmaceutical use of wood creosote?

RESPONSE: *The comment by the Reviewer refers to the following sentence in Section 2.6*: "Pharmaceutical use of wood creosote derived from the processing of beechwood is used as a "gastric sedative," a gastrointestinal antiseptic, and as an antidiarrheal agent (Kuge et al. 2004; Ogata et al. 1993)." *ATSDR did not identify any specific safety studies that were conducted for approval of wood creosote as a gastric sedative. However, as discussed in Section 2.15, tolerability studies by Kuge et al. (2003a, 2003b) reported adverse neurological effects. The additional Kuge et al. (2003a, 2003b) studies were added to the references listed in this sentence in Section 2.6.*

Pharmaceutical use of wood creosote derived from the processing of beechwood is used as a "gastric sedative," a gastrointestinal antiseptic, and an antidiarrheal agent (Kuge et al. 2003a, 2003b, 2004; Ogata et al. 1993).

COMMENT 17: (Section 2.10, page 84, lines 27–29) As mentioned above, unless there is documented increase cigarette smoking or other relevant chemicals exposures this is merely speculation.

RESPONSE: *The Reviewer commented on the following sentence in Section 2.10: "*The ability to interpret these results is potentially confounded by the possible exposure to other chemicals and cigarette smoke.*" In response to this comment, the sentence was revised for clarity.*

The ability to determine the relationship between exposure and possible renal effects is challenged due to the lack of information on smoking, medical history, and possible exposure to other chemicals in the workplace history in the Koppers Company (1979) report.

COMMENT 18: (Section 2.11, page 87, lines 4–5) If exposures are unknown, it is just speculation and not a limitation.

RESPONSE: *The comment above pertains to the following sentence in Section 2.11: "*These studies are limited due to their reliance on self-reported health effects and potential confounding by unknown co-exposures.*" In response to this comment, the sentences were revised as follows.*

These studies are limited due to their reliance on self-reported health effects. In addition, no information was provided on the possible co-exposures to other chemicals.

COMMENT 19: (Section 2.13, page 90, lines 6–12) Have there been no studies on creosote effects on blood levels of these hormones?

RESPONSE: *The Reviewer's comment refers to the introductory paragraph in the introduction to animal studies in Section 2.13: "*Several studies have identified changes to weights of endocrine organs, but effects are not consistently observed. In addition, due to the lack of histopathological and functional assessments or observations, the toxicological significance of changes to organ weights cannot be determined." *No information on the effects of creosote on endocrine hormone levels was identified. The following revision was made to note this lack of information.*

In addition, due to the lack of histopathological and functional assessments or observations, and endocrine hormone levels, the toxicological significance of changes to organ weights cannot be determined.

COMMENT 20: (Section 2.14, page 104, lines 3–5) Are there any human or animal studies on creosote effects on autoimmune disorders?

RESPONSE: *The comment above pertains to the following sentences in Section 2.14: "*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)"; *and* "Animal studies have provided evidence of weight and morphological changes in lymphoreticular tissues following exposure to coal tar (Hackett et al. 1984; Zangar et al. 1989), but no information regarding changes in the immune system function have been reported." *No studies on the potential effects of creosote on autoimmune disorders in humans or animals were identified. The sentences were added/revised as shown below.*

No additional information on immune function or autoimmune disorders in humans was identified.

Animal studies have provided evidence of weight and morphological changes in lymphoreticular tissues following exposure to coal tar (Hackett et al. 1984; Zangar et al. 1989), but no information regarding changes in the immune system function, including autoimmune disorders, have been reported.

COMMENT 21: (Section 2.15, page 104, lines 29–34) There is a relevant animal literature concerning neurobehavioral effects of components of creosote especially benzo[a]pyrene.

RESPONSE: *The Reviewer provided the above general comment on the following paragraph in Section 2.15:* Animal Studies. Similar to human studies, animal studies have shown that neurotoxicity may be the first sign of creosote exposure. Although brain weight changes were reported in several studies, other studies have reported no changes, suggesting that brain weight changes are not likely related to creosote exposure. Studies on the neurological effects of creosote compounds include intermediate-duration inhalation studies on coal tar aerosols, and acute-, intermediate-, and chronic-duration oral studies on wood creosotes.

ATSDR acknowledges that there is a relevant and informative animal literature on the neurobehavioral effects of individual chemical components of creosote, including benzo[a]pyrene. ATSDR's approach to the evaluation and interpretation of the toxicology of the "whole" mixture includes any joint toxic actions of the chemicals in the mixture (e.g., additive or other interactions) and how they influence the overall toxicity of the mixture. Although 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, it is also understood that the toxicity of the individual components may not be representative of the actual toxicity of the mixture, therefore the health effects of the individual components (e.g., PAHs, phenol, or others) are not discussed in detail in this profile, but are discussed in the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons. The intent of this profile is to discuss the creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. More information on ATSDR's approach to evaluation of chemical mixtures can be found in ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov) and Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors (Update) (cdc.gov).

COMMENT 22: (Section 2.15, page 94, line 3) Is this locomotor activity?

RESPONSE: *The Reviewer's comment pertains to the following sentence in Section 2.15: "*In a series of acute inhalation toxicity studies, male and female rats exposed to creosote aerosol ≥600 mg/m^3 for 4 hours exhibited decreased activity immediately after exposure and throughout a 2-week follow-up period (EPA 1994)*." The decrease in activity was based on cage-side observations. Although the study report does not explicitly state that this is a decrease in locomotor activity, this is assumed. The sentence was revised to provide more clarity.*

> In a series of acute inhalation toxicity studies, male and female rats exposed to creosote aerosol ≥600 mg/m^3 for 4 hours exhibited decreased activity (based on cage-side observations) immediately after exposure and throughout a 2-week follow-up period (EPA 1994).

COMMENT 23: (Section 2.15, page 94, line 15) Specify what was measured.

RESPONSE: *The comment above refers to the following sentence in Section 2.15:* " In a series of acute dermal toxicity studies, application of 2,000 mg/kg creosote did not produce clinical signs of neurotoxicity in male and female rabbits (EPA 1994)." *In the referenced study, assessments of neurotoxicity were based on cage-side observations. The sentence was revised to specify this.*

> In a series of acute dermal toxicity studies, application of 2,000 mg/kg creosote did not produce clinical signs of neurotoxicity (based on cage-side observations) in male and female rabbits (EPA 1994).

COMMENT 24: (Section 2.17, page 188, lines 32–33) What of studies of the effects of development to creosote or its principal components on neurobehavioral development of the offspring?

RESPONSE: *The comment above pertains to the following sentence in Section 2.17: "*Studies in rats and mice have demonstrated developmental toxicity following exposure to coal tar by all routes of administration (see **Error! Not a valid bookmark self-reference.**)*." No studies evaluating the neurodevelopmental effects of creosote were identified. ATSDR recognizes that the neurodevelopmental effects of the principal components of creosote have been studied, and that this additional information would be informative. ATSDR's approach to the evaluation and interpretation of the toxicology of the "whole" mixture includes any joint toxic actions of the chemicals in the mixture (e.g., additive or other interactions) and how they influence the overall toxicity of the mixture. Although 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, it is also understood that the toxicity of the individual components may not be representative of the actual toxicity of the mixture, therefore the health effects of the individual components (e.g., PAHs, phenol, or others) are not discussed in detail in this profile, but are discussed in the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons. The intent of this profile is to discuss the creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. More information on ATSDR's approach to evaluation of chemical mixtures can be found in ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov) and Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors (Update) (cdc.gov).*

COMMENT 25: (Section 2.20, page 96, line 6) This seems to be the most consistent and prominent effect which is key for carcinogenesis as well as reproduction and development. It should be featured more prominently in the introduction and conclusions.

RESPONSE: *The Reviewer's comment is in reference to the following sentence: "*Numerous studies provide consistent evidence that exposure to coal tar is genotoxic.*" In response, the following was added to Sections 1.2 and 2.1.*

In addition, numerous studies provide consistent evidence that exposure to coal tar is genotoxic.

COMMENT 26: (Section 3.1.1, page 123, line 9) Specify which PAHs.

RESPONSE: *The Reviewer's comment requests additional information on the identity of the PAHs studied in the following sentence in Section 3.1.1: "*PAHs extracted from coal fly ash were 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 sentence was revised to specify the specific PAH as shown below.*

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).

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature?

COMMENT 27: Yes, but see above notes.

RESPONSE: *Comments in the above notes have been addressed, as indicated in respective responses above.*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT 28: Generally, this is fine. See specific notes above.

RESPONSE: *Comments in the above specific notes have been addressed, as indicated in respective responses above.*

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT 29: The necessity of determining the limits of sensitivity imposed by control group variability should be addressed.

RESPONSE: *ATSDR agrees with the Reviewer that variance in the response observed in the control group will affect the power of a study to detect statistically significant differences between control and treatment groups. However, in general, ATSDR does not evaluate statistical power of the studies reported in ATSDR Toxicological Profiles as it would require a much more detailed analysis of each study than needed to achieve the objectives of Toxicological Profiles, which is to identify and summarize*

the pertinent literature on health effects. The profile is written in accordance with ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov).

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT 30: Rodent models are very appropriate for helping to understand toxicity. There are complementary models that can help inform as well, for example zebrafish models.

RESPONSE: *ATSDR appreciates the Reviewer's comment above regarding consideration of non-mammalian models. However, it is ATSDR practice to rely on studies in mammalian species to define the toxicology of chemical, which is in accordance with ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov).*

QUESTION: Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

COMMENT 31: Yes.

RESPONSE: *No response needed.*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of the substance?

COMMENT 32: No.

RESPONSE: *Response is not required.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers?

COMMENT 33: No.

RESPONSE: *No response needed.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations?

COMMENT 34: There are limitations to defining these thresholds due to the multiple mixtures in the general designation of creosote.

RESPONSE: *In response to the Reviewer's comment, the following sentence was added to Section 2.1.*
For chemical mixtures, note that interpretation of NOAELs and LOAELs may have some limitations if exposure is based on only one chemical of the mixture.

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT 35: The conclusions seem merited, but see the notes listed above.

RESPONSE: *All comments noted above have been addressed in respective responses.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT 36: There will always be newly discovered mechanisms to be made so all possible mechanisms is a goal that can be approached but there is always room for improvement. This document as any is necessarily an interim report. Further editions will be needed as our understanding of biology improves.

RESPONSE: *ATSDR agrees that newly discovered information on mechanisms is important. If identified, such information will be included in subsequent versions of the profile.*

QUESTION: Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.

COMMENT 37: The conclusions are fine. Also, it should be added that the toxicity information of individual chemicals within the creosote mixtures should be cited and potential limitations of sensitivity of some studies due to increased variability of the control group needs to be addressed. Addition of nonmammalian model information about toxicity would enhance the database.

RESPONSE: *As noted in responses to previous comments above: (1) ATSDR's approach to the evaluation and interpretation of the toxicology of the "whole" mixture includes any joint toxic actions of the chemicals in the mixture (e.g., additive or other interactions) and how they influence the overall toxicity of the mixture. Although 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, it is also understood that the toxicity of the individual components may not be representative of the actual toxicity of the mixture, therefore the health effects of the individual components (e.g., PAHs, phenol, or others) are not discussed in detail in this profile, but are discussed in the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons. The intent of this profile is to discuss the creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. More information on ATSDR's approach to evaluation of chemical mixtures can be found in ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov) and Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors (Update) (cdc.gov). (2) ATSDR agrees with the Reviewer that variance in the response observed in the control group will affect the power of a study to detect statistically significant differences between control and treatment groups. However, in general, ATSDR does not evaluate statistical power of the studies reported in ATSDR Toxicological Profiles as it would require a much more detailed analysis of each study than needed to achieve the objectives of Toxicological Profiles, which is to identify and summarize the pertinent literature on health effects. (3) It is ATSDR practice to rely on studies in*

mammalian species to define the toxicology of chemicals, in accordance with ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov).

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

In response to the statement, "Chapter 3 overviews other relevant information for evaluating health effects which includes toxicokinetics, susceptible populations, biomarkers of exposure and effect, and interactions with other chemicals", the Reviewer provided the following specific comments.

COMMENT 38: (Section 3.1.3, page 134, line 7) This is an important section. Changes of metabolism with induction of liver enzyme systems with chronic exposure to creosote and other exposures like diesel exhaust and cigarette smoke should be covered in greater depth.

RESPONSE: *Induction of metabolism is discussed in Section 3.1.3. For example, the text following Figure 3-1 identifies CYP pathways induced by application of coal tar to skin. Induction resulting from exposures to individual constituents of creosote mixtures is not discussed because the profile is focused on studies that have evaluated creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. In the Introduction to Section 3.1, Toxicokinetics, the reader is referred to the profiles on individual constituents of these mixtures. Section 3.1.3, Metabolism (last paragraph) was revised to emphasize the importance of induction in the profile of urinary metabolites observed following exposure:*

> 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.

COMMENT 39: (Section 3.2, page 153, line 21) The developmental neurobehavioral toxicity of individual chemicals in creosote have been studied and this should be referred to here.

RESPONSE: *ATSDR is recognizes that the neurodevelopmental effects of the chemical components of creosote have been studied. ATSDR's approach to the evaluation and interpretation of the toxicology of the "whole" mixture includes any joint toxic actions of the chemicals in the mixture (e.g., additive or other interactions) and how they influence the overall toxicity of the mixture. Although 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, it is also understood that the toxicity of the individual components may not be representative of the actual toxicity of the mixture, therefore the health effects of the individual components (e.g., PAHs, phenol, or others) are not discussed in detail in this profile, but are discussed in the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons. The intent of this profile is to discuss the creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. More information on ATSDR's approach to evaluation of chemical mixtures can be found in ATSDRs Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors (Update) (cdc.gov). Additional information on the scope and development of toxicological profiles can be found in ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov).*

Toxicokinetics

QUESTION: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance?

COMMENT 40: Yes.

RESPONSE: *No response needed.*

QUESTION: Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented?

COMMENT 41: Yes.

RESPONSE: *No response needed.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT 42: Yes.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be?

COMMENT 43: Neurobehavioral impairments with developmental exposure to chemicals in creosote should be addressed more fully.

RESPONSE: *As noted in responses to comments above, for toxicological profiles on mixtures, ATSDR's approach to the evaluation and interpretation of the toxicology of the "whole" mixture includes any joint toxic actions of the chemicals in the mixture (e.g., additive or other interactions) and how they influence the overall toxicity of the mixture. Although 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, it is also understood that the toxicity of the individual components may not be representative of the actual toxicity of the mixture, therefore the health effects of the individual components (e.g., PAHs, phenol, or others) are not discussed in detail in this profile, but are discussed in the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons. The intent of this profile is to discuss the creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. More information on ATSDR's approach to evaluation of chemical mixtures can be found in ATSDRs Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors (Update) (cdc.gov). Additional information on the scope and development of toxicological profiles can be found in ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov).*

QUESTION: Are the biomarkers of effect specific for the substance?

COMMENT 44: Since there are different complex mixtures in the spectrum of creosote formulations there is not a specific marker.

RESPONSE: *No response needed.*

Biomarkers of Exposure and Effect

QUESTION: Are the biomarkers of exposure specific for the substance?

COMMENT 45: Creosote is defined by a family of complex mixtures so there are different markers for the different mixture types.

RESPONSE: *ATSDR agrees with the Reviewer's statement. This issue is discussed in Section 3.3.2.*

QUESTION: Are the biomarkers of effect specific for the substance?

COMMENT 46: Since there are different complex mixtures in the spectrum of creosote formulations there is not a specific marker.

RESPONSE: *ATSDR agrees with the Reviewer's statement. This is discussed in Section 3.3.2.*

Interactions with Other Chemicals

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites?

COMMENT 47: Additional discussion of the chemical changes with "weathering" at dump sites is warrented.

RESPONSE: *In Section 3.4, the following was added to address the Reviewer's comment on "weathering."*

> 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.

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions?

COMMENT 48: This is covered.

RESPONSE: *No response needed.*

Chapter 4. Chemical and Physical Information

In response to the charge question statement, "Chapter 4 summarizes the chemical and physical information. This chapter should contain very little text. Most of the information should be presented in tabular form.", the Reviewer provided the following specific comments.

COMMENT 49: (Section 4.1, page 153, Table 4-1) This should be "chemical mixture name" to be more accurate and the same for the following tables as well.

RESPONSE: *In Table 4-1, "chemical name" was replaced with "chemical mixture name."*

COMMENT 50: (Section 4.2, page 163, line 1) This is a very valuable section. The lipophilicity of many of the chemical components of creosote makes it important to consider the correct vehicles for experimental studies and to not use plastic containers for storage or administration because of adsorption of these chemicals to plastic.

RESPONSE: *In response to the comment above, the following statement was added a discussion of analytical methods in Section 5.5.*

> Due to the lipophilic nature of many of the components of this mixture, care should be given to storage and handling of samples to avoid adsorption to a storage vehicle, which could lead to inaccurate measurements.

COMMENT 51: (Section 4.2, Table 4-6) This is an important section showing the diversity of mixtures in the range of creosote mixtures. Also, there should be more details on the impact of "weathering" on the components of the mixtures. It is important because of the exposure to creosote in the environment are to old dump sites.

RESPONSE: *Additional details on "weathering" were added to Section 5.5.3.*

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

COMMENT 52: (Section 4.2, page 214, line 10) The toxic effects that have been found for chemicals within the complex creosote mixtures should be used to direct further research for the complex mixtures.

RESPONSE: *ATSDR agrees with the Reviewer's statement above that "toxic effects that have been found for chemicals within the complex creosote mixtures should be used to direct further research for the complex mixtures."*

QUESTION: Are any of the values or information provided in the chemical and physical properties tables wrong or missing? Please explain and provide any additional references.

COMMENT 53: Generally, the tables are fine. See minor notes above.

RESPONSE: *All notes above have been addressed in respective responses.*

QUESTION: Is information provided on the various forms of the substance?

COMMENT 54: The different chemicals in the mixtures are well presented.

RESPONSE: *ATSDR appreciates the Reviewer's comment.*

Chapter 5. Potential for Human Exposure

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.

COMMENT 55: The production of the family of creosote mixtures is pretty comprehensive.

RESPONSE: *No response needed.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT 56: With the variability of creosote mixtures the relevant receptor mechanisms are multiple.

RESPONSE: *In this context, receptor does not refer to receptor mechanisms of toxicity, but rather to the population (e.g., general population) that will be exposed to the chemical.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT 57: There should be more discussion of "weathering" effects on creosote.

RESPONSE: *Additional details on "weathering" were added to Section 5.5.3.*

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

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT 58: This is generally well addressed.

RESPONSE: *No response needed.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations?

COMMENT 59: Yes.

RESPONSE: *No response needed.*

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap?

COMMENT 60: The developmental neurobehavioral toxicity of individual chemicals in creosote have been studied and this should be referred to here.

RESPONSE: *ATSDR recognizes that the neurodevelopmental effects of the principal components of creosote have been studied and are informative.*
However, ATSDR's approach to the evaluation and interpretation of the toxicology of the "whole" mixture includes any joint toxic actions of the chemicals in the mixture (e.g., additive or other interactions) and how they influence the overall toxicity of the mixture. Although 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, it is also understood that the toxicity of the individual components may not be representative of the actual toxicity of the mixture, therefore the health effects of the individual components (e.g., PAHs, phenol, or others) are not discussed in detail in this profile, but are discussed in the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons. The intent of this profile is to discuss the creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. More information on ATSDR's approach to evaluation of chemical mixtures can be found in ATSDR's Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors (Update) (cdc.gov). Additional information on the scope and development of toxicological profiles can be found in ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov).

QUESTION: Do you agree with the identified data needs?

COMMENT 61: Yes.

RESPONSE: *No response needed.*

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion?

COMMENT 62: The presentation is fairly even handed.

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

QUESTION: Are you aware of any additional regulations or guidelines that should be included?

COMMENT 63: No.

RESPONSE: *No response needed.*

QUESTION: Are there any that should be removed?

COMMENT 64: No.

RESPONSE: *No response needed.*

Appendices

No comments were provided on the appendices.

Annotated Comments

The Reviewer provided annotated comments on the toxicological profile. Many of these comments are identical or nearly identical to specific comments above. This section focuses on comments not previously addressed

COMMENT 65: (Section 2.3, page 70, lines 5–7) How is this known?

RESPONSE: *The Reviewer's comment refers to the following sentence in Section 2.3: "*Note that for dietary exposure studies, decreased body weight and body weight gain is frequently accompanied by decreased food consumption due to palatability; in these cases, effects on body weight are not considered to be an adverse effect of creosote compounds.*" In the absence of data identifying the mechanism of decreased food consumption or specific effects of creosote on sensory systems, ATSDR considers decreased body weight gain to not be adverse when palatability alone may be an issue, as is the case for creosote. Should data become available to identify the underlying cause for decreased consumption of food containing creosote, this would be included in the next update of the creosote profile. To provide additional clarity in the profile, the following sentence was added to Section 2.3. The following sentence was added to the beginning of Section 2.3.*

> In the absence of information that decreased food consumption is due to a chemical-specific adverse effect rather than due to palatability alone, effects on body weight accompanied by decreased food consumption are not considered to be an adverse effect (e.g., not a LOAEL) of oral exposure to creosote compounds.

COMMENT 66: (Section 2.3, page 70, lines 6–7) What is the rationale for this? Chemical injury to sensory systems, in this case olfaction and taste, is a toxic effect of concern.

RESPONSE: *This comment pertains to the following sentence: "*Note that for dietary exposure studies, decreased body weight and body weight gain is frequently accompanied by decreased food consumption due to palatability; in these cases, effects on body weight are not considered to be an adverse effect of creosote compounds.*" As noted in the comment above, in the absence of data identifying the mechanism of decreased food consumption or specific effects of creosote on sensory systems, ATSDR considers decreased body weight gain to not be adverse when palatability alone may be an issue, as is the case for creosote. Should data become available to identify the underlying cause for decreased consumption of food containing creosote, this would be included in the next update of the creosote profile. To provide additional clarity in the profile, the following sentence was added to Section 2.3. The following sentence was added to the beginning of Section 2.3.*

> In the absence of information that decreased food consumption is due to a chemical-specific adverse effect rather than due to palatability alone, effects on body weight accompanied by decreased food consumption are not considered to be an adverse effect (e.g., not a LOAEL) of oral exposure to creosote compounds.

Comments provided by Reviewer #3

Note that the superscripted numbers in the Reviewer's comments refer to a list of numbered references listed at the end of this Reviewer's comments.

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1. Relevance to Public Health

QUESTION: Do you agree with those effects known to occur in humans as reported in the text?

COMMENT 1: This reviewer concurs with the executive summary of the relevance of wood and coal tar creosotes to human health.

Wood Creosotes: The human health effects of wood creosotes are fairly well documented due to their wide-spread medicinal uses in treatment of constipation and enhancing expectorant (not currently in U.S.). The impacts on human health following ingestion are not surprising seen mostly in liver and kidney, tend to be reversible and considered to be a non-serious endpoint.

Coal Tar: A major source of human exposure has been through use of coal tar creosote as a wood preservative and primary routes of exposure are then dermal and inhalation. Other coal tar fractions have been studied in occupational settings and the primary non-cancer impact appears to be on respiratory function. High occupational exposures are associated with increased cancers at a number of sites. Dermal exposures have been studied based on the use of coal tar in treatment of psoriasis and dermatitis sometimes in conjunction with uv light. No cancer-related impacts are seen but there may be a developmental toxicity concern for dermal exposures during pregnancy. With respect to cancer, a number of regulatory agencies have classified coal tar products as known or probable human carcinogens.

RESPONSE: *No response needed.*

QUESTION: Are the effects only observed in animals likely to be of concern to humans?

COMMENT 2: Probably- see discussion below on PAH exposure to pregnant women and fetal/infant toxicities.

Coal Tar: The epidemiology studies from high exposure populations and occupational studies supporting the carcinogenic nature of coal tar products was taken into account in the classifications by IARC, EPA and other agencies. This reviewer would like to note that there may not be enough concern expressed over developmental/reproductive toxicities. Animal studies have documented a number of toxic impacts on the fetus following maternal exposures and even higher incidences of some cancers later in life. Dr. Fredrica Perera, Columbia University, has done elegant studies on maternal exposure to PAHs (inhalation as determined by personal air sampling) and negative impacts on birth weight, premature delivery and cognitive deficits in the children born to mothers with the greatest exposure[1-4]. A higher impact in children born to African-American women may be an environmental justice issue[5]. Although not studying creosote directly this data correlates the levels of a major component of coal tar products (PAHs) with the reproductive and development toxicities.

RESPONSE: *ATSDR agrees with the Reviewer that data on the developmental/reproductive toxicities of PAHs are very important. Although PAHs are components of creosote, the focus of this toxicological profile is creosote.*

ATSDR's approach to the evaluation and interpretation of the toxicology of the "whole" mixture includes any joint toxic actions of the chemicals in the mixture (e.g., additive or other interactions) and how they influence the overall toxicity of the mixture. Although 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, it is also understood that the toxicity of the individual components may not be representative of the actual toxicity of the mixture, therefore the health effects of the individual components (e.g., PAHs, phenol, or others) are not discussed in detail in this profile, but are discussed in the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons. The intent of this profile is to discuss the creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. More information on ATSDR's approach to evaluation of chemical mixtures can be found in ATSDR's Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors (Update) (cdc.gov). Additional information on the scope and development of toxicological profiles can be found in ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov).

The additional references 1-6 (Choi et al. 2006, 2012; Jedrychowski et al. 2005, 2015; Perera et al. 2012) that the Reviewer suggested for inclusion in the profile are studies evaluating effects of PAHs; these publications do not include information on the effects of creosote compounds. Therefore, the studies have not been added to the profile.

The profile is in accordance with ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov) and includes populations most at risk for exposure and most at risk for adverse health effects (susceptible populations). Regarding environmental justice issues, this is currently beyond the scope of toxicological profiles. ATSDR will consider addressing environmental justice issues in future updates to ATSDR's Guidance for the Preparation of Toxicological Profiles.

Minimal Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation?

COMMENT 3: Yes, given the complex composition of both creosotes but especially those derived from coal tar and the inconsistency of the composition depending on source makes accurate determination of LOAELs impractical and unreliable for setting MRLs.

RESPONSE: *No response needed.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 4: NA.

RESPONSE: *No response needed.*

QUESTION: Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT 5: No comment on MRL database.

RESPONSE: *No response needed.*

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature?

COMMENT 6: Yes.

RESPONSE: *No response needed.*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)?

COMMENT 7: The studies cited, with the exception of medicinal applications) do not provide exposure data or length of exposure.

RESPONSE: *Little detailed information is available on exposure data in epidemiological studies. If available, data were included in the profile. In addition, measures of exposure are typically for a single chemical in creosote. Measures of exposure (either external exposures or urinary biomarkers) based on a single chemical component of creosote do not provide information on the exposure to other chemicals present in the mixture. This is further limited because the composition of creosote mixtures is not a consistent mix of chemicals.*

QUESTION: Were the major study limitations sufficiently described in the text without going into lengthy discussions?

COMMENT 8: Yes.

The occupational studies (no studies show mortality to individual creosote compounds including wood or coal tar creosote, coal tar, coal tar pitch, or coal tar volatiles) were from workers exposed to creosote, coke, gas, aluminum, roofing and paving and chimney sweeps. The size of the cohorts ranged from 400-58,862 for non-cancer mortality. The most common mortalities were from respiratory disease. The text (2.5, lines 27–29) state there is not sufficient evidence that creosote compound produce adverse cardiovascular effects or cardiovascular toxicity. This reviewer does not concur given that aluminum workers and chimney sweeps exhibit cardiovascular-related deaths in some studies. There is little evidence for creosote exposures significantly impacting body weight, GI (with exception of some reports from ingestion of wood creosote), hematology, muscle/skeleton, liver or kidney (again, with the exception of ingestion of wood creosote for medicinal purposes), eye, endocrine systems, CNS, reproductive or developmental. Most of the studies were controlled for smoking and/or other confounders. There is no breakdown by sex, length of exposure or dose information. The best controlled studies for dose and length of exposure for non-mortality endpoints are those examining dermal impacts following coal tar treatments. Contact dermatitis is the most common toxicity reported in those studies. Occupational and environmental exposures that do not have dose or length of exposure information are consistent with these studies (skin irritation eczema, folliculitis and benign growths).

RESPONSE: *The Reviewer "*does not concur given that aluminum workers and chimney sweeps exhibit cardiovascular-related deaths in some studies." *ATSDR disagrees with the Reviewer's statement. As*

shown in Table 2-5 in Section 2.2, associations between exposure and cardiovascular-related mortality have been reported in aluminum workers (Gibbs and Sevigny 2007a; Gibbs et al. 2007, 2014) and chimney sweeps (Evanoff et al. 1993; Hansen et al. 1983). Available studies do not provide sufficient information to determine if exposure of humans to creosote compounds produces sublethal adverse effects to the cardiovascular system. Note that increases in mortality due to cardiovascular effects of creosote compounds is discussed in Section 2.2.

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT 9: The animal studies cited are extensive and Table 2-1 summarizes the endpoints examined, route of exposure and length of exposure. Some studies seem to be underpowered (EPA 1994, Table 2-1 has an n=5 for males and females) and the dose ranges are limited. The lack of a defined mixture, for reasons discussed above, makes interpretation and comparison of studies problematic. The best studies would use standards from the National Institute of Standards and Technology (NIST). This reviewer's laboratory has utilized SRM 1597a (Coal Tar extract, https://www.nist.gov/search?s=SRM+1597a) in mouse skin cancer studies[6]. If possible ATSDR should encourage use of NIST in future creosote studies examining both cancer and non-cancer endpoints

RESPONSE: *ATSDR agrees with the Reviewer that some studies may be underpowered due to a lower number of animals studies and that dose ranges are limited in some studies. However, these studies do provide information to develop a profile of the toxicological effects of creosote. ATSDR also agrees that assessments of the toxicological effects of complex chemical mixtures, especially those for which the chemical composition is not consistent (as is the case for creosote compounds), is challenging. ATSDR agrees that using NIST SRM for coal tar extract, would provide a consistent chemical mixture for toxicological assessments in animal laboratories and allow for comparison between studies. Regarding the Reviewer's comment to "*encourage use of NIST in future creosote studies,*" this is beyond the scope for the profile. The profile was written in accordance with ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov) and the Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors (Update) (cdc.gov).*

The Reviewer noted the mouse skin cancer study on NIST SRM 1597a (coal tar extract) by Siddens et al. (2012; reference number 6). This study was not added to the profile because coal tar extract was co-administered with diesel particulate extract. There is no information on effects of coal tar extract alone in this publication.

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT 10: The choice of animal species appears appropriate with both inbred and outbred strains. Future studies could make use of knock out/knock in (humanized) mice to enhance translational value.

RESPONSE: *ATSDR agrees with the Reviewer's statement that future studies with knock out/knock in mice would enhance the understanding of the toxicity of creosote compounds.*

QUESTION: Has adequate attention been paid to dose-response relationships for both human and animal data? No information is available on dose-response for human studies

COMMENT 11: In the future, personal monitoring devices, e.g., passive sampler[7], could be employed with defined length of exposure.

RESPONSE: *ATSDR agrees with the Reviewer's statement that personal monitoring devices, such as that described in reference 7 (Bonner et al. 2023) would provide useful information in future studies.*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT 12: There are studies using defined coal tar mixtures as mouse skin carcinogens in addition to the Marston et al., 2001 studied cited in the text. These include Siddens et al., 2012[6] cited in the document as well as Tilton et al., 2015[8] and Siddens et al., 2015[9].

RESPONSE: *ATSDR has reviewed the studies noted above (Siddens et al. 2012, 2015; Tilton et al. 2015). The Siddens et al. (2015) tumor promoter study was added to the profile in Section 2.19.*

> While creosote compounds alone have been shown to cause skin tumors (Boutwell and Bosch 1958; EPA 1997; Emmett et al. 1981; Kligman and Kligman 1994; Lijinsky et al. 1957; Niemeier et al. 1988; Poel and Kammer 1957; Wallcave et al. 1971), several studies have also evaluated the initiating and promoting activity of coal tar and coal tar creosote (Boutwell and Bosch 1958; EPA 1997; Lijinsky et al. 1957; Mahlum 1983; Marston et al. 2001; Phillips and Alldrick 1994; Siddens et al. 2015; Springer et al. 1989).

Siddens et al. (2012) and Tilton et al. (2015) were not added to the profile because coal tar extract was co-administered with diesel particulate extract. There is no information on effects of coal tar extract alone.

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

COMMENT 13: The study cited above[6] used a defined coal tar extract from NIST but only a single dose making deriving an MRL unlikely.

RESPONSE: *The Siddens et al. (2012) study (reference 6) was not included in the profile because coal tar extract was co-administered with diesel particulate extract; no information on effects of coal tar extract alone was reported in the paper. Furthermore, as noted in Appendix A of the profile, "*MRLs are based on noncancer health effects only; cancer effects are not considered,*" in accordance with ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov). The Siddens et al. (2012) study does not include evaluations of noncancer health effects of creosote extract.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT 14: The NOAELs/LOAELs listed in the tables and figures of section 2 for the animal studies provide adequate justification.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT 15: This reviewer is in agreement with the designation of less serious or serious LOAELs. It is difficult, however to classify body weight gain in this system in the absence of information on food consumption. If the studies did not employ pair-feeding than this reviewer suggests keeping in the serious designation but include a footnote concerning pair-feeding.

RESPONSE: *ATSDR categorizes a decrease in body weight gain as an adverse effect if is it not accompanied by decreased food consumption. The categorizations of this endpoint in the profile conform to this approach in accordance with ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov).*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT 16: There is little information on mechanism of action (MOA) for any of the health effects listed in the animal or human studies although that is to be expected given the complex and variable nature of these mixtures.

RESPONSE: *No response needed.*

QUESTION: Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.

COMMENT 17: The overview of health effects (p. 12, lines 19–36 and p. 13, lines 1–15) is an excellent and succinct distillation of the many animal and human studies included in the database.

RESPONSE: *ATSDR appreciates the Reviewer's comment.*

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

Toxicokinetics

QUESTION: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

COMMENT 18: As pointed out through the document the complex nature of the mixtures does not allow for ADME calculations. Rather, ADME studies can be performed with major components such as the PAHs.

Dermal absorption following coal tar components for psoriasis/dermatitis is evident from urinary excretion of metabolites such as 1-hydroxypyrene as is inhalation exposure from occupational settings. There is recent data from my group utilizing the remarkable sensitivity (atto- to zepto-mole) of accelerator mass spectrometry (AMS)[10,11]. When coupled to UPLC PAHs and their metabolites can be assessed in plasma and urine over time (48-72 hours following a single dose of 25-250 ng [^{14}C]-benzo[*a*]pyrene (BaP) or [^{14}C]-dibenzo[*def,p*]chrysene (DBC)) and toxicokinetic parameters (T_{max}, C_{max}, AUC, V_d, Cl, $T_{1/2}$, etc). These studies have the advantage of describing ADME at actual environmental levels of exposure in the general population. Extensive metabolism of both these carcinogenic PAHs, especially BaP, is seen along with extensive inter-individual variability.

With respect to metabolism, Figure 3-1 could be enhanced by inclusion of the aldo-keto reductase pathway that converts dihydrodiols to the reactive catechols. The redox cycling of catechols leads to oxidative stress and toxicity. This pathway can be important for PAHs such as BaP in tissues with lower cytochrome P450 (CYP) levels. There are a couple of minor corrections. Below Figure 3-1 (lines 7–8) I think it should be gamma-glutamyl cysteine synthetase

RESPONSE: *ATSDR agrees with Reviewer's statement that the complex nature of the mixtures does not allow for estimation of pharmacokinetics parameters for the mixtures. ATSDR appreciates the Reviewer making the Agency aware of these recent studies of metabolism of PAHs and agrees that this additional information would be informative. However, ATSDR's approach to the evaluation and interpretation of the toxicology of the "whole" mixture includes any joint toxic actions of the chemicals in the mixture (e.g., additive or other interactions) and how they influence the overall toxicity of the mixture. Although 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, it is also understood that the toxicity of the individual components may not be representative of the actual toxicity of the mixture, therefore the health effects of the individual components (e.g., PAHs, phenol, or others) are not discussed in detail in this profile, but are discussed in the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons. The intent of this profile is to discuss the creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. More information on ATSDR's approach to evaluation of chemical mixtures can be found in ATSDR's Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors (Update) (cdc.gov). Additional information on the scope and development of toxicological profiles can be found in ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov).*
The Toxicological Profile for Creosote is focused on studies that have evaluated creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. In the Introduction to Section 3.1, Toxicokinetics, the reader is referred to the profiles on individual constituents of these mixtures, including PAHs.

Regarding the Reviewer's comment on Figure 3-1, the figure is intended to provide a simplification of the complex metabolic pathways for benzo[a]pyrene and does not include every pathway. The aldo-keto pathway referred to by the Reviewer is one of several pathways to the formation of phenol-diols, which would include catechols. Since catechols are classified as phenol diols (which are included in Figure 3-1), Figure 3-1 has not been revised. Instead, the text in Section 3.13 was revised to state that catechols are metabolic products:

> The principal products include phenols, phenol diols (including catechols), dihydrodiols, quinones, anhydrides, and conjugates of these products.

Regarding the minor correction of the gamma-glutamyl transferase, c-glutamyl cysteine synthetase was revised to:

> gamma-glutamyl cysteine synthetase.

QUESTION: Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

COMMENT 19: Again, due to the complex nature of the wood creosote and coal tar products, development of a PBPK model is not possible. There are models now for individual components such as DBC and BaP[12,13].

RESPONSE: *ATSDR appreciates the Reviewer making the Agency aware of these recent studies of PBPK models for PAHs and agrees that this additional information would be informative. However, ATSDR's approach to the evaluation and interpretation of the toxicology of the "whole" mixture includes any joint toxic actions of the chemicals in the mixture (e.g., additive or other interactions) and how they influence the overall toxicity of the mixture. Although 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, it is also understood that the toxicity of the individual components may not be representative of the actual toxicity of the mixture, therefore the health effects of the individual components (e.g., PAHs, phenol, or others) are not discussed in detail in this profile, but are discussed in the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons. The intent of this profile is to discuss the creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. More information on ATSDR's approach to evaluation of chemical mixtures can be found in ATSDR's Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors (Update) (cdc.gov). Additional information on the scope and development of toxicological profiles can be found in ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov). The Toxicological Profile for Creosote is focused on studies that have evaluated creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. In the Introduction to Section 3.1, Toxicokinetics, the reader is referred to the profiles on individual constituents of these mixtures, including PAHs.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT 20: The assessment by this reviewer is that the differences and relevance of rodent versus human toxicokinetics is adequately described given the limited information available.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Please provide any relevant references.

COMMENT 21: In addition to the studies by Dr. Perera's laboratory with exposure of PAHs to pregnant women[1-5], PAHs are known to be transplacental carcinogens in mice confirming that the fetus/infant are most likely exhibit enhanced sensitivity[14].

RESPONSE: *The Reviewer's comment refers to recommended studies 1–5 (Choi et al. 2006, 2012; Jedrychowski et al. 2005, 2015; Perera et al. 2012) and 14 (Yu et al.2006). These studies evaluate the toxicity of PAHs, not creosote compounds. As noted in response to previous comments, ATSDR's approach to the evaluation and interpretation of the toxicology of the "whole" mixture includes any joint toxic actions of the chemicals in the mixture (e.g., additive or other interactions) and how they influence the overall toxicity of the mixture. Although 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, it is also understood that the toxicity of the individual components may not be representative of the actual toxicity of the mixture, therefore the health effects of the individual*

components (e.g., PAHs, phenol, or others) are not discussed in detail in this profile, but are discussed in the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons. The intent of this profile is to discuss the creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. More information on ATSDR's approach to evaluation of chemical mixtures can be found in ATSDR's Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors (Update) (cdc.gov). Additional information on the scope and development of toxicological profiles can be found in ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov).

QUESTION: Is there a discussion of populations at higher risk of susceptibility? Do you agree with the choice of populations? Please explain and provide any additional relevant references.

COMMENT 22: In addition to children, factors that are said to enhance susceptibility include genetic polymorphisms, age, health and nutritional status and exposure to other toxic substances. The document describes each of these. The CYPs, EH, GSTs, SULTs and UGTs responsible for metabolism of PAHs all exhibit genetic polymorphisms. Some epidemiology studies have documented occupational risk with PAH exposure is correlated with certain CYP1A1 or CYP1B1 allelic variants. The same holds for GSTs (GSTM1*0 or nulls increase risk). As many CYPs as well as GSTs, SULTs and UGTs can be induced, environmental as well as genetic factors can enhance or reduce susceptibility. Combinations of these can synergistically enhance susceptibility e.g., cigarette smoking induces CYP1A1/1B1 formation of toxic epoxides in people with no active GSTM1 to detoxify the epoxide.

RESPONSE: *In response to the Reviewer's comment, the following sentence was added to Section 3.2.*
Theoretically, combinations of polymorphisms many enhance or reduce susceptibility to creosote.

Biomarkers of Exposure and Effect

QUESTION: Are the biomarkers of exposure specific for the substance? Please explain.

COMMENT 23: No, there are no biomarkers specific for exposure to the wood creosotes or coal tar product mixtures. The biomarkers used (e.g., urinary 1-hydroxypyrene) are common to any PAH source.

RESPONSE: *No response needed.*

QUESTION: Are the biomarkers of effect specific for the substance? Please explain.

COMMENT 24: Again, no. Biomarkers of effects such as CYP induction or DNA adduction are not specific to wood creosotes or coal tar product mixtures.

RESPONSE: *ATSDR agrees with the Reviewer's comment.*

Interactions with Other Chemicals

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? Please explain and provide any additional references.

COMMENT 25: Not much information is available. The fact that toxicity and carcinogenicity of PAHs can be significantly impacted by co-exposures with heavy metals, dioxins, PCBs and other chemicals found at NPL sites should be of importance.

RESPONSE: *Specific information on the effects of co-exposure of creosote compounds and other chemicals at NPL sites on the toxicity and carcinogenicity of creosote was not identified. Available information on interactions between creosote compounds and other chemicals is reviewed in Section 3.4.*

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

COMMENT 26: The text does mention the studies that have documented the ability of creosotes to promote skin tumors initiated by PAHs and conversely creosote initiation can be promoted by croton oil. Such evidence suggests creosotes can be effective at all stages of initiation-promotion-progression driven by other chemicals or chronic infections. One area that could use more attention is the interaction between the components of the creosote, especially the PAHs. Prediction of the carcinogenicity of PAH mixtures was initially tried with a Relative Potency Factor (RPF) approach similar to the Toxic Equivalence Factor approach used with dioxins/dibenzofurans/PCBs. This has turned out not to be of use for PAH mixture risk assessment as the assumption of additivity and independence of individual components is not met (i.e., different PAHs can exhibit inhibition or synergy rather than the additivity)[15]. We found that was the case in the mouse skin tumor model when comparing individual PAHs with known RPFs to coal tar in which the total RPF in terms of BaP equivalents was markedly different than what would have been predicted by the RPF approach. EPA has since dropped the RPF approach for PAH mixtures[16].

RESPONSE: *As noted in previous comments, for toxicological profiles on mixtures, ATSDR's approach to the evaluation and interpretation of the toxicology of the "whole" mixture includes any joint toxic actions of the chemicals in the mixture (e.g., additive or other interactions) and how they influence the overall toxicity of the mixture. Although 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, it is also understood that the toxicity of the individual components may not be representative of the actual toxicity of the mixture, therefore the health effects of the individual components (e.g., PAHs, phenol, or others) are not discussed in detail in this profile, but are discussed in the ATSDR Toxicological Profiles for phenol, cresols, and polycyclic aromatic hydrocarbons. The intent of this profile is to discuss the creosotes, coal tar, coal tar pitch, and coal tar pitch volatiles. More information on ATSDR's approach to evaluation of chemical mixtures can be found in ATSDR's Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors (Update) (cdc.gov). Additional information on the scope and development of toxicological profiles can be found in ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov).. For this reason, the studies noted in the comment above—Jarvis et al. 2014 (reference 15) and Haber et al. 2022 (reference 16)—were not added to the profile as these studies evaluated effects of PAHs.*

Chapter 4. Chemical and Physical Information

QUESTION: Are any of the values or information provided in the chemical and physical properties tables wrong or missing? Please explain and provide any additional references.

COMMENT 27: This reviewer could not find any mistakes in the text or tables regarding the chemical and physical properties.

RESPONSE: *No response needed.*

QUESTION: Is information provided on the various forms of the substance? Please explain.

COMMENT 28: Yes. The components of beechwood creosote are provided along with eight different coal tar creosote mixtures (which underlines the issue of variability between sources) and coal tar pitch.

RESPONSE: *No response needed.*

Chapter 5. Potential for Human Exposure

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.

COMMENT 29: The information provided appears complete. One potentially additional source could be from carbon black produced from coal tar used in the production of tires. Carbon black contains high levels of the higher MW carcinogenic PAHs and air-borne debris from tire wear and disposal could be a significant but understudied aspect of coal tar use and disposal[17].

RESPONSE: *In response to this comment, the following sentence was added to Section 5.2.3.*

> Carbon black is also produced from the combustion of coal tar.

Note that reference 17 (Sadiktsis et al. 2012) in the Reviewer's comment does not include any information on creosote compounds.

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT 30: The information provided does discuss coal-tar based pavement sealants but the impact may be understated for oral[18] and inhalation[19] exposures as well as deposition in lakes from runoff[20]. Children may be at enhanced risk[21].

RESPONSE: *A sentence was added to Section 5.6 to state that the general population may be exposed through these pathways by the use of pavement sealant. References 18–21 (Van Metre et al. 2010, 2012; Williams et al. 2012, 2013) were added as shown below.*

> The general public may also be exposed via dermal or inhalation routes to PAHs or from accidental ingestion of contaminated dust particles from the use of coal tar-based driveway sealants (Van Metre et al. 2010, 2012; Williams et al. 2012, 2013).

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT 31: Text appears complete.

RESPONSE: *No response needed.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels?

COMMENT 32: Yes. This reviewer notes that the LOD listed in Table 5-5 for blood of 20 ng/mL is markedly higher that a publication from the same year[22].

RESPONSE: *Reference 22 in the above comment refers to Anderson et al. (2015). In Table 5-5, the LOD of ~2 ng/mL cited in the Anderson et al. (2015) publication was added.*

QUESTION: Are proper units used for each medium?

COMMENT 33: Yes.

RESPONSE: *No response needed.*

QUESTION: Does the information include the form of the substance measured?

COMMENT 34: Yes.

RESPONSE: *No response needed.*

QUESTION: Is there an adequate discussion of the quality of the information?

COMMENT 35: As PAHs in many cases are the surrogate for creosote it is acknowledged that other sources can contribute to the levels reported. The best studies are those which document the levels as a function of distance from the point source.

RESPONSE: *ATSDR has mentioned this observation in multiple sections in Chapter 5. For example: "*PAH levels in environmental media are typically used as a metric for coal tar creosote releases from nearby point sources such as wood treatment facilities. However, levels in these media are confounded by the many sources of PAHs in the environment including vehicle emissions, coke-oven emissions, and coal, oil, and wood combustion that result in atmospheric deposition of PAHs to water, soil, sediment, and vegetation. PAH levels near a known source (e.g., wood treatment facility using coal tar creosote) are most reflective of releases from that source."

QUESTION: Do you know of other relevant information? Please provide references for added information.

COMMENT 36: No.

RESPONSE: *No response needed.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures?

COMMENT 37: The occupational exposures are well documented.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT 38: This appears elsewhere but this could be a place to re-emphasize the higher susceptibility in children. Also, this reviewer is not sure if this document is the place for this but environmental justice issues could be addressed.

RESPONSE: *Susceptibility of children is addressed in Section 3.2. The following statement was added at the end of Section 5.7.*

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

The profile is in accordance with ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov) and includes populations most at risk for exposure and most at risk for adverse health effects (susceptible populations). Regarding environmental justice issues, this is currently beyond the scope of toxicological profiles. ATSDR will consider addressing environmental justice issues in future updates to ATSDR's Guidance for the Preparation of Toxicological Profiles.

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap? Please provide any relevant references.

COMMENT 39: No, but ATSDR should search Clinicaltrials.gov.

RESPONSE: *To identify ongoing research, ATSDR currently searches the National Institutes of Health (NIH) RePORTER (2022) database. ATSDR will consider adding search of the Clinicaltrials.gov in future profiles and future updates of ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov).*

QUESTION: Do you agree with the identified data needs? Please explain.

COMMENT 40: Yes, and in addition should, based on studies cited from Dr. Perera's lab[1-5] perform developmental studies in rodents by exposing pregnant animal to creosote through dermal, inhalation and oral routes of exposure and examine behavior and neurocognitive impacts on offspring. On page 214, lines 1–3 there is a statement concerning the issue of maternal toxicity impacting developmental studies. This could be addressed with a cross-foster study design.

RESPONSE: *In response to the Reviewer's comment, the following was added to Section 6.2.*

Additional studies on developmental effects, including neurodevelopmental effects, of inhalation, oral, and dermal exposure to coal tar creosote would be important to fully evaluate the developmental toxicity of coal tar creosote. Concerns regarding the contribution of material toxicity to developmental effects could be addressed by employing a cross-foster study design.

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion? Please note any bias in the text.

COMMENT 41: No bias apparent to this reviewer.

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

QUESTION: Are you aware of any additional regulations or guidelines that should be included? Please provide citations.

COMMENT 42: No.

RESPONSE: *No response needed.*

QUESTION: Are there any that should be removed? Please explain.

COMMENT 43: No.

RESPONSE: *No response needed.*

Appendices

QUESTION: Please provide any comments on the content, presentation, etc. of the included appendices.

COMMENT 44: The appendices were very useful, especially the discussion on the rationale for not establishing an MRL (A and D).

RESPONSE: *ATSDR appreciated the Reviewer's positive comments on the appendices.*

Annotated Comments

The Reviewer did not provide annotated comments.

The Reviewer provided the following list of references for review and consideration for inclusion in the profile. ATSDR has reviewed all publications listed below. Throughout the comments above, the Reviewer referred to these references by the numbers listed below.

RESPONSE: *Information regarding each reference is addressed as called out in the Reviewer's specific comments above.*

1. Jedrychowski W, Galas A, Pac A, Flak E, Camman D, Rauh V, Perera F., (2005) Prenatal ambient air exposure to polycyclic aromatic hydrocarbons and the occurrence of respiratory symptoms over the first year of life. Eur. J. Epidemiol. 20:775-82, doi: 10.1007/s10654-005-1048-1.
2. Choi H, Jedrychowski W, Spengler J, Camann DE, Whyatt RM, Rauh V, Tsai WY, Perera FP. (2006) International studies of prenatal exposure to polycyclic aromatic hydrocarbons and fetal growth. Environ. Health. Perspect.114:1744-50, doi: 10.1289/ehp.8982.
3. Jedrychowski WA, Perera FP, Camann D, Spengler J, Butscher M, Mroz E, Majewska R, Flak E, Jacek R, Sowa A. (2015) Prenatal exposure to polycyclic aromatic hydrocarbons and cognitive dysfunction in children. Environ. Sci. Pollut. Res. Int. 22:3631-9, doi: 10.1007/s11356-014-3627-8.
4. Perera FP, Tang D, Wang S, Vishnevetsky J, Zhang B, Diaz D, Camann D, Rauh V. (2012) Prenatal polycyclic aromatic hydrocarbon (PAH) exposure and child behavior at age 6-7 years. Environ. Health. Perspect. 120:921-6, doi: 10.1289/ehp.1104315.
5. Choi H, Perera FP. (2012) Sources of greater fetal vulnerability to airborne polycyclic aromatic hydrocarbons among African Americans. J. Epidemiol. Community Health 66:121-6, doi: 10.1136/jech.2009.099051.
6. Siddens LK, Larkin A, Krueger SK, Bradfield CA, Waters KM, Tilton SC, Pereira CB, Löhr CV, Arlt VM, Phillips DH, Williams DE Baird WM (2012) Polycyclic aromatic hydrocarbons as Skin Carcinogens: Comparison of Benzo[a]pyrene, Dibenzo[def,p]chrysene and Three Environmental Mixtures in the FVB/N Mouse. Toxicol Appl Pharmacol 264:377-86, doi:10.1016/j.taap.2012.08.014.
7. Bonner EM, Horn GP, Smith DL, Kerber S, Fent KW, Tidwell LG, Scott RP, Adams KT, Anderson KA. (2023) Silicone passive sampling used to identify novel dermal chemical exposures of firefighters and assess PPE innovations. Int J Hyg Environ Health 248:114095, doi: 10.1016/j.ijheh.2022.114095.
8. Tilton SC, Siddens LK, Krueger SK, Larkin AJ, Löhr CV, Williams DE, Baird WM, Waters KM (2015) Mechanism-Based Classification of PAH Mixtures to Predict Carcinogenic Potential. Toxicol Sci 146:135-45, doi: 10.1093/toxsci/kfv080.
9. Siddens LK, Bunde KL, Harper TA Jr, McQuistan TJ, Löhr CV, Bramer LM, Waters KM, Tilton SC, Krueger SK, Williams DE, Baird WM (2015) Cytochrome P450 1b1 in Polycyclic Aromatic Hydrocarbon (PAH)-Induced Skin Carcinogenesis: Tumorigenicity of Individual PAHs and Coal-Tar Extract, DNA Adduction and Expression of Select Genes in the Cyp1b1 Knockout Mouse. Toxicol Appl Pharmacol 287:149-160, doi: 10.1016/j.taap.2015.05.019.
10. Madeen EP, Ognibene TJ, Corley RA, McQuistan TJ, Henderson MC, Baird WM, Bench G, Turteltaub KW, Williams DE. (2016) Human Microdosing with Carcinogenic Polycyclic Aromatic Hydrocarbons: In Vivo Pharmacokinetics of Dibenzo[def,p]chrysene and Metabolites by UPLC Accelerator Mass Spectrometry. Chem Res Toxicol 29:1641-50, doi: 10.1021/acs.chemrestox.6b00169.
11. Maier MLV, Siddens LK, Pennington JM, Uesugi SL, Anderson KA, Tidwell LG, Tilton SC, Ognibene TJ, Turteltaub KW, Smith JN, Williams DE (2022) Benzo[a]pyrene (BaP) metabolites predominant in human plasma following escalating oral micro-dosing with [14C]-BaP. Environ Int 159:107045, doi: 10.1016/j.envint.2021.107045.

12. Smith JN, Gaither KA, Pande P. (2022) Competitive Metabolism of Polycyclic Aromatic Hydrocarbons (PAHs): An Assessment Using In Vitro Metabolism and Physiologically Based Pharmacokinetic (PBPK) Modeling. Int J Environ Res Public Health 19:8266, doi: 10.3390/ijerph19148266.
13. Pande P, Madeen EP, Williams DE, Crowell SR, Ognibene TJ, Turteltaub KW, Corley RA, Smith JN. (2022) Translating dosimetry of Dibenzo[def,p]chrysene (DBC) and metabolites across dose and species using physiologically based pharmacokinetic (PBPK) modeling. Toxicol Appl Pharmacol 438:115830, doi: 10.1016/j.taap.2021.115830.
14. Yu Z, Loehr CV, Fischer KA, Louderback MA, Krueger SK, Dashwood RH, Kerkvliet NI, Pereira CB, Jennings-Gee JE, Dance ST, Miller MS, Bailey GS, Williams DE. (2006) In utero exposure of mice to dibenzo[a,l]pyrene produces lymphoma in the offspring: role of the aryl hydrocarbon receptor. Cancer Res 66:755-62, doi: 10.1158/0008-5472.CAN-05-3390.
15. Jarvis IW, Dreij K, Mattsson Å, Jernström B, Stenius U. (2014) Interactions between polycyclic aromatic hydrocarbons in complex mixtures and implications for cancer risk assessment. Toxicology 321:27-39, doi:10.1016/j.tox.2014.03.012.
16. Haber LT, Pecquet AM, Vincent MJ, White LM (2022) The Long Goodbye: Finally moving on from the relative potency approach to a mixtures approach for polycyclic aromatic hydrocarbons (PAHs). Int J Environ Res Public Health 19: 9490, doi:10.3390/ijerph19159490.
17. Sadiktsis I, Bergvall C, Johansson C, Westerholm R. (2012) Automobile tires--a potential source of highly carcinogenic dibenzopyrenes to the environment. Environ Sci Technol 46:3326-34, doi: 10.1021/es204257d.
18. Williams ES, Mahler BJ, Van Metre PC. (2013) Cancer risk from incidental ingestion exposures to PAHs associated with coal-tar-sealed pavement. Environ Sci Technol 47:1101-9, doi: 10.1021/es303371t.
19. Van Metre PC, Majewski MS, Mahler BJ, Foreman WT, Braun CL, Wilson JT, Burbank TL. (2012) Volatilization of polycyclic aromatic hydrocarbons from coal-tar-sealed pavement. Chemosphere 88:1-7, doi: 10.1016/j.chemosphere.2011.12.072.
20. Van Metre PC, Mahler BJ. (2010) Contribution of PAHs from coal-tar pavement sealcoat and other sources to 40 U.S. lakes. Sci Total Environ 409:334-44, doi: 10.1016/j.scitotenv.2010.08.014.
21. Williams ES, Mahler BJ, Van Metre PC. (2012) Coal-tar pavement sealants might substantially increase children's PAH exposures. Environ Pollut 164:40-1, doi: 10.1016/j.envpol.2012.01.010.
22. Anderson KA, Szelewski MF, Wilson G, Quimby BD, Hoffman PD (2015) Modified ion source triple quadrupole mass spectrometer gas chromatograph for polycyclic aromatic hydrocarbon analyses. J Chromatogr A 1419:89-98, doi: 10.1016/j.chroma.2015.09.054.