DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR PENTACHLOROPHENOL

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

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Comments provided by Peer Reviewer #1

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1

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: I think that the focus on hepatic and reproductive effects in humans was good, given that these were the most sensitive. The other potential candidate for sensitive human effects would have been immunologic effects, which also had some interesting human effects.

I think the description of the cancer effects in humans could be stronger, especially given the conclusions of NTP, EPA and IARC. For the description of the human epidemiology, Ramlow et al, 1996 should be replaced by Collins et al, 2006, a 9-year update of the same population that had a better analysis consideration of the contaminants. The study by Kogevinas et al, 1995 was described as a negative study, but their results were in line with the positive studies; they found an association, but only had three cases. You can leave it out for being too low power, but it is not a negative study. Epidemiologic studies should be evaluated using a weight of evidence approach and are not experiments that should be judged solely on the basis of statistical significance. I will discuss the cancer epidemiology further in Chapter 2.

RESPONSE: *The discussion of cancer effects in Section 1.2 was revised. The revised text does not discuss individual epidemiological studies; it includes the Department of Health and Human Services (HHS), U.S. Environmental Protection Agency (EPA), and International Agency for Research on Cancer (IARC) assessment of the epidemiological data:*

> A number of epidemiological cohort and case-control studies have evaluated the potential associations between pentachlorophenol and cancer. In evaluating the available epidemiological data, the Department of Health and Human Services (HHS) (NTP 2016), U.S. Environmental Protection Agency (EPA) (IRIS 2010), and International Agency for Research on Cancer (IARC 2019) concluded that the data suggested an association between pentachlorophenol exposure and increased risk of non-Hodgkin lymphoma based on the consistent findings across epidemiological studies. The data for other cancer types were considered inadequate.

The Collins et al. (2006) study was added to Section 2.19.

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: In reading Chapter 2, other than for cancer, the human evidence seemed too sparse, conflicting, or potentially confounded to draw firm conclusions regarding many of the health effects observed in animals.

RESPONSE: *ATSDR agrees with the Reviewer that the epidemiological data are inadequate for noncancer effects. However, based on the systematic review (discussed in Appendix C) of the limited epidemiological studies and the high-quality animal studies, ATSDR concluded that hepatic and developmental effects are presumed health effects in humans.*

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

COMMENT 3: I think that the potential for human exposure is currently greatest by the dermal route, so I would lead with that. In the Health Effects Chapter there was frequent reference to a group of infants exposed because pentachlorophenol which was used as an anti-mildew agent. Perhaps a sentence that mentions historic uses, such as in textiles, might be appropriate.

RESPONSE: *It is typical for ATSDR to discuss health effects in this route-specific order: inhalation, oral, dermal. Pentachlorophenol was not used to treat textiles. In the case of the infants exposed to pentachlorophenol, the exposure resulted from the misuse of an anti-mildew agent containing sodium pentachlorophenate.*

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: Not applicable.

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.

a. Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT 5: I am an epidemiologist and MRLs are not one of my areas of expertise.

RESPONSE: *No response needed.*

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

COMMENT 6: I am an epidemiologist and MRLs are not one of my areas of expertise.

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 7: A problem I have with Chapter 2 is that clear conclusions regarding the body of evidence in each section are rarely stated, with the exception of some statements with the exception of some statements regarding absence of effects or lack of evidence in animal studies. In preparation for this review I looked at the TP for CDDs, given that the goal was to separate the effects of pentachlorophenol from contaminants. It is over 20 years old, but at the end of each health effects section they had a clear

and concise conclusion, generally in one or two sentences. In looking at recent TPs, I see that having conclusions in every section does not seem to be the style. It is not clear what the conclusions are for most health effects in Chapter 2.

RESPONSE: *The inclusion of summary paragraphs in Chapter 2 is profile specific. Unlike CDDs, the discussions of specific health endpoints are relatively short, and a summary statement was not considered necessary.*

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 8: Generally, yes, but there were exception for some specific studies in various sections, which I detail below. Although the case reports are generally described in sufficient detail, sometimes too little detail was provided for epidemiologic studies.

The Reviewer provided several examples (see Comments 9-18).

COMMENT 9: The study by Walls et al, 1998 in Section 2.3 provides almost no detail. Although the study was limited, it is the only human study under body weight and was also cited elsewhere (in 2.16, 2.18) and should have at least stated that is was a survey, with limited information on exposure. At the minimum, route, any information on level of exposure (or the absence of information on exposure) and anything regarding does-response deserves mention.

RESPONSE: *The discussion of the Wall et al. (1998) study in Section 2.3 was expanded:*

> In a survey of 127 current and former timber sawmill workers, Walls et al. (1998) reported increases in weight loss in workers exposed to high levels of pentachlorophenol. The workers were assigned into three exposure categories based on duration of pentachlorophenol exposure, type of work, use of personal protection, and intensity of exposure; no air monitoring data were reported.

Additionally, a note was added to Sections 2.15 and 2.18 referring the reader to Section 2.3 for more information on the Walls et al. (1998) study.

COMMENT 10: The 1980 study by Klemmer et al in Section 2.4 (and in 2.7, 2.11, 2.12) also deserved more details, such as the fact that it included two groups of wood treatment workers, one only exposed to PCP and the other exposed to a mix of wood treatment chemicals.

RESPONSE: *The Klemmer et al. (1980) study included farmers with mixed exposure to pesticides and workers who processed lumber and other wood products treated with pentachlorophenol and other wood preservative chemicals. The profile only presented the results for the wood processing workers. The profile includes a statement that the workers in the Baader and Bauer (1951) and Klemmer et al. (1980) studies were exposed to pentachlorophenol contaminants and other compounds (such as dieldrin, chromium, fluorine, arsenic, copper, boron, and tin compounds).*

COMMENT 11: The study by Daniel, 1995 in Section 2.14 on page 47 also lacks significant details, including the fact that it was a study with 188 participants.

I was quite surprised that the 2001 study by Daniel et al with dose-response relationship between blood levels of PCP and cellular and humoral immune parameters was not included in 2.14.

Daniel V, Huber W, Bauer K, Suesal C, Mytilineos J, Melk A, Conradt C, Opelz G. Association of Elevated Blood Levels of Pentachlorophenol (PCP) With Cellular and Humoral Immunodeficiencies. Arch Environ Health 2001;56(1):77-83.

RESPONSE: *The Daniel et al. (2001) study was added to Section 2.14. In addition, the discussion of the Daniel et al. (1995) and Colosio et al. (1993b) studies, which examined associations between blood pentachlorophenol levels and immune function, was expanded:*

Immune function was examined in 188–190 individuals exposed to pesticides containing pentachlorophenol (Daniel et al. 1995, 2001) and 32 workers treating wood with pentachlorophenol (Colosio et al. 1993b). Daniel et al. (1995) found that the likelihood of having an impaired response to at least one lymphocyte-stimulating agent was increased among individuals with blood pentachlorophenol levels of ≥10 μg/L. Impaired responses were observed in 50, 65, and 71% of subjects with blood pentachlorophenol levels of ≤10, 11–20, and >20 μg/L, respectively. In the Daniel et al. (2001) study, inverse associations were found between blood pentachlorophenol levels and several cellular and humoral immune parameters including total lymphocyte count, specific lymphocyte subpopulations (CD3+, CD4+, CD16+, CD19+, DR+, and CD4/CD8 ratio), interleukin levels (IL-2, IL-2R, IL-6, IL-10), interferon gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and IgM-antiFab. An association was also found between pentachlorophenol blood levels and the number of impaired stimulation assays per person. Similar to the Daniel et al. (1995) study, individuals with blood pentachlorophenol levels of >10 μg/L were more likely to have blood lymphocyte counts and subpopulation counts that were below the mean level of healthy controls. In the Colosio et al. (1993b) study of workers who brushed technical-grade pentachlorophenol onto wood strips, a significant reduction in the lymphocyte response to phytohemagglutinin was observed among the highly exposed workers, as compared to controls.

COMMENT 12: A fertility paper Heacock et al, 1998 that was based on the same population as Dimich-Ward et al, 1996 should have been included in Section 2.16.

Heacock H, Hogg R, Marion SA, Hershler R, Teschke K, Dimich-Ward H, Demers P, Kelly S, Ostry A, Hertzman C. Fertility among a cohort of male sawmill workers exposed to chlorophenate fungicides. Epidemiology 1998;9(1):56-60.

RESPONSE: *The results of the Heacock et al. (1998) study was added to Section 2.16.*

A second epidemiological study examined fertility in approximately 24,000 men who worked for at least 1 year in 1 of 11 sawmills (Heacock et al. 1998); the men were exposed to chlorophenates (compounds not specified) and contaminants. A decrease in fertility was observed among the chlorophenate-exposed workers, as compared to controls. However, there was no relationship between cumulative exposure and fertility when adjusted for time since first hire.

COMMENT 13: In the description of Dimich-Ward et al, 1996 (Section 2.17) the authors describe the exposure as "CDD-contaminated chlorophenate." This is true of all pentachlorophenol that people are exposed to, so it is strange to call it out here. There were actually several validation studies conducted for the exposure assessment approach (which was also used for the cancer study by Demers et al in 2.19), where the exposure assessment was considered a strength.

RESPONSE: *The text was revised to indicate that the workers were exposed to chlorophenate and contaminants. Throughout the profile, co-exposure to contaminants is called out.*

Information on the developmental toxicity of pentachlorophenol in humans is limited. In a study of over 9,500 male sawmill workers exposed to chlorophenate (a mixture of the sodium salts of pentachlorophenol and tetrachlorophenol) and contaminants such as CDDs…

COMMENT 14: The paper below could be added as an additional reference.

Teschke K, Marion SA, Ostry A, Hertzman C, Hershler R, Dimich-Ward H, Kelly S. Reliability of retrospective chlorophenol exposure estimates over five decades. Am J Ind Med 1996;30(5):616-22.

RESPONSE: *The Teschke et al. (1996) study, which evaluated reliability of retrospective chlorophenol exposure estimates, was not considered relevant to the toxicological profile.*

COMMENT 15: I was surprised at the lack of text describing the key studies in Section 2.19. Although some key details are included in Table 2.3, this is one of the key disease outcomes so I expected more. For Demers et al in Table 2.3 selected results are only presented for the 4th quartile of exposure, which should be stated, and the correct RR for NHL in Table 2.3 is 1.71. Given that the dose-response analyses for this study are presented in Table 2.4, providing the overall SIRs and numbers observed for the cancers of interest would have been more useful.

RESPONSE: *It is beyond the scope of the profile to include detailed description of studies in Chapter 2. Table 2-3 was revised to list the overall standardized incidence ratio (SIR) values for non-Hodgkin lymphoma, multiple myeloma, and kidney cancer in the Demers et al. (2006) study.*

COMMENT 16: Hardell et al, 1995 says it is a meta-analysis that includes a 1999 study. I did not time to check this error.

RESPONSE: *The Hardell et al. (1995) study is a meta-analysis of four case-control studies.*

COMMENT 17: Ramlow et al, 1996 should be replaces by Collins et al, 2009. It a study of the same population with 9 additional years of follow-up and does have results for PCP workers not exposed to TCP (in a manner similar to Ruder and Yiin) with more detailed information on exposure to the trace contaminants and dose-response results.

Collins JJ, Bodner K, Aylward LL, Wilken M, Swaen G, Budinsky R, Rowlands C, Bodnar CM. Mortality Rates Among Workers Exposed to Dioxins in the Manufacture of Pentachlorophenol. J Occup Environ Med 2009;51(10):1212-9.

RESPONSE: *The Collins et al. (2009) study was added to Table 2-3.*

COMMENT 18: The results for Ruder and Yiin are for PCP workers not exposed to TCP rather than the full cohort. That is the results of interest, but it should say that in the Table.

RESPONSE: *In the Table 2-3* Reference and study population *column, it is noted that the Ruder and Yiin (2011) study excluded workers exposed to trichlorophenol.*

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 19: This is not my area of expertise.

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 20: This is not my area of expertise.

RESPONSE: *No response needed.*

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

COMMENT 21: Few of the human studies had dose-response analyses. However, Klemmer et al, 1980 did have some analyses examining the relationship with PCP, including serum cholinesterase that deserved mention. Daniel et al, 2001, which needs to be added to the document, had a number of dose-response analyses that will need to be added to the immune section. Collins et al, 2009, which needs to be added to the document has relevant dose-response results for NHL that should be reported. Animal studies are not my area of expertise.

RESPONSE: *Although the Klemmer et al. (1980) study found an association between pentachlorophenol and plasma cholinesterase levels, the average levels were within the normal range; the investigators noted that there were few clinically abnormal plasma cholinesterase levels. This association was not considered to be clinically relevant and was not included in the profile. The Daniel et al. (2001) study and the Collins et al. (2009) studies were added to the profile in Sections 2.14 and 2.19, respectively.*

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 22: Only those described above. I will send copies.

RESPONSE: *See Response to Comment 21.*

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 23: No, but the MRLs are derived from experimental studies and this is not my area of expertise

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 24: There was not adequate data on levels of exposure in the human studies to propose NOAELs or LOAELS.

RESPONSE: *ATSDR agrees with the Reviewer that the epidemiological data are inadequate for establishing NOAEL and LOAEL values.*

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 25: Yes, death and cancer, as well as significant developmental disorders and weight loss seemed reasonable.

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 26: This is not my area of expertise.

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 27: As mentioned earlier, I don't believe that Chapter 2 has a clear set of conclusions, with the exception of some clear sentences that state there is strong evidence for the liver as a target and that there is evidence for neurologic and developmental effects in the middle of those sections. In addition, for cancer Chapter 2 cites others conclusions (NTP, EPA, IARC) at the end. It would be good to have some conclusions regarding the other effects.

RESPONSE: *As noted in Section 2.1, the data for endpoints other than hepatic and developmental are inadequate to determine whether observed effects are due to pentachlorophenol or pentachlorophenol contaminants. HHS, EPA, and IARC conclusions regarding carcinogenicity are included in the profile since ATSDR does not conduct a weight-of-evidence evaluation as to carcinogenic potential in humans.*

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

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

COMMENT 28: This is not my area of expertise.

RESPONSE: *No response needed.*

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

COMMENT 29: 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 30: This is not my area of expertise**.**

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 31: The study by Dimich-Ward et al, 1996 (reported in Section 2.17), which observed congenital eye cataracks in the children of PCP exposed sawmill workers deserves mention here, especially given the animal evidence for developmental toxicity.

RESPONSE: *The findings of the Dimich-Ward et al. (1996) study was added to Section 3.2:*

> There are limited data on potential developmental effects in humans. One study did find an increase in congenital cataracts in children of male sawmill workers exposed to chlorophenate (Dimich-Ward et al. 1996).

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 32: I agree with the groups identified. I might have added highly exposed workers, especially those in hot environmental with a high potential for dermal exposure.

RESPONSE: *Section 3.2 discusses susceptible populations that may exhibit different or enhanced responses to pentachlorophenol than most persons exposed to the same level of pentachlorophenol in the environment. Populations with potential high exposures are discussed in Section 5.7. In Section 5.7, it is noted that there is a high risk for dermal contact in workers. ATSDR did not identify a source for the statement that there is an increased risk associated with hot environments.*

Biomarkers of Exposure and Effect

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

COMMENT 33: Although this is not my area of expertise, pentachlorophenol can be measured in urine and blood and has been, and could still be, used in studies of health effects. Although there are some other chemicals that metabolize to PCP (hexachlorobenzene (banned in the US in 1966 and lindane only used for head lice) should be rare.

RESPONSE: *As discussed in Section 3.3.1, ATSDR considers measurement of pentachlorophenol in body fluids and tissues to be a biomarker of exposure. Although the likelihood that the pentachlorophenol measured in body fluids is due to the metabolism of other compounds (e.g., hexachlorobenzene and lindane), the Agency considered it important to note this possibility in the profile.*

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

COMMENT 34: Not that I know of.

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 35: This is not my area of expertise.

RESPONSE: *No response needed.*

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 36: This is not my area of expertise.

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 37: It appears correct to me.

RESPONSE: *No response needed.*

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

COMMENT 38: I think that the focus on pentachlorophenol and sodium pentachlorophenate was appropriate.

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 39: I do not know of any better data to include. However, the second bullet (line 17, page 88) starts with "Professional pesticide applicators applying pentachlorophenol…". Perhaps practices are different in the US, but that does not happen in Canada (at least that I am aware of). Wood treatment is only allowed for limited products, such as utility poles and that is done in wood treatment facilities, where the highest exposures still occur. I would replace pesticide applicators with wood treatment workers and this is supported by Section 5.2.3.

RESPONSE: *The suggested revision was made in Section 5.1:*

- Professional wood treatment applicators applying pentachlorophenol as a wood preservative or employees involved in the manufacture and formulation of pentachlorophenol products are expected to have the greatest exposure, primarily through dermal and inhalation routes.

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 40: I do not know of any better information, though this is not my area of expertise.

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 41: I do not know of any better information, though this is not my area of expertise.

RESPONSE: *No response needed.*

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 42: I do not know of any better information and I thought the level of the descriptions were good.

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? If not, why? Which additional populations should be included in this section?

COMMENT 43: I found all of Chapter 5 to be quite well written. However, the first two sentences of Section 5.6 are odd. It starts with a broad statement on "contaminated environmental media, particularly contaminate waste sites," which is not supported by any of the following text. The second sentence begins with "Important routes of exposure inhalation of contaminated air" followed by a generic list. These two generic sentences were a bad way to start a very well-written section. Interestingly, the third sentence goes on to describe a Canadian study that says that food sources account for 74-89% and indoor air accounted for 10-25% of daily intake.

I think there is a solid case for children having a greater potential for exposure.

I agree with the authors that occupational groups are potentially highly exposed. I don't know where the authors of EPA(2008) visited, but I have visited wood treatment facilities and agree with the authors and NCI that there is a potential for high exposure. There is certainly strong evidence for occupational exposure being higher overall, although with few allowed uses that exposure should be rare. I also agree with the remaining observations in this section.

RESPONSE: *The first sentence of Section 5.6 was deleted. The second sentence was revised:*

> Potential sources of pentachlorophenol exposure for the general population included air, drinking water sources, food, soils, and dermal contact with contaminated products treated with the compound.

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 44: No studies, other than those I have already identified.

RESPONSE: *As noted in the Responses to Comments 11, 12, and 17, the studies identified by the Reviewer were added to the profile.*

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

COMMENT 45: It seems as though cancer is totally ignored in this chapter. Cancer as a health outcome, cancer epidemiology studies, and even studies of cancer in animals are never mentioned. Is that normal?

RESPONSE: *ATSDR did not identify a data gap for cancer effects. Thus, it was not included in Section 6.2.*

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

COMMENT 46: I think this was fine.

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 47: I am not aware of others that should be included.

RESPONSE: *No response needed.*

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

COMMENT 48: No.

RESPONSE: *No response needed.*

Comments provided by Peer Reviewer #2

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1

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: Additional emphasis on cancer effects is warranted. In particular, in humans, non-Hodgkin lymphoma is another health effect of PCP that would merit inclusion. In all of the epidemiological studies available at the time of the review by the IARC Working Group (2019), exposure to PCP was associated with an increased risk of non-Hodgkin lymphoma. This recent IARC Working Group classified PCP as "carcinogenic to humans" (Group 1) on the basis of the findings in epidemiological studies. The earlier reviews, in 2016 by DHHS and in 2010 by US EPA, also identified cancer effects to be of concern. Given the availability of three recent reviews that independently reached this conclusion, this issue merits additional attention and the relevant literature identified in these published reviews should be cited. In particular, results from a large cohort study of Canadian sawmill workers showed a significant increase in the incidence of non-Hodgkin lymphoma with cumulative exposure to PCP[1]. Significantly increased risk of non-Hodgkin lymphoma was also reported for a cohort of US pesticide manufacturing workers exposed to PCP[2] and results from two smaller studies[3,4] including pesticide manufacturing workers showed positive associations between exposure to PCP and non-Hodgkin lymphoma. Positive associations with non-Hodgkin lymphoma were also seen in three case-control studies in Sweden and New Zealand. Risk of multiple myeloma, now classified as a subtype of non-Hodgkin lymphoma, was also increased in several studies. Importantly, the pattern of excess cancers differed from that observed in populations that are highly exposed to dioxins, which are possible impurities of PCP.

RESPONSE: *The discussion of cancer effects in Section 1.2 was revised to indicate an association between pentachlorophenol and non-Hodgkin lymphoma based on HHS, EPA, and IARC assessments:*

> A number of epidemiological cohort and case-control studies have evaluated the potential associations between pentachlorophenol and cancer. In evaluating the available epidemiological data, the Department of Health and Human Services (HHS) (NTP 2016), U.S. Environmental Protection Agency (EPA) (IRIS 2010), and International Agency for Research on Cancer (IARC 2019) concluded that the data suggested an association between pentachlorophenol exposure and increased risk of non-Hodgkin lymphoma based on the consistent findings across epidemiological studies. The data for other cancer types were considered inadequate.

A more detailed discussion of cancer effects is presented in Section 2.19. The Demers et al. (2006), Kogevinas et al. (1995), and Ruder and Yiin (2005) studies are discussed in Section 2.19; the Collins et al. (2009) study was added to this section.

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[1] Demers PA, Davies HW, Friesen MC, et al. Cancer and occupational exposure to pentachlorophenol and tetrachlorophenol (Canada). Cancer Causes Control 2006;17: 749–58.
[2] Collins JJ, Bodner K, Aylward LL, et al. Mortality rates among workers exposed to dioxins in the manufacture of pentachlorophenol. J Occup Environ Med 2009; 51: 1212–19.
[3] Kogevinas M, Kauppinen T, Winkelmann R, et al. Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case-control studies. Epidemiology 1995; 6:396–402.
[4] Ruder AM, Yiin JH. Mortality of US pentachlorophenol production workers through 2005. Chemosphere 2011; 83: 851–61.

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: Cancer effects were also induced in animals, including in several studies that are not cited, encompassing those that used transgenic models. Given the strength of evidence that PCP causes non-Hodgkin lymphoma in humans, it would be appropriate to fully cite the relevant studies of cancer in experimental animals.

RESPONSE: *The discussion of cancer effects in Section 1.2 is intended to be a high-level summary. A discussion of all the available animal cancer studies is included in Section 2.19.*

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

COMMENT 3: Although the review is quite comprehensive, it may be beneficial to include incinerator emissions as a source of human exposure. It could also be useful to note that PCP is a persistent organic pollutant (listed in Annex A of the Stockholm Convention).

RESPONSE: *ATSDR was unable to find a reliable source of human exposure from incinerator emission. A study of trial burns of hazardous waste incinerators, some of which were specifically conducted to measure semivolatile compounds such as pentachlorophenol, found that the risk associated with stack emission appeared to be inconsequential (Sedman and Esparza 1991; Environ Health Perspect 94:181-187). Additionally, IARC (2019) reported that urinary pentachlorophenol levels in hazardous waste and municipal waste incinerator workers were similar to those in unexposed workers.*

A statement was added to Section 5.1 regarding the Stockholm Convention:

- Pentachlorophenol is a persistent organic pollutant listed in the Stockholm Convention, Annex A.

Minimal Risk Levels (MRLs)

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

COMMENT 4: The MRLs are reasonable as derived.

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 5: Please see comments in the document. In general, the discussion of cancer could be enhanced by a more complete citation and appropriate discussion of the relevant literature. The recent reviews by USEPA, DHHS and IARC may be useful as a source of references and the important considerations for interpreting the available evidence.

RESPONSE: *Several epidemiological studies (Collins et al. 2009; Hardell et al. 2002; Pearce et al. 1986a, 1986b; Ward et al. 2009) suggested by this Reviewer and other Peer Reviewers were added to Section 2.19. ATSDR does not draw conclusions regarding the carcinogenic potential of pollutants. A statement regarding HHS, EPA, and IARC conclusions were added to Section 2.19:*

> A number of epidemiological cohort and case-control studies have evaluated the potential associations between pentachlorophenol and cancer. In evaluating the available epidemiological data, the Department of Health and Human Services (HHS) (NTP 2016), U.S. Environmental Protection Agency (EPA) (IRIS 2010), and International Agency for Research on Cancer (IARC 2019) concluded that the data suggested an association between pentachlorophenol exposure and increased risk of non-Hodgkin lymphoma based on the consistent findings across epidemiological studies. The data for other cancer types were considered inadequate.

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 6: This issue is generally well-addressed, however, the discussion of the epidemiological studies of cancer may merit review. Although it may be appropriate to focus on a selection of studies, this selection should rely on the latest publications from a population (e.g., of a cohort) and should also rely on the most adjusted values that are reported within a publication. A key concern in interpreting the PCP studies of cancer is the possible confounding by dioxins, but this issue is not discussed. As noted above, the pattern of excess cancers differed from that observed in populations that are highly exposed to dioxins

RESPONSE: *As noted in the Response to Comment 5, the discussion of epidemiological data has been expanded to include additional studies. Regarding the comment on possible confounding by dioxins, the following text was added to Section 2.19:*

> Exposure to technical-grade and commercial-grade pentachlorophenol can result in concomitant exposure to a number of contaminants, particularly other chlorophenols, CDDs, and CDFs. As discussed in IARC (2019), some of the epidemiological studies (e.g., Collins et al. 2009; Demers et al. 2006) have assessed co-exposure to other chlorophenols and several CDDs and CDFs by using high-quality exposure assessment techniques, including measurement of CDD and CDF serum levels and estimation of cumulative dermal exposure to pentachlorophenol. IARC (2019) and EPA (2010) noted that the types of cancers observed in the pentachlorophenol workers (primarily non-Hodgkin lymphoma) differed from the pattern reported in epidemiological studies of persons highly exposed to dioxins (all cancers combined, lung cancer, soft tissue sarcoma, and non-Hodgkin lymphoma). Additionally, EPA (2010) noted that in the Kogevinas et al. (1995) study, the association between non-Hodgkin lymphoma and pentachlorophenol was stronger than the associations with CDDs and CDFs. In studies of laboratory animals, the pattern of excess cancers was similar for pure pentachlorophenol, technical-grade pentachlorophenol, and commercial-grade pentachlorophenol.

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 7: There are several high-quality animal studies not cited in the text (see comments).

RESPONSE: *See Responses to specific comments in the Annotated Comments section of this document.*

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 8: Yes.

RESPONSE: *No response needed.*

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

COMMENT 9: 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? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT 10: As identified as comments in the document, there are several key studies of cancer in humans and of cancer in experimental animals that were cited in other reviews, notably that by IARC (2019), that are not included in the review. As US EPA, DHHS and IARC have conducted recent reviews, it is advisable to obtain the reference lists and any relevant full text articles from these three organizations for inclusion in the present document.

RESPONSE: *See Response to specific comments in the Annotated Comments section of this document.*

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 11: No, but it would be prudent to review the studies identified as suggested above for relevance to deriving MRLs.

RESPONSE: *The studies suggested by the Reviewer (see Comments 34, 37, 38, and 39) are cancer studies and were not considered adequate for MRL derivation because they did not examine noncancer endpoints, were in transgenic mice, or involved exposure to other compounds (initiation-promotion studies).*

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 12: 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 13: 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 14: It is challenging to address all possible mechanisms of action, however, some gaps are notable. In particular, greater emphasis is warranted on evidence that PCP is metabolically activated to electrophiles and redox-cycling metabolites; and that it induces oxidative stress, which when enhanced in transgenic mouse models increases susceptibility to carcinogenesis (see Tasaki et al., 2014; PMID:23988840). PCP is also genotoxic, inducing oxidative damage to DNA (as noted in the review) and also increases cell proliferation in various experimental systems. It may be helpful to structure the discussion in the review according to the key characteristics of carcinogens (see see Smith et al., 2016; PMID: 26600562) as these provide a systematic approach to assembling and organizing the relevant literature, and a greater focus on evidence that is directly relevant to carcinogens.

RESPONSE: *Section 2.21 is intended to be a discussion of the mechanisms of action that span across health effects. A brief discussion of the carcinogenic mechanism was added to Section 2.19.*

As reviewed by EPA (2010) and IARC (2019), there is evidence of several carcinogenic mechanisms of action for pentachlorophenol:

- *Oxidative stress.* Increases in reactive oxygen species, oxidative stress markers, and deoxyribonucleic acid (DNA) adducts associated with oxidative stress have been found in *in vitro* studies in human cells and mammalian cells, *in vivo* studies in laboratory animals, and non-mammalian test systems in response to exposure with pentachlorophenol or its metabolites (tetrachlorohydroquinone [TCHQ] and tetrachlorobenzoquinone). Several studies in mice have found dose- and time-related increases in 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels in the liver; the cumulative oxidative DNA damage could result in critical mutations.
- *Genotoxicity.* Genotoxic effects (e.g., chromosomal aberrations, sister chromatid exchanges, and single strand breaks) have been observed in *in vitro* mammalian cells exposed to pentachlorophenol or TCHQ. Mixed results have been found in *in vivo* studies for micronuclei formation, chromosomal aberrations, or sister chromatid exchanges in human lymphocytes or in rats or mice exposed to pentachlorophenol.
- *Modulation of receptor-mediated effects.* There are some suggestive data that pentachlorophenol can interact with several nuclear receptor subtypes including estrogen receptors and the Ah receptor.
- *Alterations in cell proliferation or death. In vitro* studies in human cell lines have demonstrated pentachlorophenol- and/or TCHQ-induced alterations in the expression of several genes relevant to apoptosis. *In vivo* mouse studies have demonstrated increased cell proliferation and inhibition of gap junction intercellular communication in hepatocytes.

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 15: It would be appropriate to better align the conclusions on carcinogenicity with those other expert reviews, including as recently conducted by US EPA, DHHS and IARC. As PCP is a persistent organic pollutant, it is especially important to characterize appropriately the chronic health effects including cancer.

RESPONSE: *The discussion of the epidemiological carcinogenicity studies has been revised and includes HHS', EPA's, and IARC's conclusions:*

> Based on the results of cohort and case-control studies, HHS (NTP 2016), EPA (IRIS 2010), and IARC (2019) concluded that the available data demonstrated an association between pentachlorophenol and non-Hodgkin lymphoma. IARC (2019) considered the data sufficient to establish a causal relationship; HHS (NTP 2016) considered the data to be suggestive of a causal relationship but noted that it has not been established. Although increases in the risk of other tumor types were observed in some studies, IARC (2019) concluded that the findings for other tumor sites were inconsistent across studies.

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 16: Yes.

RESPONSE: *No response needed.*

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

COMMENT 17: 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 18: Yes.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

COMMENT 19: The data cited are appropriate to this issue.

RESPONSE: *No response needed.*

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 20: Yes, this discussion is appropriate.

RESPONSE: *No response needed.*

Biomarkers of Exposure and Effect

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

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

COMMENT 21: Both are appropriate. Given the prominence of oxidative damage to DNA as a biomarker, it would be appropriate to enhance the discussion of this endpoint under "Mechanisms of Action" (see also above).

RESPONSE: *As noted in the Response to Comment 14, a discussion of carcinogenicity mechanisms of action, including oxidative DNA damage was added to Section 2.19.*

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 22: Yes

RESPONSE: *No response needed.*

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 23: Yes

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.

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

COMMENT 24: The information is appropriately presented.

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.

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.

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.

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.

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 25: While the text is appropriate in providing the information as outlined above, it may be useful to include mention that PCP is a Persistent Organic Pollutant that is included in Annex A of the Stockholm Convention. This has certain implications, including that parties must take steps to eliminate production and use unless they have registered for an exemption. In addition, the reader may not be aware that PCP is recognized to be a persistent organic pollutant.

RESPONSE: *The following bullet was added to Section 5.1:*

- Pentachlorophenol is a persistent organic pollutant listed in the Stockholm Convention, Annex A.

Chapter 6. Adequacy of the Database

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

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

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

COMMENT 26: In general these points are well-covered. However, given that several important references cited in other reviews have been not been cited in this review, it would be useful to revisit this text if a more inclusive approach to the references may be adopted.

RESPONSE: *The Reviewer suggested the addition of several epidemiological and toxicological studies that examined the carcinogenicity of pentachlorophenol. These studies were added to Section 2.19. The addition of these studies did not result in changes in the identified data gaps or prompt additional data needs.*

Chapter 7. Regulations and Guidelines

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

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

COMMENT 27: This section is appropriate.

RESPONSE: *No response needed.*

Appendices

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

COMMENT 28: Please see the comments on the literature search strategy, and the screening according to inclusion and exclusion criteria. While the risk of bias tool employed does capture some key issues, it doesn't necessarily reflect the key issues with respect to any of the data streams relied upon in the review. Major limitations of these tools include that it is not possible to account for the direction of bias, and that various factors are given apparently equal weight. As a result this can complicate consideration of the key issues across the database

RESPONSE: *ATSDR thanks the Reviewer for their comments on the systematic review framework and will take these recommendations into consideration in future updates of the framework.*

Annotated Comments on the Toxicological Profile

Responses to Reviewer comments that were not considered editorial or stylistic are presented below.

COMMENT 29: The Reviewer made the following comment in Section 1.2, Cancer Effects: "Given the comments, and that other organisations have categorized PCP as a reasonably anticipated/likely to be carcinogenic or carcinogenic, would it be appropriate to give greater weight to cancer effects?"

RESPONSE: *The discussion of the epidemiological carcinogenicity studies was revised and includes HHS', EPA's and IARC's weight-of-evidence conclusions:*

A number of epidemiological cohort and case-control studies have evaluated the potential associations between pentachlorophenol and cancer. In evaluating the available epidemiological data,

the Department of Health and Human Services (HHS) (NTP 2016), U.S. Environmental Protection Agency (EPA) (IRIS 2010), and International Agency for Research on Cancer (IARC 2019) concluded that the data suggested an association between pentachlorophenol exposure and increased risk of non-Hodgkin lymphoma based on the consistent findings across epidemiological studies. The data for other cancer types were considered inadequate.

COMMENT 30: Referring to the statement in Section 1.2, Cancer Effects — Some cohort studies and case-control studies have found associations between pentachlorophenol exposure and increased cancer risks (Demers et al. 2006; Hardell et al. 1994, 1995; Ramlow et al. 1996; Ruder and Yiin 2011), but other studies have not found associations (Hardell and Eriksson 1999; Kogevinas et al. 1995) — the Reviewer commented "These conclusions may merit review, and would require further justification, if they are retained. It is also not clear if they apply to cancer generally or to a particular type of cancer. As noted below, other expert reviews have concluded that all of the available epidemiological studies are essentially showing an increased risk of NHL with PCP exposure. This conclusion may be more appropriately supported, given the available evidence."

RESPONSE: *As noted in the Response to Comment 29, the discussion of the human cancer studies has been revised; the revision includes HHS', EPA's, and IARC's conclusion that there is an increased risk of non-Hodgkin lymphoma associated with pentachlorophenol exposure.*

COMMENT 31: Referring to the statement and references sited in Section 1.2, Cancer Effects — …but other studies have not found associations (Hardell and Eriksson 1999; Kogevinas et al. 1995) — the Reviewer commented " Hardell and Eriksonn (1999) was included in a later pooled analysis (Hardell et al. 2002), which is not referenced. It is of note it would not be appropriate to consider that this case-control would not balance out the positive findings in the larger, higher-quality cohort studies from different geographical regions (including Demers et al., 2006 and Collins et al. 2009 [this study also isn't referenced?] as well as the smaller cohort studies e.g., by Ruder and Yiin 2011). It's also not clear why Kogeveinas et al. 1995 was considered to not find an association; there were only 3 cases of NHL reported, all in the highest PCP exposure category, albeit from the British cohort."

RESPONSE: *In the revision to the discussion of cancer effects in Section 1.2 (see revised text in the Response to Comment 29), the referenced statement was deleted.*

COMMENT 32: Referring to animal studies in Section 1.2, Cancer Effects, the Reviewer made the following comment: "The IARC review discuses additional tumour sites in additional studies in experimental animals, which could be included here for completeness; the studies are detailed in Section 3 of the Monograph on Pentachlorophenol available at https://publications.iarc.fr/574."

RESPONSE: *The text in Section 1.2 was revised to include the increased incidence of hemangiosarcomas in mice:*

Oral exposure to a commercial-grade pentachlorophenol (EC-7) or technical-grade pentachlorophenol resulted in hepatocellular adenomas/carcinomas, adrenal pheochromocytomas, and hemangiosarcomas in mice (NTP 1989).

COMMENT 33: Referring to the classification of pentachlorophenol as a carcinogen in Section 1.2, Cancer Effects, the Reviewer commented "As the findings of these organisations would seem to contrast

with those given above with regard to the epidemiological evidence regarding carcinogencity, it may be appropriate to review and adjust these conclusions accordingly."

RESPONSE: *As noted in the Response to Comment 29, the discussion of the epidemiological studies in Section 1.2 was revised and is consistent with the HHS, EPA, and IARC cancer classifications.*

COMMENT 34: Referring to Table 2-2 Chronic Exposure, the Reviewer commented "Several of the available chronic studies are not included in this list, including:

Tasaki M, Kuroiwa Y, Inoue T, Hibi D, Matsushita K, Kijima A, et al. (2014). Lack of nrf2 results in progression of proliferative lesions to neoplasms induced by long-term exposure to non-genotoxic hepatocarcinogens involving oxidative stress. *Exp Toxicol Pathol*, 66(1):19–26. doi:10.1016/j.etp.2013.07.003 PMID:23988840

Spalding JW, French JE, Stasiewicz S, Furedi-Machacek M, Conner F, Tice RR, et al. (2000). Responses of transgenic mouse lines p53(+/-) and Tg.AC to agents tested in conventional carcinogenicity bioassays. *Toxicol Sci*, 53(2):213–23. doi:10.1093/toxsci/53.2.213 PMID:10696769

Umemura T, Kai S, Hasegawa R, Kanki K, Kitamura Y, Nishikawa A, et al. (2003a). Prevention of dual promoting effects of pentachlorophenol, an environmental pollutant, on diethylnitrosamine-induced hepato- and cholangiocarcinogenesis in mice by green tea infusion. *Carcinogenesis*, 24(6):1105–9. doi:10.1093/carcin/bgg053 PMID:12807750

Umemura T, Kai S, Hasegawa R, Sai K, Kurokawa Y, Williams GM (1999). Pentachlorophenol (PCP) produces liver oxidative stress and promotes but does not initiate hepatocarcinogenesis in B6C3F1 mice. *Carcinogenesis*, 20(6):1115–20. doi:10.1093/carcin/20.6.1115 PMID:10357797

Umemura T, Kodama Y, Kanki K, Iatropoulos MJ, Nishikawa A, Hirose M, et al. (2003b). Pentachlorophenol (but not phenobarbital) promotes intrahepatic biliary cysts induced by diethylnitrosamine to cholangio cystic neoplasms in B6C3F1 mice possibly due to oxidative stress. *Toxicol Pathol*, 31(1):10–3. doi:10.1080/01926230390173806 PMID:12597444"

RESPONSE: *The Umemura et al. (1999, 2003a, 2003b), and Tasaki et al. (2014) studies were added to Section 2.19, but were not added to the oral LSE table (Table 2-2). The LSE table does not typically include mechanistic studies utilizing transgenic strains or initiation-promotion studies. The Spalding et al. (2000) dermal study with transgenic mice was also added to Section 2.19.*

COMMENT 35: The Reviewer made the following comment in Section 2.7: "Suggest to include McConnachie & Zahalsky, 1991 (PMID:2069434); Colosi et al., 1993 (PMID:8476309), which together with Roberts (1983) indicate effects such as increased activation of T cells, increased incidence of autoimmunity, and immunosuppression and B-cell dysregulation."

RESPONSE: *Effects on T-cells and B-cells are considered immune effects and are discussed in Section 2.14; the McConnachie and Zahalsky (1991) and Colosio et al. (1993b) studies are included in the discussion of immune effects in Section 2.14. The Roberts (1983) study is discussed in the Hematological section (Section 2.7).*

COMMENT 36: Referring to the Begley et al. (1977) study discussion in Section 2.10 — Considerable improvement in these symptoms was seen following a 20-day absence from work — the Reviewer commented "It may be important to note that the values for creatine clearance remained depressed in 6 (1/3) of the workers whereas phosphorus reabsorption remained depressed in several subjects despite the relatively long (20 d) absence from work. Therefore, conclusion that renal toxicant effects are reversible merits review. In addition, the study noted renewed impairment following renewed work exposure."

RESPONSE: *The discussion of the Begley et al. (1977) study was revised to note that depressed creatinine clearance and phosphorus reabsorption were still found in some of the workers.*

Considerable improvement in these symptoms was seen following a 20-day absence from work, although creatinine clearance was still depressed in 6 of the 18 workers and phosphorus reabsorption was depressed in 3 of 18 workers.

COMMENT 37: Referring to the cohort studies cited in Section 2.19, the Reviewer made the following comment: "Suggest to include Collins et al. (2009):

Collins JJ, Bodner K, Aylward LL, Wilken M, Swaen G, Budinsky R, et al. (2009). Mortality rates among workers exposed to dioxins in the manufacture of pentachlorophenol. *J Occup Environ Med*, 51(10):1212–9. doi:10.1097/JOM.0b013e3181badd4e PMID:19786897"

RESPONSE: *The results of the Collins et al. (2009) study were added to Table 2-3 in Section 2.19.*

COMMENT 38: Referring to the case-control studies cited in Section 2.19, the Reviewer made the following comments: "Suggest to include the New Zealand study of Pearce et al (1986) and also the study by Ward et al (2009):

Pearce NE, Smith AH, Howard JK, Sheppard RA, Giles HJ, Teague CA (1986a). Non-Hodgkin's lymphoma and exposure to phenoxyherbicides, chlorophenols, fencing work, and meat works employment: a case-control study. *Br J Ind Med*, 43(2):75–83. PMID:3753879

Pearce NE, Smith AH, Howard JK, Sheppard RA, Giles HJ, Teague CA (1986b). Case-control study of multiple myeloma and farming. *Br J Cancer*, 54(3):493–500. doi:10.1038/bjc.1986.202 PMID:3756085

Ward MH, Colt JS, Metayer C, Gunier RB, Lubin J, Crouse V, et al. (2009). Residential exposure to polychlorinated biphenyls and organochlorine pesticides and risk of childhood leukemia. *Environ Health Perspect*, 117(6):1007–13. doi:10.1289/ehp.0900583 PMID:19590698

RESPONSE: *The Ward et al. (2009) and Pearce et al. (1986a, 1986b) studies were added to Section 2.19.*

COMMENT 39: The Reviewer made the following comment in Section 2.19 referring to the Hardell et al. (1994, 1995) case-control studies: "The later pooled analysis by Hardell et al (2002) could be cited."

RESPONSE: *The Hardell et al. (2002) paper was added to Section 2.19.*

COMMENT 40: Referring to Table 2-3, the Reviewer commented "It is not clear how these studies were "selected". In some cases they are not the most recent publication from the population under study. In addition, the most adjusted odds ratios are usually most appropriate to include from any of the studies."

RESPONSE: *As noted in the Responses to Comments 37, 38, and 39, Table 2-3 was updated to include the Collins et al. (2009), Ward et al. (2009), Pearce et al. (1986a, 1986b), and Hardell et al. (2002) papers. The adjusted odds ratios, if available, are reported in Table 2-3.*

COMMENT 41: Referring to the statement in Section 2.19— The carcinogenicity of pentachlorophenol has been evaluated in several oral exposure studies in rats and mice (NCI 1968; NTP 1989, 1999; Schwetz et al. 1978) — the Reviewer commented "As noted above (see comment on Table), there are additional chronic studies in rodents that reported on carcinogenicity could be added to this discussion."

RESPONSE: *As noted in the Response to Comment 34, the Umemura et al. (1999, 2003a, 2003b), Tasaki et al. (2014), and Spalding et al. (2000) studies were added to Section 2.19.*

COMMENT 42: Referring to the discussion of mechanism of action in Section 2.21, the Reviewer commented: "This discussion may benefit from structuring it according to key characteristics of carcinogens (see Smith et al., 2016; PMID: 26600562). It is of note that PCP is metabolically activated to electrophiles (benzoquinone) as well as redox-cycling semiquinones. In addition, PCP induces oxidative stress and is genotoxic; notably, studies in Nrf2-knockout mice demonstrated that dysregulation of antioxidant expression increased PCP-induced oxidative damage, cholangiofibrosis and cholangiocarcinomas (Tasaki et al., 2014; PMID:23988840). PCP induces oxidative damage to DNA as well as other types of DNA damage (in human cells in vitro, in yeast and in bacterial assays that are sensitive to this type of DNA damage). Metabolites such as TCHQ induce mutation, micronulei, and DNA strand breaks. PCP also increases cell proliferation in mouse hepatocytes, intrahepatic bile duct epithelia and skin."

RESPONSE: *The intent of Section 2.21 is a general discussion of the mechanisms of action; it is not specific to carcinogenic mechanisms. A discussion of carcinogenic mechanisms was added to Section 2.19:*

As reviewed by EPA (2010) and IARC (2019), there is evidence of several carcinogenic mechanisms of action for pentachlorophenol:

- *Oxidative stress.* Increases in reactive oxygen species, oxidative stress markers, and deoxyribonucleic acid (DNA) adducts associated with oxidative stress have been found in *in vitro* studies in human cells and mammalian cells, *in vivo* studies in laboratory animals, and in non-mammalian test systems in response to exposure with pentachlorophenol or its metabolites (tetrachlorohydroquinone [TCHQ] and tetrachlorobenzoquinone). Several studies in mice have found dose- and time-related increases in 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels in the liver; the cumulative oxidative DNA damage could result in critical mutations.
- *Genotoxicity.* Genotoxic effects (e.g., chromosomal aberrations, sister chromatid exchanges, and single strand breaks) have been observed in *in vitro* mammalian cells exposed to pentachlorophenol or TCHQ. Mixed results have been found in *in vivo* studies for micronuclei formation, chromosomal aberrations, or sister chromatid exchanges in human lymphocytes or in rats or mice exposed to pentachlorophenol.
- *Modulation of receptor-mediated effects.* There are some suggestive data that pentachlorophenol can interact with several nuclear receptor subtypes including estrogen receptors and the Ah receptor.

- *Alterations in cell proliferation or death. In vitro* studies in human cell lines have demonstrated pentachlorophenol-and/or TCHQ-induced alterations in the expression of several genes relevant to apoptosis. *In vivo* mouse studies have demonstrated increased cell proliferation and inhibition of gap junction intercellular communication in hepatocytes.

COMMENT 43: The Reviewer made the following comment in Section 6.2, Production, Import/Export, Use, Release and Disposal: "It may be important to note that PCP is listed in Annex A of the Stockholm Convention on Persistent Organic Pollutants, under which parties must take steps to eliminate production and use unless they have registered for an exemption."

RESPONSE: *A note was added to Section 5.1:*

- Pentachlorophenol is a persistent organic pollutant listed in the Stockholm Convention, Annex A.

COMMENT 44: Referring to Table B-1, the Reviewer commented "It is very helpful to see the Inclusion criteria, but a list of exclusion criteria may also be helpful, especially if the references recommended above for citation in the review were identified by the search, but deemed not relevant to include for some reason."

RESPONSE: *Some studies identified by the Reviewer were not found in the literature search; this could be due to the literature search database keywords not including the term "pentachlorophenol."*

COMMENT 45: Referring to the PubMed Query string in Table B-2, the Reviewer commented "This appears to be an exhaustive list of possible keywords, but it would be interesting to know what may be gained by the additional terms compared with a more simple combination of MH and TW (e.g., Pentachlorophenol[mh] OR pentachlorophenol[tw])."

RESPONSE: *The tag [mh] indicates that the paper was indexed to pentachlorophenol and was deemed by the Pubmed index team to be relevant to the compound of interest. For those items not yet indexed, the search is broadened to include any abstract that contains the text word [tw] pentachlorophenol. The strategy with additional keywords and synonyms further expands the search to make sure that no relevant papers are missed.*

COMMENT 46: Referring to the statement in section C.2.1 –Number of studies considered relevant and moved to the next step: 181– the Reviewer commented "This number is lower than would be expected; for instance, Guyton et al. (PMID: 29562322; see Figure 1) reported including 611 articles for the Section on "Mechanistic and other relevant data" of the IARC Monograph on PCP (2019), which is more limited in scope than the present review."

RESPONSE: *In Section C.2.2, the initial title and abstract screen identifies studies examining health effects; it does not include mechanistic data.*

COMMENT 47*:* Referring to the Umemura et al. (2006) study in Table C-9, confidence in the exposure characterization, the Reviewer commented "The rationale for this rating is not clear."

RESPONSE: *Confidence in the exposure characterization for the Umemura et al. (2006) study was rated as "high risk of bias" because the study did not provide information (e.g., body weight or food*

intake) that could be used to estimate doses; ATSDR had to rely on reference body weight and food intake data to calculate doses. Using reference values may have resulted in an over- or underestimation of the dose.

Comments provided by Peer Reviewer #3:

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1

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: Yes, as many of these effects can only be observed in animals in well controlled studies. Should exposures in humans achieve the levels tested in animals, similar effects may occur in humans. Maintaining exposure below these toxic levels is important in the risk assessment process.

RESPONSE: *No response needed.*

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

COMMENT 3: As noted in my comments in the text, the fourth endpoint of developmental toxicity, functional deficit has not evaluated in animal studies. Juvenile toxicity, exposure to young animals has been evaluated especially for some functional deficits, for example to the immune system and these should be noted in this section.

RESPONSE: *There are limited data on effects in children, which are discussed As discussed in in Section 3.2, there are some data in humans on functional impairment in children exposed to pentachlorophenol; however, there are a limited number of quality studies evaluating this aspect of developmental toxicity in animals. A data need was identified in Section 6.2 (Health Effects, Developmental) for studies in evaluating possible effects on the reproductive system and other possible functional impairments, such as development of the nervous system or immune system.*

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: It is agreed that the inhalation database was not adequate for deriving inhalation MRLs. The oral database was considered adequate for derivation of acute- and chronic-duration oral MRLs for pentachlorophenol.

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.

a. Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT 5: Agree with proposed MRL values.

RESPONSE: *No response needed.*

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

COMMENT 6: There needs to be a definition of developmental toxicity falling in both acute and intermediate exposure and the mg/kg/day values differed slightly.

RESPONSE: *Studies are categorized based on the duration of exposure (defined in Section 2.1); thus, developmental studies could be categorized as acute or intermediate duration. The doses are not duration specific.*

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 7: 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)? 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 8: Adequate human studies were not identified nor, do they probably exist as most human studies have limitations. The limitations of the studies were adequately described in the text and appendices.

RESPONSE: *No response needed.*

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: There were several adequately designed animal studies identified to cover most toxicology endpoints. There is a paucity of data on the potential effects of pentachlorophenol, with or without contaminants to study functional deficiencies that might have resulted from in utero exposure.

RESPONSE: *A data need for additional developmental studies evaluating possible function impairments was added to Section 6.2:*

> One study reported impaired development of the reproductive system (Bernard et al. 2002). Additional studies are needed to further evaluate possible effects on the reproductive system and to evaluate other possible functional impairments, such as impaired development of the nervous system or immune system.

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: Animal studies in the common laboratory species were conducted. There is a paucity of data on the potential effects of pentachlorophenol, with or without contaminants to study functional deficiencies that might have resulted from in utero exposure.

RESPONSE: *See the Response to Comment 9.*

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

COMMENT 11: As appropriate, dose-response relationships were considered. In some cases, in the text indicating the % change in a parameter would help the reader to assess the impact of a change.

RESPONSE: *The percent change in a parameter is reported in the LSE tables (Tables 2-1 and 2-2).*

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: The studies evaluated and the nature of the search to obtain all available reports appears to be complete.

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 13: 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? Please suggest appropriate changes.

COMMENT 14: This reviewer feels the NOAELs and LOAELs identified were appropriate.

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: The categorization of "less serious" verses "serious" for effects cited in the LSE tables does not seem appropriate for a finding like resorption (embryo fetal death) or malformation. It is the opinion of this Reviewer that these end points of developmental toxicity should be considered serious.

RESPONSE: *Malformations are categorized as less serious or serious based on the endpoint. For example, skeletal anomalies such as sternebrae variations are considered less serious, and cleft palate are considered a serious effect. Resorptions are categorized as serious effects. The increased resorptions in the Bernard and Hoberman (2001), Schwetz et al. (1974), and Walsh et al. (1987) studies were corrected to be serious LOAELs in Table 2-2.*

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: Little in the report noted that a functional deficit may result from an in-utero exposure. The embryo-fetal toxicity studies presented only cover three of the four developmental manifestations of exposure (death, malformation and fetal growth) it should be recognized that only in a study in which offspring are delivered could functional deficits be evaluated. Some of these endpoints are evaluated in a multigenerational study but information from these studies are not noted under developmental toxicity. Information from a multigenerational study or one generational study such as an extended one-generational study does provide supportive information on the evolution of effects observed on delays in development or fetal weight effects that may be observed in the developmental toxicity studies.

RESPONSE: *ATSDR assumes that the multigeneration study referenced by the Reviewer is the Bernard et al. (2002) study. The findings that exposure to pentachlorophenol may impair the development of the reproductive system is discussed in Section 2.17 (Developmental). As noted in the Response to Comment 9, a data need for additional studies examining potential functional deficits is discussed in Section 6.2.*

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 conclusions are appropriate but could be strengthened for developmental toxicity if as noted above in "10)" information on functional development is included in the text under developmental toxicity.

RESPONSE: *See Response to Comment 9.*

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: The discussion of ADME was adequate.

RESPONSE: *No response needed.*

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

COMMENT 19: Yes, the PK/PD models are adequate.

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 20: With the exception that effects in very young rodents may have been due to differences in the functionality of the blood brain barrier and the development of metabolic enzymes compared to other species including humans, there was adequate discussion of the data.

RESPONSE: *As noted in the Response to Comment 3, a data need for studies examining juvenile animals is discussed in Section 6.2.*

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: See response to "3)" above. The Reviewers comment: "Response to "3)" above" refers to Comment 20.

RESPONSE: *See Response to Comment 20.*

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: See response to "3)" above. The Reviewers comments: "Response to "3)" above" refers to Comment 20.

RESPONSE: *See Response to Comment 20.*

Biomarkers of Exposure and Effect

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

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

COMMENT 23: The biomarker discussion on exposure and effects appears adequate.

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 24: As noted, the information on interactive effects is limited.

RESPONSE: *No response needed.*

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 25: I know of no other information on mechanisms of interactions.

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.

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

COMMENT 26: The information presented appears adequate and correct.

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.

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.

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.

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.

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 27: This is not area of expertise for this Reviewer. The information presented appears to summarize what would be needed to aid in any risk assessment that might be conducted for the various sources of exposure.

RESPONSE: *No response needed.*

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 28: I am not aware of any other studies that should have been reviewed.

RESPONSE: *No response needed.*

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

COMMENT 29: The acute and intermediate MRLs discusses developmental toxicity, but the reasons for inclusion under both categories is not noted. Are there different endpoints considered for each category? Reproductive toxicity is noted in a separate section but as noted above, some of the endpoints evaluated in these studies will be important in the complete evaluation of developmental toxicity. These reproductive studies, especially multigenerational studies should be noted in the intermediate MRLs.

RESPONSE: *As discussed in Section 2.1, studies are categorized into three exposure periods (acute, intermediate, or chronic) based on the duration of the study. Thus, developmental toxicity studies could fall into the acute exposure period if the study duration is ≤14 days or intermediate duration if it is between 15 and 364 days. ATSDR acknowledges that it can be difficult to distinguish between reproductive and developmental effects. For the purpose of the profile, ATSDR defines reproductive effects as effects resulting from exposures during the interval from the generation of the parental germ cell to conception through implantation of the offspring. Post-implantation effects are considered developmental effects. When evaluating the potential developmental toxicity of a chemical, ATSDR considers both reproductive and developmental effects. The 2-generation study conducted by Bernard et*

al. (2002) is considered an intermediate-duration study and was evaluated during the derivation of the intermediate-duration oral MRL.

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

COMMENT 30: The data need was fair and presented adequately. As is noted and as was noted by this Reviewer, "Studies are required to identify childhood-specific means of decreasing exposure to pentachlorophenol.".

RESPONSE: *The need for studies on reducing childhood exposures is identified in Section 6.2 (Exposures to Children).*

Chapter 7. Regulations and Guidelines

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

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

COMMENT 31: There would be values in including information from an OECD 443 Extended One - Generational Study, however it is understood that the database was developed prior to the issuance of this guidance or the issuance of OECD guidelines for conduct of embryo fetal toxicity studies that included evaluations of potential endocrine interactions.

RESPONSE: *Chapter 7 discusses regulations and guidelines developed to protect human health. It does not evaluate whether studies in the profile meet OECD guidelines.*

Appendices

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

COMMENT 32: The appendices were very helpful in understanding the entire document. It was valuable to be pointed to them prior to reviewing the entire document.

RESPONSE: *No response needed.*

Annotated Comments on the Toxicological Profile

Responses to Reviewer comments that were not considered editorial or stylistic are presented below.

COMMENT 33: Referring to the exposure conditions in the statement in Section 1.2—These studies have evaluated a wide range of potential endpoints following acute, intermediate, or chronic exposure. – the Reviewer commented "Did not mention DART or juvenile. Might want to add including during pregnancy and in juvenile animals."

RESPONSE: *The referenced sentence is a generic statement; no specific endpoints were called out. The available developmental and reproductive toxicity (DART) studies would fall under acute- or intermediate-duration studies.*

COMMENT 34: Referring to the statement in Section 1.2 -- Developmental effects are a presumed health effect for humans--, the Reviewer commented "Including offspring"

RESPONSE: *ATSDR is unclear about the meaning of the Reviewer's comment.*

COMMENT 35: Referring to the statement in section 1.2, Developmental Effects-- …and decreases in growth (Bernard and Hoberman 2001; Courtney et al. 1976; Larsen et al. 1975; Schwetz et al. 1974)—the Reviewer highlighted the Schwetz study and commented "Nothing on functional deficiet, this fact should be noted."

RESPONSE: *As noted in the Response to previous comments, a data need for studies evaluating potential function deficits was added to Section 6.2:*

> One study reported impaired development of the reproductive system (Bernard et al. 2002). Additional studies are needed to further evaluate possible effects on the reproductive system and to evaluate other possible functional impairments, such as impaired development of the nervous system or immune system.

COMMENT 36: Referring to critical effect of acute oral exposure found in Table 1-1 the Reviewer commented "Difference between GD 20 and 21, in the Schwetz et al. study the day of euthanasia was GD 20. The later studies used GD 21 as this additional day of gestational helps to remove many developmental delays."

RESPONSE: *Based on the limited description in the papers, the Schwetz et al. (1974, 1978) studies appeared to sacrifice the dams on GD 21.*

COMMENT 37: Referring to the developmental less serious LOAEL for the Bernard and Hoberman (2001) for acute duration study in Table 2-2, the Reviewer commented "Less serious – malformation?"

RESPONSE: *The 80 mg/kg/day dose in the Bernard and Hoberman (2001) study was re-categorized as a serious LOAEL due to the increased incidence of resorptions.*

COMMENT 38: Referring to the developmental serious LOAEL for the Bernard et al. (2002) intermediate study in Table 2-2, the Reviewer commented "This is serious but malformation is not?"

RESPONSE: *The 60 mg/kg/day dose level was considered a serious LOAEL because there was a decrease in pup survival at this dose level.*

COMMENT 39: Referring to the statement in Section 2.2— Oral LD_{50} studies have found similar values across species but did find age-related differences— the Reviewer commented "Juvenile toxicity?"

RESPONSE: *As discussed in the last two sentences of the referenced paragraph in Section 2.2, age-related differences in mortality were observed in the St. Omer and Gadusek (1987) study. As noted in previous responses to this comment, no studies were identified that evaluated potential juvenile toxicity; the need for studies examining potential differences between juveniles and adults was identified in Section 6.2.*

COMMENT 40: Referring to the statement in Section 2.4—No alterations in the lungs were observed in rats exposed to 36 mg/kg/day pure pentachlorophenol or 32 mg/kg/day technical-grade pentachlorophenol for 8 months (Kimbrough and Linder 1978) — the Reviewer commented "Dietary study? add the ppm concentration –or state that this is an average dose, give the range, as this will be significantly higher in younger rats"

RESPONSE: *As noted in the LSE table, the Kimbrough and Linder (1978) study is a dietary exposure study; the text in Section 2.4 was revised to specify that it is a dietary study:*

> No alterations in the lungs were observed in rats exposed to 36 mg/kg/day pure pentachlorophenol or 32 mg/kg/day technical-grade pentachlorophenol in the diet for 8 months (Kimbrough and Linder 1978)...

It is ATSDR's practice to include estimated doses rather than the dietary concentrations in the toxicological profile; the dietary concentrations are presented in the Supplemental Document. The doses were calculated using by the investigators and were referred to as an average daily dose.

COMMENT 41: Referring to the statement in Section 2.13—Significant alternation in thyroid hormone levels…, the Reviewer commented "What is meant by significant? or add %"

RESPONSE: *In the referenced sentence in Section 2.13, the term significant is used to refer to statistical significance. The percent change in thyroid hormone levels were added to the text:*

> Gavage administration of 3 mg/kg/day pure pentachlorophenol to young adult female rats for 28 days produced decreases in serum free thyroxine (T4) levels (50%), serum thyroid stimulating hormone levels (30%), and serum T4:T3 ratio (60%) (Jekat et al. 1994). Decreases in serum T3 (50%) and free T3 (55%) were also observed at 30 mg/kg/day. In a multigeneration study in mink, significant decreases in serum T4 levels were observed in the F1 males (18%) and the F2 males (20%) and females (16%) exposed to 1 mg/kg/day pentachlorophenol (purity not reported) (Beard and Rawlings 1998).

COMMENT 42: Referring to the statement in Section 2.19 —IARC (2019) concluded that pentachlorophenol is "carcinogenic to humans" (Group1) — the Reviewer commented on (Group 1) "Did not mention IARC here"

RESPONSE: *ATSDR is uncertain about the meaning of the Reviewer's comment since IARC is referenced in this sentence.*

COMMENT: Referring to the statement in Section 2.21—However, testing has not been performed on animals exposed to pentachlorophenol, either prenatally or postnatally, to examine the potential for the anti-thyroid effects of pentachlorophenol to produce adverse effects on neurobehavior—, the Reviewer commented "Refer to the multigeneration study – no behavioral effects"

RESPONSE: *The Bernard et al. (2002) 2-generation study did not evaluate potential neurobehavioral effects.*

COMMENT 43: Referring to the statement in Section 3.1.1 — Oral bioavailability of pentachlorophenol in several soil samples ranged from 36 to 55 and from 46 to 77% at 100 and 200 mg/kg doses, respectively (Pu et al. 2003) — the Reviewer commented "Is the mg/kg for the soil or oil or pentachorophenol."

RESPONSE: *The mg/kg dose is the amount of pentachlorophenol in the soil sample.*

COMMENT 44: Referring to the statement in Section 3.2 —Lower LD_{50} values were found in preweaning animals, as compared to juvenile rats…—, the Reviewer commented "Add the details of rodents are not a good model here for humans – due to blood brain barrier still developing and development of enzymes."

RESPONSE**:** *ATSDR does not agree with the Reviewer that rodents are not a good model for evaluating age-specific differences in toxicity.*

COMMENT 45: The Reviewer made the following comment in Section 6.2 regarding the identification of data needs for reproductive health effects: "No developmental or Juvenile?"

RESPONSE: *A discussion of developmental toxicity data needs was added to Section 6.2:*

> ***Developmental.*** Developmental effects have been reported in several laboratory animal studies; these effects include increases in mortality, malformations/variations, and decreased growth. One study reported impaired development of the reproductive system (Bernard et al. 2002). Additional studies are needed to further evaluate possible effects on the reproductive system and to evaluate other possible functional impairments, such as impaired development of the nervous system or immune system.

A discussion of the need for studies evaluating juveniles is discussed in the Children's Susceptibility subsection of Section 6.2.

COMMENT 46: The Reviewer made the following comment regarding Guidelines in the Chapter 7 title—Regulations and Guidelines—: "No comparison to levels found in animals?"

RESPONSE: *Chapter 7 discusses regulations and guidelines developed to protect human health.*