DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR CHLOROPHENOLS

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: Yes. Pertinent details are provided. No change is suggested.

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. Especially significant are those where relevant routes of human exposure are used at reasonable doses.

RESPONSE: *No response needed.*

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

COMMENT 3: Exposure conditions are adequately described.

RESPONSE: *No response needed.*

Minimal Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation? 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. 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: Yes. Provisional intermediate-duration oral MRL has been derived for 2-chlorophenol, 2,4,5-trichlorophenol, and 2,3,4,6-tetrachlorophenol while provisional acute-duration oral MRL only for 2,34,6-tetrachlorophenol. All derivations are sound and well justified.

RESPONSE: *No response needed.*

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

COMMENT 6: None.

RESPONSE: *No response needed.*

Specific Comments on Chapter 1

COMMENT 7*:* Referring to the statement in Section 1.1—Chlorophenols are a group of chemicals in which chlorines (between one and five) have been added to phenol—the Reviewer commented "The sentence has been modified to be consistent with subsequent sentence." The Reviewer suggested a revision to the first sentence in Section 1.1, Overview and U.S. Exposures, so that it reads: "Chlorophenols are a group of chemical in which hydrogens are replaced by chloride (between one ~~and five) have been added~~ to phenol."

RESPONSE: *The first sentence in Section 1.1 has been revised as shown below.*

> Chlorophenols are a group of chemicals in which hydrogens are replaced by chlorines (between one and five) on phenol.

COMMENT 8*:* Referring to the statement in Section 1.1—There are five basic types of chlorophenols: mono[one]chlorophenols, di[two]chlorophenols, tri[three]chlorophenols, tetra[four]chlorophenols, and penta[five]chlorophenols—the Reviewer commented "'Pentachlorophenol' does not exist in isomeric forms as reflected by suggested changes by deleting 's' from the name."

RESPONSE: *The text in paragraph 1 of Section 1.1 has been corrected as suggested.*

> There are five basic types of chlorophenols: mono[one]chlorophenols, di[two]chlorophenols, tri[three]chlorophenols, tetra[four]chlorophenols, and penta[five]chlorophenol.

COMMENT 9*:* Referring to the statement in Section 1.2—The most sensitive health endpoints observed in laboratory animals exposed to chlorophenols after oral exposure were effects on the liver, central nervous system, body weight, immune system, and reproductive function, as shown in Figures 1-1 (2-CP), 1-2 (4-CP), 1-3 (2,4-DCP), 1-4 (2,4,5-TCP), 1-5 (2,4,6-TCP), 1-6 (2,3,4,6-TCP), and 1-7 (other chlorophenols).—the Reviewer commented "'Tetrachlorophenol' is now properly abbreviated by adding "e" after "T" which has been consistently used in the document."

RESPONSE: *The abbreviation for 2,3,4,6-TeCP in the second paragraph of Section 1.2 has been corrected as suggested.*

> Several sensitive health endpoints observed in laboratory animals exposed to chlorophenols after oral exposure were effects on the liver, central nervous system, body weight, immune system, and reproductive function, as shown in Figures 1-1 (2-CP), 1-2 (4-CP), 1-3 (2,4-DCP), 1-4 (2,4,5-TCP), 1-5 (2,4,6-TCP), 1-6 (2,3,4,6-TeCP), and 1-7 (other chlorophenols).

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 10: 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 11: No changes are suggested as the studies are described adequately with pertinent details.

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 12: Yes.

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 13: Yes.

RESPONSE: *No response needed.*

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

COMMENT 14: 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 15: No.

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 16: 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 17: 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 18: Yes, these are subjective assessments.

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 19: Yes.

RESPONSE: *No response needed.*

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

COMMENT 20: Yes.

RESPONSE: *No response needed.*

Specific Comments on Chapter 2

COMMENT 21: Referring to the statement in Section 2.1—The discussion of the available data for health effects in this chapter begins with an overview of the health effects and comparisons across the different chlorophenols—the Reviewer commented "This document does not contain the information about pentachlorophenol is now reflected in the modified sentence."

RESPONSE: *The introductory text in Section 2.1 has been revised as shown below.*

> The discussion of the available data for health effects in this chapter begins with an overview of the health effects and comparisons across the different chlorophenols (except pentachlorophenol, which is addressed in a separate toxicological profile).

COMMENT 22: Referring to the statement in Section 2.9—In separate studies, similar treatment doses of 4-CP had no effect on relative liver weights, microsomal zoxazolamine 6-hydroxylase activity, or measures of serum lipid and lipoprotein concentrations, but did increase fasting glucose levels (Phornchirasilp et al. 1989a)—the Reviewer commented " 'measures of' is not needed and, therefore deleted while lipid is changed to lipids."

RESPONSE: *The text in Section 2.9 has been corrected as suggested.*

> In separate studies, similar treatment doses of 4-CP had no effect on relative liver weights, microsomal zoxazolamine 6-hydroxylase activity, or serum lipids and lipoprotein concentrations, but did increase fasting glucose levels (Phornchirasilp et al. 1989a).

COMMENT 23: Referring to the statement in Section 2.9—When guinea pigs were administered 40 mg/kg 2,4-DCP perorally 3 times/week for 2 weeks, lipid peroxidation was increased in the liver (Clerhata et al. 1996)—the Reviewer commented " 'peronally' is not commonly used in literature and therefore can be changed to "orally"."

RESPONSE: *The text in Section 2.9 has been revised as suggested.*

> When guinea pigs were administered 40 mg/kg 2,4-DCP orally 3 times/week for 2 weeks, lipid peroxidation was increased in the liver (Clerhata et al. 1996).

COMMENT 24: Referring to the statement in Section 2.9—Newborn rats (12/sex/group) were administered 4-CP at doses of 0, 12, 60, or 300 mg/kg/day in olive oil by gavage on PNDs 4–21 (Hasegawa et al. 2005)—the Reviewer commented "'PNDs' need to be spelled out."

RESPONSE: *In accordance with ATSDR style guidelines, PND (postnatal day) was defined at first occurrence in the text (Section 2.2 under 2-CP). No change was made to the profile.*

COMMENT 25: Referring to the statement in Section 2.16—The potential for 2,4-DCP to potentiate 5α-dihydroxytestosterone action, as assessed by cell proliferation, was evaluated in human prostate cancer cells (lines AR expressed 22v1 and PC3) (Kim et al. 2005)—the Reviewer commented "'dihydrotestosterone' is misspelled as 'dihydroxytestosterone' which is not a natural metabolite of testosterone."

RESPONSE: *The text in Section 2.16 has been corrected as suggested.*

The potential for 2,4-DCP to potentiate 5α-dihydrotestosterone (DHT) action, as assessed by cell proliferation, was evaluated in human prostate cancer cells (lines AR expressed 22v1 and PC3) (Kim et al. 2005).

COMMENT 26: Referring to the statement in Section 2.18—In a study of 54 pregnant women (participants in the Puerto Rico Testsite for Exploring Contamination Threats, or PROTECT), urinary markers of oxidative stress (OHdG and isoprostate) were not correlated with urinary concentrations of 2,4-DCP or 2,5-DCP (Watkins et al. 2015)—the Reviewer commented "'isoprostane' is misspelled as 'isoprostate'."

RESPONSE: *The spelling of isoprostane in Section 2.18 has been corrected as suggested.*

In a study of 54 pregnant women (participants in the Puerto Rico Testsite for Exploring Contamination Threats, or PROTECT), urinary markers of oxidative stress (OHdG and isoprostane) were not correlated with urinary concentrations of 2,4-DCP or 2,5-DCP (Watkins et al. 2015).

COMMENT 27: Referring to the statement in Section 2.19—In a retrospective cohort study on Danish phenoxy herbicide workers, there were no cases of soft tissue sarcoma or malignant lymphoma among subjects (n=615) in the factory manufacturing only 2,4-DCP and 4-chloro-o-tolyloxy-acetic (MCPA) (Lynge 1985)—the Reviewer commented "' acid' is added after (MCPA) to complete the name.

RESPONSE: *The full chemical name for MCPA was corrected as suggested in Section 2.19.*

In a retrospective cohort study on Danish phenoxy herbicide workers, there were no cases of soft tissue sarcoma or malignant lymphoma among subjects (n=615) in the factory manufacturing only 2,4-DCP and 4-chloro-*o*-tolyloxy-acetic acid (MCPA) (Lynge 1985).

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: Yes. No additions or deletions are suggested.

RESPONSE: *No response needed.*

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

COMMENT 29: 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 30: Yes.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

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

COMMENT 31: No.

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 32: Yes.

RESPONSE: *No response needed.*

Biomarkers of Exposure and Effect

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

COMMENT 33: No.

RESPONSE: *No response needed.*

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

COMMENT 34: No.

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: 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 36: 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.

COMMENT 37: No.

RESPONSE: *No response needed.*

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

COMMENT 38: Yes.

RESPONSE: *No response needed.*

Specific Comments on Chapter 4

COMMENT 39: Referring to Table 4-1, the Reviewer commented "Structure and Synonym need to be corrected for 2,3,4,5-Tetrachlorophenol. Synonym should be 2,3,4,5-TeCP. For structure Cl and H needed to be exchanged."

RESPONSE: *The synonym and chemical structure for 2,3,4,5-TeCP in Table 4-1 have been corrected as suggested.*

COMMENT 40: Referring to the solubility in organic solvents entry for 2,4-DCP in Table 4-2, the Reviewer commented "For consistency 'Ethyl' should be removed as 'Alcohol' is sufficient descriptor and commonly used in the document."

RESPONSE: *The solubility in organic solvents entry for 2,4-DCP in Table 4-2 has been corrected as suggested.*

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 41: Yes.

RESPONSE: *No response needed.*

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

COMMENT 42: Yes. Nothing to add.

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 43: Yes. Nothing to add.

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 44: Yes. Nothing to add.

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 45: Yes. Nothing to add.

RESPONSE: *No response needed.*

Specific Comments on Chapter 5

COMMENT 46: Referring to the statement in Section 5.1—The environmental fate and transport of chlorophenols is pH-dependent since they can exist as the fully protonated acid or its conjugate base (phenolate anion)—the Reviewer commented " 'acid' is wrong and should be changed to 'phenol' ".

RESPONSE: *The bulleted text in Section 5.1 has been corrected as suggested.*

The environmental fate and transport of chlorophenols are pH-dependent since they can exist as the fully protonated phenol or its conjugate base (phenolate anion).

COMMENT 47: Referring to the statement in Section 5.4.2—The aerobic degradation of chlorophenols by microorganisms requires the participation of the enzyme's oxygenases to incorporate atmospheric oxygen into their substrates—the Reviewer commented "suggested change is 'oxygenase enzymes' rather than 'enzyme's oxygenase'."

RESPONSE: *The text in Section 5.4.2 has been revised as suggested.*

The aerobic degradation of chlorophenols by microorganisms requires the participation of the oxygenase enzymes to incorporate atmospheric oxygen into their substrates.

COMMENT 48: Referring to the statement in Section 5.2.3—The largest uses for 2,4-DCP and 2,4,5-TCP have also been used as an intermediate, especially in the production of the herbicides, 2,4-D and 2,4,5-T (WHO 1989)—the Reviewer commented " '2,4-D' needs be define for clarity."

RESPONSE: *The acronym definition was added at the first occurrence in the text, in Section 2.19.*

Several other epidemiological studies (Eriksson et al. 1981, 1990; Hardell and Eriksson 1981, 1988; Hardell et al. 1995; Hooiveld et al. 1998; Kogevinas et al. 1997; Lynge 1985; Saracci et al. 1991; Zendehel et al. 2014) have examined potential associations between cancer and occupational exposure to chlorophenols during the manufacture or use of phenoxy herbicides (e.g., 2,4-D [2,4-dichlorophenoxyacetic acid], 2,4,5-T [2,4,5-trichlorophenoxyacetic acid], Agent Orange [mixture of 2,4-D and 2,4,5-T], and related compounds).

COMMENT 49: Referring to the statement in Section 5.7—The observation of higher urinary concentrations of mixed tetrachlorophenols during hot humid weather when use of protective clothing was minimal (geometric means 196.7 ppm hot humid weather; 98.5 ppm cooler weather) suggests that dermal exposure is an important route of tetrachlorophenol exposure in these workers (Kleinman et al. 1986)—the Reviewer commented "should be 'tetrachlorophenols'."

RESPONSE: *The text in Section 5.7 has been revised for clarity as follows:*

The observation of higher urinary concentrations of tetrachlorophenols during hot humid weather when use of protective clothing was minimal (geometric means of 196.7 ppm in hot humid weather and 98.5 ppm in cooler weather) suggests that dermal contact is an important route of exposure to tetrachlorophenols in these workers (Kleinman et al. 1986).

COMMENT 50: Referring to the statement in Section 5.7—The higher volatility of tetrachlorophenols in warmer weather may have also contributed to the higher urinary concentrations of mixed tetrachlorophenols found when the weather was hot—the Reviewer commented " 'mixed' should be deleted."

RESPONSE: *The text in Section 5.7 has been revised for clarity as follows:*

The higher volatility of tetrachlorophenols in warmer weather may have also contributed to the higher urinary concentrations of tetrachlorophenols found when the weather was hot.

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 51: No.

RESPONSE: *No response needed.*

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

COMMENT 52: Yes.

RESPONSE: *No response needed.*

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

COMMENT 53: Yes.

RESPONSE: *No response needed.*

Specific Comments on Chapter 6

COMMENT 54: Referring to the title of Figure 6-6, the Reviewer commented "It is 'Tetrachlorophenol' not 'Trichlorophenol'."

RESPONSE: *The title of Figure 6-6 in Section 6.1 has been corrected as suggested.*
Figure 6-6. Summary of Existing Health Effects Studies on 2,3,4,6-Tetrachlorophenol By Route and Endpoint

Chapter 7. Regulations and Guidelines

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

COMMENT 55: No.

RESPONSE: *No response needed.*

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

COMMENT 56: No.

RESPONSE: *No response needed.*

Annotated Comments

The Reviewer suggested a number of editorial revisions, most of the suggested revisions were made to the profile. Some stylistic changes that were purely arbitrary were not incorporated. Responses to Reviewer comments that were not considered editorial or stylistic are presented below.

COMMENT 57: The Reviewer suggested a revision to the first sentence in Section 1.1, Overview and U.S. Exposures, so that it reads: "Chlorophenols are a group of chemical in which hydrogens are replaced by chloride (between one and five) ~~have been added to phenol~~."

RESPONSE: *The first sentence in Section 1.1 has been revised as shown below.*

Chlorophenols are a group of chemicals in which hydrogens are replaced by chlorines (between one and five) on phenol.

COMMENT 58: Referring to the Section 2.1, the introduction to Chapter 2, the Reviewer suggested the following text revision: "The discussion of the available data for health effect in this chapter begins with an overview of the health effects and comparison across the direct chlorophenols except pentachlorophenol which has a sperate document".

RESPONSE: *The introductory text in Section 2.1 has been revised as shown below.*

The discussion of the available data for health effects in this chapter begins with an overview of the health effects and comparisons across the different chlorophenols (except pentachlorophenol, which is addressed in a separate toxicological profile).

Comments provided by Peer Reviewer #2

General Comment

COMMENT 1: My comments on the document follow this completed questionnaire. There is a new reference included in my comments that should probably be included, and a full copy of this Fundamental and Applied Toxicology paper is attached. This new reference probably describes the same study as the one cited as Borzelleca 1985a, but provides actual data instead of just summarizing a 90 day drinking water study of 2,4-DCP in CD1 mice

RESPONSE: *The new paper was reviewed and added as a citation (Borzelleca et al. 1985c) to Chapter 2 and Appendix A. No changes to the study descriptions or effect levels were needed.*

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 2: 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 3: YES.

RESPONSE: *No response needed.*

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

COMMENT 4: YES.

RESPONSE: *No response needed.*

Minimal Risk Levels (MRLs)

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

COMMENT 5: YES.

RESPONSE: *No response needed.*

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

COMMENT 6: YES, but see comment following question 6.

RESPONSE: *The Reviewer is referring to Comment 8 below, which itself refers to Comments 70 and 71. See Responses to Comments 70 and 71.*

QUESTION: 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 7: YES, I agree with all derived MRLs and their methodology/assumptions. Minor edits are in the document.

RESPONSE: *See Responses to Comments 70 and 71.*

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

COMMENT 8: PLEASE see comments on MRLs for 2,4,6-TCP and 2,3,4,6-TeCP regarding selection of NOAEL.

RESPONSE: *The Reviewer is referring to Comments 70 and 71; see Responses to Comments 70 and 71.*

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 9: 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 10: Human studies very limited but adequately described.

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 11: YES.

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 12: YES.

RESPONSE: *No response needed.*

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

COMMENT 13: 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 14: YES see above. The Reviewer is referring to Borzelleca, Hayes, Condie and Egle published in Fundamental and Applied Toxicology 5(3):478-486 (1985).

RESPONSE: *The new paper was reviewed and added as a citation (Borzelleca et al. 1985c) to Chapter 2 and Appendix A. No changes to the study descriptions or effect levels were 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 15: 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 16: 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 17: YES with one exception, see comment. The Reviewer is referring to Comment 45.

RESPONSE: *See response to Comment 45.*

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 18: YES but limited data available.

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 19: YES.

RESPONSE: *No response needed.*

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 20: YES.

RESPONSE: *No response needed.*

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

COMMENT 21: 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 22: YES.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

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

COMMENT 23: YES.

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 24: YES.

RESPONSE: *No response needed.*

Biomarkers of Exposure and Effect

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

COMMENT 25: Specifity or lack thereof discussed.

RESPONSE: *No response needed.*

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

COMMENT 26: Specifity or lack thereof discussed.

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 27: Yes, to limited extent possible.

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 28: Yes, to limited extent possible.

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 29: NO.

RESPONSE: *No response needed.*

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

COMMENT 30: Yes, to limited extent possible.

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 31: Yes, to limited extent possible.

RESPONSE: *No response needed.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites?

COMMENT 32: YES.

RESPONSE: *No response needed.*

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

COMMENT 33: NO.

RESPONSE: *No response needed.*

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

COMMENT 34: YES.

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?

COMMENT 35: YES.

RESPONSE: *No response needed.*

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

COMMENT 36: NO.

RESPONSE: *No response needed.*

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

COMMENT 37: YES.

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 38: NO.

RESPONSE: *No response needed.*

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

COMMENT 39: YES.

RESPONSE: *No response needed.*

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

COMMENT 40: YES.

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 41: NO.

RESPONSE: *No response needed.*

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

COMMENT 42: NO.

RESPONSE: *No response needed.*

Specific Comments on Toxicological Profile

COMMENT 43: Referring to the statement – 2,4-DCP is the only chlorophenol that has shown effects on immune system function; 2-CP and 2,4-TCP, both tested for the same endpoints by the same investigators, did not show evidence of immunotoxicity – the Reviewer commented "2,4-TCP should be 2,4,6-TCP."

RESPONSE: *The text in Section 1.2 under Immune System Effects was corrected as follows*

> 2,4-DCP is the only chlorophenol that has shown effects on immune system function; 2-CP and 2,4,6-TCP, both tested for the same endpoints by the same investigators, did not show evidence of immunotoxicity.

COMMENT 44: Referring to Table 2-4, the Reviewer commented "Reference to Borzelleca, Condie, and Hayes (1985a); however, could this be the same or different study by Borzelleca, Hayes, Condie and Egle published in Fundamental and Applied Toxicology 5(3):478-486 (1985) which does not appear in reference list? For the 90 drinking water study of 2,4-DCP in CD1 mice, this new reference, which probably describes the same study, actually provides the data instead of summary conclusions."

RESPONSE: *The new paper was reviewed and added as a citation (Borzelleca et al. 1985c) to Table 2-4 and elsewhere in Chapter 2 and Appendix A. No changes to the study descriptions or effect levels were needed.*

COMMENT 45: Referring to Table 2-5, the Reviewer commented "The presence of focal necrosis, bile duct proliferation, and early portal cirrhosis (McCollister et al, 1861) should be considered a serious adverse effect (therefore, possibly move to Serious LOAEL)."

RESPONSE: *McCollister et al. (1961) did not provide quantitative histopathology incidence or severity data. At the high dose (1,000 mg/kg/day), the authors described liver effects consisting of "mild centrilobular degenerative changes characterized by cloudy swelling and an occasional area of focal necrosis… slight proliferation of the bile ducts and early portal cirrhosis." At 300 mg/kg/day, the authors noted only that the animals "showed slight changes in the liver and kidney…similar to, but milder than, the changes observed in the animals at the 1% level" (1,000 mg/kg/day). The study authors considered the liver changes at both 300 and 1,000 mg/kg/day to be "of a mild, reversible nature and probably of minor significance." ATSDR defines serious effects as "those that evoke failure in a biological system and can lead to morbidity or mortality." Based on information provided by McCollister et al. (1961), neither the 300 mg/kg/day nor 1,000 mg/kg/day doses is considered a serious LOAEL. The hepatic effect description for the McCollister et al. (1961) LOAEL of 300 mg/kg/day (in the intermediate-duration rat study of 2,4,5-TCP) in Table 2-5 was revised to "mild centrilobular degeneration" to reflect the mild severity and lack of specific information at this dose.*

COMMENT 43: Referring to the statement in Section 2.3—Body weights were not affected in mice treated with 2,4-DCP in the diet at doses up to 230 mg/kg/day (Kobayashi et al. 1972) or in drinking water at doses up to 491 mg/kg/day (in females) or 383 mg/kg/day (in males) (Borzelleca et al. 1985a).—the Reviewer commented "Add reference [Fundamental and Applied Toxicology 5(3):478-486 (1985)]"

RESPONSE: *The new paper was added as a citation (Borzelleca et al. 1985c) in Section 2.3.*

COMMENT 46: Referring to the statement in Section 2.4—Histopathological changes have not been observed in the lungs of rats or mice exposed to 2,4-DCP in drinking water for 90 days at doses up to 491 mg/kg/day (in females) or 383 mg/kg/day (in males) (Borzelleca et al. 1985a) or up to 5,200 mg/kg/day in feed (NTP 1989)—the Reviewer commented "Unable to confirm any histopathology done in Borzelleca 1985a or in new reference (Fundamental and Applied Toxicology 5(3):478-486, 1985).

RESPONSE: *The Reviewer is correct. Histopathology examinations were not performed by Borzelleca et al. 1985a or 1985c (Fundamental and Applied Toxicology 5(3):478-486, 1985). The text pertaining to Borzelleca et al. (1985a or 1985c) in Section 2.4 was deleted.*

> Histopathological changes have not been observed in the lungs of rats exposed to 2,4-DCP at doses up to 5,200 mg/kg/day in feed (NTP 1989).

COMMENT 47: Referring to the statement in Section 2.7—Groups of 12 male and 12 female mice administered up to 638 mg/kg/day 2,4-DCP for 14 days showed no adverse effects on hematological parameters, including total and differential white blood cells, red blood cells, platelets, hematocrit, hemoglobin, and coagulation measures relative to unexposed controls (Borzelleca et al. 1985a)—the Reviewer commented "Should include mode of administration (corn oil gavage)."

RESPONSE: *The mode of administration was added to the text in Section 2.7.*

> Groups of 12 male and 12 female mice administered up to 638 mg/kg/day 2,4-DCP (by gavage in corn oil vehicle) for 14 days showed no adverse effects on hematological parameters, including

total and differential white blood cells, red blood cells, platelets, hematocrit, hemoglobin, and coagulation measures relative to unexposed controls (Borzelleca et al. 1985a).

COMMENT 48: Referring to the statement in Section 2.7—However, when groups of 20 male and 20 female mice were dosed with up to 383 mg/kg/day of 2,4-DCP (male) and 49 mg/kg/day (female) in drinking water for 90 days, the number of white blood cells was increased in the high-dose males (Borzelleca et al. 1985a, 1985c)—the Reviewer commented "Should include mode of administration (in drinking water containing 10% Emulphor)."

RESPONSE: *The mode of administration was added to Section 2.7.*

However, when groups of 20 male and 20 female mice were dosed with up to 383 mg/kg/day of 2,4-DCP (male) and 49 mg/kg/day (female) in drinking water (containing 10% Emulphor) for 90 days, the number of white blood cells was increased in the high-dose males (Borzelleca et al. 1985a, 1985c).

COMMENT 49: Referring to the statement in Section 2.7—Groups of 12 male and 12 female mice administered up to 638 mg/kg/day 2,4-DCP for 14 days showed no adverse effects on hematological parameters, including total and differential white blood cells, red blood cells, platelets, hematocrit, hemoglobin, and coagulation measures relative to unexposed controls (Borzelleca et al. 1985a)—the Reviewer commented "Add reference [Fundamental and Applied Toxicology 5(3):478-486 (1985)]."

RESPONSE: *The new paper added as a citation (Borzelleca et al. 1985c) to Section 2.7.*

COMMENT 50: L1403-1405: Referring to the statement in Section 2.9—When mice were fed 383 or 230 mg/kg/day for 90 days or 6 months, respectively, no effects were noted on serum AST or ALT activities (Borzelleca et al. 1985a; Kobayashi et al. 1972)—the Reviewer commented "Add reference [Fundamental and Applied Toxicology 5(3):478-486 (1985)]"

RESPONSE: *The new paper was added as a citation (Borzelleca et al. 1985c) to Section 2.9.*

COMMENT 51: Referring to the statement in Section 2.9—It is possible that these lesions were precursors of the hepatocellular adenomas and carcinomas also observed in this study—the Reviewer commented "Evidence for precursor lesions for hepatocellular adenomas and carcinomas in 2,4,6-TCP treated mice is not supportive since the incidence of non-neoplastic lesions is much lower and they were not observed after shorter or intermediate treatment (prior to ocurrence of tumors); therefore remove sentence."

RESPONSE: *The sentence was deleted as suggested.*

COMMENT 52: Referring to the statement in Section 2.10—Treatment of mice for 90 days with 2,4 DCP in drinking water at doses up to 491 mg/kg/day (in females) or 383 mg/kg/day (in males) had no effect on kidney weights or clinical chemistry values including urine protein, phosphorus, calcium, sodium, chloride, potassium, or creatinine levels; histopathological examinations were not completed (Borzelleca et al. 1985a).—the Reviewer commented "Add reference [Fundamental and Applied Toxicology 5(3):478-486 (1985)]"

RESPONSE: *The new paper was added as a citation (Borzelleca et al. 1985c).*

COMMENT 53: Referring to the statement in Section 2.14—No changes in spleen weight were observed in mice treated with 2,4-DCP in the diet at 230 mg/kg/day for 6 months (Kobayashi et al. 1972), and no changes in spleen or thymus weight were noted in mice treated with 2,4-DCP in the drinking water at doses up to 491 mg/kg/day (in females) or 383 mg/kg/day (in males) for 90 days (Borzelleca et al. 1985a).—the Reviewer commented "Add reference [Fundamental and Applied Toxicology 5(3):478-486 (1985)]

RESPONSE: *The new paper was reviewed and added as a citation (Borzelleca et al. 1985c) in Section 2.14.*

COMMENT 54: Referring to the statement in Section 2.11—Rabbits given single applications of 250 mg/kg 2,4-DCP or more became lethargic (Carreon et al. 1980a, 1980b; Monsanto 1976), and two rabbits in the 2,000-mg/kg group and one in the 4,000 mg/kg group became anorexic (Carreon et al. 1980b)—the Reviewer commented "Should include mode of administration of 2,4-DCP to rabbits (Carreon et al and Monsanto studies)."

RESPONSE: *The mode of administration was added to Section 2.11.*

Rabbits given single dermal applications of 250 mg/kg 2,4-DCP or more became lethargic (Carreon et al. 1980a, 1980b; Monsanto 1976), and two rabbits in the 2,000-mg/kg group and one in the 4,000 mg/kg group became anorexic (Carreon et al. 1980b).

COMMENT 55: Referring to the statement in Section 2.15—No effect on brain weight was observed in mice treated for 90 days with 2,4-DCP in the drinking water at doses up to 491 mg/kg/day (in females) or 383 mg/kg/day (in males) (Borzelleca et al. 1985a)—the Reviewer commented "Add reference [Fundamental and Applied Toxicology 5(3):478-486 (1985)]."

RESPONSE: *The new paper was added as a citation (Borzelleca et al. 1985c) to Section 2.15.*

COMMENT 56: Referring to the statement in Section 2.17—Groups of 6–13 female Sprague-Dawley rats receiving a single dose of 333, 667, or 1,000 mg/kg 4-CP on GD 11 showed no adverse changes in litter sizes, perinatal loss, pup weight, or litter biomass (Kavlock 1990)—the Reviewer commented "Should include mode of administration of 2,4-DCP to rabbits (Kavlock study)"

RESPONSE: *The mode of administration was added to Section 2.17.*

Groups of 6–13 female Sprague-Dawley rats receiving a single gavage dose of 333, 667, or 1,000 mg/kg 4-CP on GD 11 showed no adverse changes in litter sizes, perinatal loss, pup weight, or litter biomass (Kavlock 1990).

COMMENT 57: Referring to Section 2.19, the Reviewer commented "Results of Kitchin and Brown (1988) for 2,4,5-TCP should not appear under section 2.19 Cancer since these results (DNA alkaline elution, ornithine decarboxylase, and ALT) are not cancer endpoints- they could go under liver, with the possible exception of DNA alkaline elution which is already listed under 2.20 Genotoxicity."

RESPONSE: *The information on hepatic ornithine decarboxylase and serum ALT for the study by Kitchin and Brown (1988) was moved to Section 2.9, and the information on DNA damage (already in Section 2.20) was deleted from Section 2.19.*

In another rat study, Kitchin and Brown (1988) examined the effects of a single gavage dose of 2,4,5-TCP on ornithine decarboxylase activity in the liver and serum ALT activity. At a 2,4,5-TCP dose of 164 mg/kg, no effects were observed on these parameters.

COMMENT 58: Referring to Section 2.19, the Reviewer commented "The NCI report of the 2,4,6-TCP bioassays includes comparison of treated groups of rats to the historical incidence of mononuclear cell leukemia in male and female mice on pages 27-28 (NCI, 1979). Therefore, this comparison should be presented in the section 2.19 Cancer."

RESPONSE: *The following sentence was added to Section 2.19:*

The increase was statistically significant compared to both concurrent and historical control incidences.

COMMENT 59: Referring to Section 2.19, the Reviewer commented "The NCI report of the 2,4,6-TCP bioassays includes comparison of treated groups of mice to the historical incidence of liver tumors (hepatocellular adenomas and carcinomas) in male and female mice on pages 34-35 (NCI, 1979). Therefore, the statement regarding the lack of this comparison should be replaced in the section 2.19 Cancer."

RESPONSE: *The statement in Section 2.19 regarding the lack of historical incidence data and the sentence that followed regarding spontaneous tumor incidence in this mouse strain were deleted, and the following sentence was added:*

Statistically significant increases in liver tumor incidences were observed in both males and females when compared with both concurrent and historical control groups.

COMMENT 60: Referring to Section 2.19, the Reviewer commented "Results of Kitchin and Brown (1988) for 2,4,6-TCP should not appear under section 2.19 Cancer since these results (DNA alkaline elution, ornithine decarboxylase, and ALT) are not cancer endpoints- they could go under liver, with the possible exception of DNA alkaline elution which is already listed under 2.20 Genotoxicity."

RESPONSE: *The information on hepatic ornithine decarboxylase and serum ALT from the study by Kitchin and Brown (1988) was moved to Section 2.9, and the information on DNA damage (already in Section 2.20) was deleted from Section 2.19.*

Kitchin and Brown (1988) observed a significant increase in liver ornithine decarboxylase activity, but no significant change in serum ALT in rats given a single oral dose of 2,4,6-TCP (500 mg/kg).

COMMENT 61: Referring to Section 2.19, the Reviewer commented "Results of Kitchin and Brown (1988) for 2,3,4,6-TeCP should not appear under section 2.19 Cancer since these results (DNA alkaline elution, ornithine decarboxylase, and ALT) are not cancer endpoints- they could go under liver, with the possible exception of DNA alkaline elution which is already listed under 2.20 Genotoxicity."

RESPONSE: *The information on hepatic ornithine decarboxylase and serum ALT from the study by Kitchin and Brown (1988) was moved to Section 2.9, and the information on DNA damage (already in Section 2.20) was deleted from Section 2.19.*

In the study by Kitchin and Brown (1988), 2,3,4,6-TeCP administration as a single dose (193 mg/kg) to rats induced an increase in ornithine decarboxylase activity in the liver without a significant change in serum ALT.

COMMENT 62: Referring to Section 2.20 Genotoxicity, the Reviewer commented "Why are the results of in vitro testing of genotoxicity but not in vivo testing of genotoxicity presented in tabular form?"

RESPONSE: *The* in vivo *results were not tabulated because each chlorophenol had too few studies to tabulate (one each for 2-CP, 2,5-TCP, and 2,3,4,5-TeCP; two each for 2,4-DCP and 2,4,5-TCP; three for 2,4,6-TCP; and none for all other subject chlorophenols). No changes were made to the document.*

COMMENT 63: Referring to the subsection on 4-CP in Section 2.20, the Reviewer commented "Insert statement that genotoxicity of 4-CP has been reported from in vitro but not in vivo studies."

RESPONSE: *A statement regarding the availability of* in vitro*, but not* in vivo*, data for 4-CP was added.*

In vitro genotoxicity data are available for 4-CP; no *in vivo* studies of genotoxicity were identified for 4-CP.

COMMENT 64: Referring to the subsection on 2,5-DCP in Section 2.20, the Reviewer commented "Insert statement that genotoxicity of 2,5-DCP has been reported from in vitro and in vivo studies."

RESPONSE: *A statement regarding the availability of* in vitro *and* in vivo *data for 2,5-DCP was added.*

The genotoxicity of 2,5-DCP has been tested in both *in vitro* and *in vivo* systems.

COMMENT 65: Referring to the subsection on 2,4,5-TCP in Section 2.20, the Reviewer commented "Insert statement that genotoxicity of 2,4,5-TCP has been reported from in vitro and in vivo studies."

RESPONSE: *A statement regarding the availability of* in vitro *and* in vivo *data for 2,4,5-TCP was added.*

Available genotoxicity data for 2,4,5-TCP include both *in vitro* and *in vivo* studies.

COMMENT 66: Referring to the subsection on 2,4,6-TCP in Section 2.20, the Reviewer commented "Insert statement that genotoxicity of 2,4,6-TCP has been reported from in vitro and in vivo studies."

RESPONSE: *A statement regarding the availability of* in vitro *and* in vivo *data for 2,4,6-TCP was added.*

2,4,6-TCP was tested for genotoxicity in both *in vitro* and *in vivo* assays.

COMMENT 67: Referring to the subsection on 2,3,4,6-TeCP in Section 2.20, the Reviewer commented "Insert statement that genotoxicity of 2,3,4,6-TeCP has been reported from in vitro and in vivo studies."

RESPONSE: *A statement regarding the availability of* in vitro *and* in vivo *data for 2,3,4,6-TeCP was added.*

Both *in vitro* and *in vivo* genotoxicity data are available for 2,3,4,6-TeCP.

COMMENT 68: Referring to the title of Table A-5, the Reviewer commented "Chlorophenol is misspelled in table title."

RESPONSE: *The spelling has been corrected in the title of Table A-5.*

COMMENT 69: Referring to Appendix A, Table A-9, the Reviewer commented "Add reference [Fundamental and Applied Toxicology 5(3):478-486 (1985)]"

RESPONSE: *The reference was added to Table A-9 (Borzelleca et al. 1985c).*

COMMENT 70: Referring to the Intermediate-Duration Oral MRL worksheet for 2,4,5-TCP in Appendix A, the Reviewer commented "It appears questionable whether a 15% increase in absolute liver weight related to 2,4,6-TCP at 4.6 mg/kg/day in an intermediate duration study of groups of SD rats of randomly selected, unspecified and perhaps unbalanced sexes (Exon and Koller, 1985) constitutes an "adverse effect" in the absence of histological or serum chemistry findings of hepatocellular injury in this or similar studies of 2,4,6-TCP (in another intermediate study of 2,4,6-TCP in SD rats, reported by Bercz et al in 1990, the No-Effect level for liver weight increase was 80 mg/kg/day in females and 240 mg/kg/day in males). Perhaps the decreased litter size observed at 46 mg/kg/day should be the most sensitive "adverse effect" in the Exon and Koller (1985) study?"

RESPONSE: *Exon and Koller (1985) did not evaluate histopathology or serum chemistry, so liver weight is the only metric available to evaluate liver effects in this study. While it is true that Bercz et al. (1990) did not observe liver effects at a much higher dose in the same strain of rat, Exon and Koller (1985) exposed Sprague-Dawley rats beginning at conception (exposure during gestation, through weaning, and for 12 additional weeks) while Bercz et al. (1990) exposed Sprague-Dawley rats beginning at 49 days of age. Thus, the lower dose at which liver effects were seen by Exon and Koller (1985) may reflect greater sensitivity of younger rats. The following text was added for clarification.*

> Exon and Koller (1985) did not evaluate clinical chemistry or histopathology. Bercz et al. (1990) did not observe liver effects at a much higher dose (80 mg/kg/day) in the same strain of rat. However, Exon and Koller (1985) exposed Sprague-Dawley rats beginning at conception while Bercz et al. (1990) exposed Sprague-Dawley rats beginning at 49 days of age. Thus, the lower dose at which liver effects were seen by Exon and Koller (1985) may reflect greater sensitivity of younger rats.

COMMENT 71: Referring to the acute-duration oral MRL worksheet for 2,3,4,6-TeCP in Appendix A, the Reviewer commented "Is it certain that a 9% or 10% increase in relative ($p<0.01$) or absolute (N.S.D.) liver weight (respectively) related to 2,3,4,6-TeCP at 10 mg/kg/day in a chronic duration study of groups of male SD rats (Dodd et al, 1985) constitutes an "adverse effect" in the absence of histological or serum chemistry findings of hepatocellular injury at this dose level in this study?

RESPONSE: *The increases in liver weight at 10 mg/kg/day in the 14-day study of 2,3,4,6-TeCP exposure by Dodd et al. (2012) were not considered adverse: this dose was designated the NOAEL for hepatic effects. The LOAEL for hepatic effects was 25 mg/kg/day based on a 15% increase in absolute*

liver weight, 14% increase in relative liver weight, and a low incidence (1/10) of centrilobular vacuolation (with dose-related increases at higher doses).

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: The effects known to occur in humans appear to be covered in this Profile.

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: Many of the observed effects found in animals are likely to also be of concern to humans. Additional concerns for humans include those of developing humans prior to developing the necessary enzymes to metabolize the chlorophenols (see later comments).

RESPONSE: *No response needed.*

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

COMMENT 3: I agree that the exposure conditions have been adequately described.

RESPONSE: *No response needed.*

Minimal Risk Levels (MRLs)

General Comment

COMMENT 4: First, Appendix A is mislabeled Appendix B on page B-1. The tables are labeled correctly.

RESPONSE: *The Appendix label was corrected.*

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

COMMENT 5: I realize that ATSDR does not determine dermal MRL's, but information about effects from dermal exposure can still inform the MRLs for inhalation and oral exposure. The Profile describes four individuals who died from dermal exposure to chlorophenols. One individual's internal dose was

determined as 2 mg/kg for 2,4-DCP, given a factor of 10 for human variability, there is no way one could conclude that the oral MRL of 0.02 mg/kg/day is adequately protective.

RESPONSE: *The 2 mg/kg dose referred to by the Reviewer is a crude minimum dose estimate that was calculated from a postmortem blood concentration of 2,4-DCP (24.3 mg/L), described as follows in Section 2.2 of the profile: "The investigators did not estimate an absorbed dose (Kintz et al. 1992), but assuming a blood volume of 5 L and a body weight of 70 kg, the dose would be approximately 2 mg/kg as a minimum." The crude estimate was deleted from the profile as it did not take into consideration the amounts of 2,4-DCP measured in urine (5.3 mg/L) or bile (18.7 mg/L), and as such may significantly underestimate the dose level. In addition, because the nature, extent, and rate of metabolism or clearance of 2,4-DCP may differ by exposure route (and little information is available to inform these differences), direct comparisons between oral and dermal doses are of uncertain utility.*

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. 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 6: See comments above for the conclusion regarding the oral MRL for 2,4-DCP (the Reviewer is referring to Comment 5). It is clear that an oral MRL should be lower. Information on human fatality from dermal exposure at the oral MRL would be an indication that the oral MRL is too high.

RESPONSE: *See Response to Comment 5.*

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

COMMENT 7: Referring to the statement in Section 1.1—There are five basic types of chlorophenols: mono[one]chlorophenols, di[two]chlorophenols, tri[three]chlorophenols, tetra[four]chlorophenols, and penta[five]chlorophenols—the Reviewer commented " "Pentachlorophenols" should be singular as there is only one.

RESPONSE: *The word pentachlorophenol in Section 1.1 was corrected to be singular.*

> There are five basic types of chlorophenols: mono[one]chlorophenols, di[two]chlorophenols, tri[three]chlorophenols, tetra[four]chlorophenols, and penta[five]chlorophenol.

COMMENT 8: Referring to the statement in Section 1.1—Chlorophenols, especially those with more chlorine atoms and certain chlorine positions, are resistant to biodegradation and thus are moderately persistent in the environment.—the Reviewer commented " 'moderately persistent' should be defined or more quantitative."

RESPONSE: *The text in Section 1.1 was revised for clarity as follows:*

> Chlorophenols, especially those with more chlorine atoms and certain chlorine positions, are resistant to biodegradation and are thus persistent (some may remain in soil for several years) in the environment.

COMMENT 9: Referring to the statement in Section 1.2—However, in the case-control studies (Garabedian et al. 1999; Hoppin et al. 1998; Mirabelli et al. 2000; Richardson et al. 2008), the subjects may have been exposed to pentachlorophenol, and in the ecological study (Lampi et al. 2008), the water supply to which the community was exposed was contaminated pentachlorophenol in addition to other chlorophenols.—the Reviewer commented " '…contaminated pentachlorophenol…' should read "…contaminated with pentachlorophenol…"

RESPONSE: *The text in Section 1.2 was corrected as suggested.*

> However, in the case-control studies (Garabedian et al. 1999; Hoppin et al. 1998; Mirabelli et al. 2000; Richardson et al. 2008), the subjects may have been exposed to pentachlorophenol, and in the ecological study (Lampi et al. 2008), the water supply to which the community was exposed was contaminated with pentachlorophenol in addition to other chlorophenols.

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 10: I disagree with the rejection of studies involving mixtures. Rarely, if ever, are humans exposed to compounds singularly. These mixture studies should be combined with single compound studies to investigate the possibility that toxicity of chlorophenols are additive, synergistic or antagonistic.

RESPONSE: *Studies of mixtures including the subject chlorophenols were not rejected. ATSDR considers studies of humans exposed to mixtures as part of hazard identification for a given compound. In addition, ATSDR evaluates animal studies involving mixtures in the assessment of interactions (Section 3.4 Interactions with Other Chemicals). The text in Section 2.1 pertaining to human studies of mixtures was revised to show that these studies were considered in the profile:*

> Although the human studies of occupational exposure and studies that use urinary chlorophenol levels to assess exposure are not included in the study counts, these studies are discussed in this chapter as they provide some (albeit limited) information that is useful for hazard identification.

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 11: Where available, the studies identified were adequate, or the limitations addressed by the Profile.

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 12: Where available, the studies identified were adequate, or the limitations addressed by the Profile.

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 13: Given the lack of human developmental information, it would be advantageous to include species that have similar development in terms of enzymes with the ability to detoxify/metabolize the chlorophenols. However, it is not clear that any exist.

RESPONSE: *ATSDR agrees that this information would be useful; however, no such data were located in the literature reviewed.*

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

COMMENT 14: It is not clear that the Profile adequately addresses dose-response relationships. The Profile seems to determine the NOEL or LOEL based on levels that had an observable effect. No dose response curves are mentioned or shown. This may perhaps be because none are available, but then this should be mentioned in the Profile.

RESPONSE: *The profile describes dose-related effects (dose-response relationships) wherever observed in the studies reviewed. In addition, where possible, dose-response curves were developed using Benchmark Dose modeling for the critical effects in the studies used to derive MRLs (see Figures A-1 through A-9).*

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 15: I am unaware of any other studies.

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 16: I am unaware of any other studies.

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 17: I cannot offer any changes to the NOAELs or LOAELs aside from what was mentioned above with regards to dose-response curves.

RESPONSE: *The Reviewer is referring to Comment 14. See Response to Comment 14.*

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 18: I agree with the categorization of less serious and serious.

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 19: It is not clear why page 22 only includes some of the mechanisms of action. How were these chosen? Why not include all?

RESPONSE: *Page 22 in Section 2.1 provides a bulleted list of health effects associated with exposure to chlorophenols and does not discuss any mechanisms of action. Data to inform mechanisms of action, where available, are reported in Chapter 2 at the end of each health effect section. For the chlorophenols, mechanistic data are reported for dermal, endocrine, neurological, reproductive, and other noncancer health effects. A sentence was added to Section 2.1 to point the reader to mechanism of action information.*

> When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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 22: I agree with the conclusions.

RESPONSE: *No response needed.*

Specific Comments on Chapter 2

COMMENT 20: Referring to the statement in Section 2.4—The exposure concentrations were characterized as 0.003 mg/L (0.02 ppm) trichlorophenol or less, with potential for considerable variability—the Reviewer commented “Is this an air concentration? If so, state it as such.”

RESPONSE: *The text in Section 2.4 was clarified to indicate that the concentration was in air.*

The air exposure concentrations were characterized as 0.003 mg/L (0.02 ppm) trichlorophenol or less, with potential for considerable variability.

COMMENT 21: Referring to the statement in Section 2.9—Porphyria cutanea tarda has been reported in workers employed in the manufacture of 2,4-DCP and 2,4,5 TCP (Bleiberg et al. 1964)—the Reviewer commented "Why is a skin condition listed in the hepatic section?"

RESPONSE: *The text in Section 2.9 was clarified to indicate the hepatic origin of porphyria cutanea.* Porphyria cutanea tarda (a skin condition caused by markedly decreased uroporphyrinogen decarboxylase activity in the liver) has been reported in workers employed in the manufacture of 2,4-DCP and 2,4,5 TCP (Bleiberg et al. 1964).

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 23: I feel that this is well laid out in the Profile.

RESPONSE: *No response needed.*

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

COMMENT 24: To the best of my knowledge, they have.

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 25: I feel that this is where the Profile may be lacking as described previously. Referring to the statement in Section 3.16—It is possible that humans may be more sensitive than animals to the toxic effects of 2,4 dichlorophonol, based on the one case of human death following dermal exposure)—the Reviewer commented "If one were to look at the statement in lines 3082-3, this appears to be an understatement given the low concentration determined for that individual." The Reviewer is referring to a statement in Section 2.2—The investigators did not estimate an absorbed dose (Kintz et al. 1992), but assuming a blood volume of 5 L and a body weight of 70 kg, the dose would be approximately 2 mg/kg as a minimum.

RESPONSE: *As noted in Response to Comments 5 and 6, the crude estimate of dose that had been reported in Section 2.2 for the victim of the fatal dermal poisoning with 2,4-DCP (Kintz et al. 1992) was deleted because it may have significantly underestimated the dose. The need for additional comparative toxicokinetic information was added to Section 6.2.*

Furthermore, the human fatalities seen after dermal and/or inhalation exposure to 2,4-DCP raise the question of whether humans may be more sensitive than rodents to the effects of this compound. Studies comparing human and rodent toxicokinetics of 2,4-DCP would provide data to inform this question.

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 26: I am not aware of any studies of child health and development.

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 27: The text does not address immunocompromised populations.

RESPONSE: *The potential susceptibility of immunocompromised populations is noted at the end of Section 3.2: "Finally, evidence from rat studies (Exon and Koller 1985; Exon et al. 1984) suggests that the cell-mediated and humoral immune systems are sensitive to 2,4-DCP. Thus, persons with immune system deficiencies may be more susceptible to the adverse effects of 2,4-DCP exposure."*

Biomarkers of Exposure and Effect

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

COMMENT 28: The Profile states that urinary biomarkers of exposure are not specific. I think for all the studies that look at urinary biomarkers, it is imperative to determine when/where the precursor molecule becomes the chlorophenol. If it is early enough, then the exposure to chlorophenol is relevant. i.e. the exposure to another chemical becomes an exposure to chlorophenol.

RESPONSE: *In order to determine when and where the precursor compound is transformed to the chlorophenol, it is necessary to have knowledge of: (a) the precursor compound to which the person was exposed (because several different compounds can be metabolized to the subject chlorophenols, and the higher chlorophenols can be dechlorinated to lower chlorophenols); (b) the route by which the person was exposed (because the location, nature, and extent of metabolism may vary by exposure route); and (c) the timing of exposure to the precursor compound relative to when the urinary chlorophenol levels were measured. The studies in which urinary chlorophenol levels were used to assess exposure did not include this information.*

ATSDR agrees that biotransformation to one of the subject chlorophenols represents exposure to the chlorophenol. However, it is also true that effects seen in humans after exposure to a compound that is metabolized to a chlorophenol may be attributable to the parent compound, the chlorophenol metabolite, or to another metabolite, even when metabolism is relatively rapid. No changes were made to the toxicological profile based on this comment.

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

COMMENT 29: No biomarkers of effect are given.

RESPONSE: *No response needed; no biomarkers of effect are given because none have been identified.*

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 30: This is another area where I believe the Profile is lacking. There appears to be a conscious decision to not include studies that looked at mixtures, or exposure to chemicals that are not chlorophenols. I think the additional references are those that were rejected by the Profile.

RESPONSE: *Studies of mixtures including the subject chlorophenols were not rejected. ATSDR considered studies of humans exposed to mixtures as part of hazard identification. In addition, ATSDR evaluated available animal studies involving mixtures including the subject chlorophenols in the assessment of interactions (Section 3.4 Interactions with Other Chemicals). The text in Section 2.1 pertaining to human studies of mixtures was revised to show that these studies were considered in the Profile:*

> Although the human studies of occupational exposure and studies that use urinary chlorophenol levels to assess exposure are not included in the study counts, these studies are discussed in this chapter as they provide some (albeit limited) information that is useful for hazard identification.

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 31: One cannot conclude this from the Profile.

RESPONSE: *ATSDR recognizes that there are limited data with which to assess potential mechanisms of interactions for chlorophenols, as indicated in the profile in Section 3.4.*

Specific Comments on Chapter 3

COMMENT 32: Referring to the statement in Section 3.1.4—Studies in in rats, rabbits, and dogs (Bray et al. 1952a, 1952b; Coombs and Hele 1926; Spencer and Williams 1950) demonstrate rapid elimination of monochlorophenols after oral exposure; in these studies, most of the administered dose was excreted in the urine within 24 hours—the Reviewer commented " "in" is duplicated.

RESPONSE: *The text in Section 3.1.4 was corrected.*

> Studies in rats, rabbits, and dogs (Bray et al. 1952a, 1952b; Coombs and Hele 1926; Spencer and Williams 1950) demonstrate rapid elimination of monochlorophenols after oral exposure; in these studies, most of the administered dose was excreted in the urine within 24 hours.

COMMENT 33: Referring to the statement in Section 3.1.6—It is possible that humans may be more sensitive than animals to the toxic effects of 2,4 dichlorophonol, based on the one case of human death following dermal exposure.—the Reviewer commented "and the mode of exposure for all four fatalities reported was thought to be dermal, so I'm not sure why this says one death following dermal exposure."

RESPONSE: *The focus on the single death from dermal exposure (as reported by Kintz et al. 1992) was because the victim was exposed to pure 2,4-DCP. However, the other fatalities may also be relevant to the species comparison; thus, the text in Section 3.1.6 was revised for clarity as follows:*

> It is possible that humans may be more sensitive than animals to the toxic effects of 2,4-dichlorophenol, based on the human deaths following dermal and/or inhalation exposures**.**

COMMENT 34: Referring to the statement in Section 3.2—Prior maternal exposure to chlorophenols is unlikely to lead to exposure of the fetus or a nursing neonate due to the relatively rapid metabolism and excretion of chlorophenols (Keith et al. 1980) and evidence for limited to no accumulation in animals after oral exposure (Bahig et al. 1981; Korte et al. 1978)—the Reviewer commented "The authors state that prior maternal exposure to chlorophenols is unlikely to lead to exposure of the fetus or neonate. I think that the Profile has to be careful here. The term "prior" means different things to the fetus versus the neonate. But I generally agree that the rapid excretion of chlorophenols will reduce exposure to the fetus or neonate given sufficient elapsed time."

RESPONSE: *The text in Section 3.2 was revised to clarify the meaning of the sentence.*

> Maternal exposure to chlorophenols prior to pregnancy is unlikely to lead to exposure of the fetus or a nursing neonate due to the relatively rapid metabolism and excretion of chlorophenols (Keith et al. 1980) and evidence for limited to no accumulation in animals after oral exposure (Bahig et al. 1981; Korte et al. 1978).

COMMENT 35: Referring to the statement in Section 3.2—In humans, activity of some hepatic UDP-glucuronosyltransferase (responsible for glucuronide conjugates) isoforms does not reach adult levels until adolescence, although others reach adult levels within a month (Badée et al. 2019)—the Reviewer commented "The fact that enzymes may be developed within a month still allows for a month's worth of exposure to offspring. This is not a trivial amount."

RESPONSE: *ATSDR agrees. No changes were made to the profile.*

COMMENT 36: Referring to the statement in Section 3.2—No specific population with particularly susceptible to chlorophenol intoxication has been identified; however, toxicokinetic and target organ information suggest some possibilities—the Reviewer commented " 'susceptible' should read 'susceptibility'."

RESPONSE: *The text in Section 3.2 was corrected.*

> No specific population with particular susceptibility to chlorophenol intoxication has been identified; however, toxicokinetic and target organ information suggest some possibilities.

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: Referring to Table 4-2, the Reviewer commented "The synonym for 2,3,4,5-tetrachlorophenol is incorrect. It should be 2,3,4,5-TeCP. The structure for 2,3,4,5-tetrachlorophenol is also incorrect."

RESPONSE: *The synonym and structure for 2,3,4,5-tetrachlorophenol were corrected in Table 4-1.*

COMMENT 38: Referring to Table 4-2, the Reviewer commented "The log Kow for 2,4-DCP and 2,4,5-TCP are incorrect. They seem out of range of what one would expect given the degree of chlorination and the log Koc, nor do they comport with what is reported in the citation (Shui et al 1994)."

RESPONSE: *Log K_{ow} values for 2,4-DCP (log K_{ow}=3.06) and 2,4,5-TCP (log K_{ow}=3.72) were corrected in Table 4-2.*

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

COMMENT 39: No, It is important to specify whether the partition coefficients, solubilities and vapor pressures are for the protonated or de-protonated forms. Better yet, provide the values for both forms.

RESPONSE: *Log K_{ow} values specifically relate to the fully protonated species. The octanol/water partition coefficient as a function of pH for ionizable compounds is commonly referred to as log D and is not a constant, but changes as the pH of the solution changes because the percentage of ionized species versus non-ionized species is a function of pH as described by the Henderson-Hasselbalch equation. These values are not typically reported in the toxicological profile, but discussions of how the speciation of a substance affects environmental fate are typically provided in Chapter 5. The vapor pressure refers only to the protonated species as the vapor pressure of ionic substances is exceedingly low. For aqueous solubilities reported in Table 4-2, the pH at which the solubility was assessed was added wherever available to enable the reader to assess the degree of protonation.*

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 40: There is no information provided on import/export. This should be available under TSCA. Now the TSCA website doesn't seem to provide a valid link, but one would assume that ATSDR could get the information from the EPA.

RESPONSE: *The Chemical Data Reporter database was searched for import/export data on the EPA Chemview site; however, no salient statistics were located.*

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 41: The text does provide this information for all sources except releases to underground injection. This is the largest volume of release presented in the TRI, but it is completely ingnored as a potential source to human exposure. Certainly underground injection could contaminate groundwater and possibly surface water should the water table intersect surface waters.

RESPONSE: *Section 5.3.2 was updated to include underground injection disposal methods as a potential source for groundwater contamination.*

> Chlorophenols may enter groundwater systems via leaching from landfills or underground injection disposal.

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 42: It appears to present this information.

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 43: It does present the information. However, in Table 5-1 the values for the total mininum and maximum amounts on site in pounds appears to be incongruous with how the other columns were summed. If the goal is to show the minimum and maximum for an individual site, then the concept of a total isn't valid. If the goal is to the minimum and maximum that could be present at all sites, then they should be summed.

RESPONSE: *ATSDR agrees; however, this is the manner in which TRI data are output in TRI Explorer*.

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 44: The text adequately addresses this.

RESPONSE: *No response needed.*

Specific Comments on Chapter 5

COMMENT 45: Referring to the statement in Section 5.4.1—Since the evaporation rate is inversely related to the depth of water, extrapolation of these data indicates that-2-CP evaporation in water 1 m deep would require approximately 15 days—the Reviewer commented "This is only for diffusion through

stagnant water. Given turbulence, the deeper water will be well-mixed and support the surface microlayer through advection."

RESPONSE: *The text in Section 5.4.1 was revised to show that the extrapolation refers to still waters.*

Since the evaporation rate is inversely related to the depth of water, extrapolation of these data indicates that-2-CP evaporation in still water 1 m deep would require approximately 15 days; evaporation would occur more rapidly in turbulent waters.

COMMENT 46: Referring to the statement in Section 5.4.1—The amount of tri- and tetrachlorophenols from water is expected to significantly lower than the monochlorophenols since their pKa values are orders of magnitude lower, indicating that a much higher percentage will exist as anions in the water column—the Reviewer commented " '…is expected to significantly lower than the…' contains a typo.

RESPONSE: *The text in Section 5.4.1 was revised to correct the typographical error and clarify the sentence.*

The amount of tri- and tetrachlorophenols evaporating from water is expected to be significantly lower than the amount of monochlorophenols evaporating, since the pKa values of tri- and tetrachlorophenols are orders of magnitude lower, indicating that a much higher percentage will exist as anions in the water column.

COMMENT 47: Referring to the statement in Section 5.4.1—At a distance of 5 m from the dipping basin, 2,3,4,6-TeCP concentrations were 430 and 1,980 µg/g fat in *Lumbricuss* and *Aporrectodea*, respectively, while the soil concentration was 336 µg/g dry soil—the Reviewer commented " '*Lumbricuss*' should read '*Lumbricus'*."

RESPONSE: *The spelling of Lumbricus was corrected in Section 5.4.1.*

At a distance of 5 m from the dipping basin, 2,3,4,6-TeCP concentrations were 430 and 1,980 µg/g fat in *Lumbricus* and *Aporrectodea*, respectively, while the soil concentration was 336 µg/g dry soil.

COMMENT 48: Referring to the statement in Section 5.4.1—The difference between the two species was attributed to greater ingestion of contaminated soil by *Aporrectodea*—the Reviewer commented "These are genera not species."

RESPONSE: *The text in Section 5.4.1 was corrected as indicated.*

The difference between the two genera was attributed to greater ingestion of contaminated soil by *Aporrectodea*.

COMMENT 49: Referring to the statement in Section 5.4.2—This bacterial species dechlorinates the chlorine atom at position 4 of various chlorophenols to yield their corresponding hydroquinones and may involve oxygenation—the Reviewer commented "It is better to say that it dechlorinates the phenol. The chlorine atom doesn't get dechlorinated."

RESPONSE: *The text of Section 5.4.2 was revised as indicated.*

This bacterial species dechlorinates the phenol at position 4 of various chlorophenols to yield their corresponding hydroquinones and may involve oxygenation.

COMMENT 50: Referring to the statement in Section 5.4.2—It was also reported that the addition to the culture medium of a vitamin solution containing biotin, folk acid, pyridoxine hydrochloride, riboflavin, thiamine hydrochloride, niacin, pantothenic acid, cyanocobalamin, p aminobenzoic acid, and thioctic acid can increase the aerobic degradation and dechlorination of 2-CP and 4-CP by Pseudomonas picketti strain LDl culture by 11–16% (Kafkewitz et al. 1996)—the Reviewer commented " did the authors mean 'folic' acid?"

RESPONSE: *The spelling of folic acid was corrected in Section 5.4.2.*

> It was also reported that the addition to the culture medium of a vitamin solution containing biotin, folic acid, pyridoxine hydrochloride, riboflavin, thiamine hydrochloride, niacin, pantothenic acid, cyanocobalamin, *p*-aminobenzoic acid, and thioctic acid can increase the aerobic degradation and dechlorination of 2-CP and 4-CP by *Pseudomonas picketti* strain LDl culture by 11–16% (Kafkewitz et al. 1996).

COMMENT 51: Referring to the statement in Section 5.5—In reviewing data on chlorophenols levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.—the Reviewer commented "However, given the high aqueous solubilities, that measured would most likely be bioavailable."

RESPONSE: *The statement in Section 5.5 is templated, recurring text used generally in all toxicological profiles (per ATSDR guideline template) and therefore not specifically directed to chlorophenols, so no changes were made. The profile identifies bioavailability studies specific to chlorophenols as data needs in Section 6.2:*

> **Bioavailability from Environmental Media.** The observation of systemic effects following inhalation, oral, and dermal exposure indicates that the chlorophenols are readily absorbed (see Chapter 3 for more details). Systematic studies of the bioavailability of the chlorophenols from different media have not been completed. Because the compounds are relatively lipophilic and become adsorbed to soil and sediments, a study of the bioavailability of these compounds from soil relative to water following oral exposure would be useful.

COMMENT 52: Referring to Table 5-4, the Reviewer commented "It would be informative to include the analytical methods employed for each of these LODs."

RESPONSE: *Table 5-4 was prepared in accordance with the template give in the current ATSDR Tox Profile guidance (see Table 5-3, page 215 in https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf). ATSDR will consider adding details of the analytical methods in future revisions of the guideline template.*

COMMENT 53: Referring to Table 5-5, the Reviewer commented " Column labeled 'High' How can some of these values be lower than the medians/means in Table 5-6? Aren't those environmental values?"

RESPONSE: *The levels in Table 5-5 are for heavily contaminated NPL sites and levels in Table 5-6 are meant to be more reflective of general environmental levels found in other monitoring studies outside of hazardous waste sites.*

COMMENT 54: Referring to the statement in Section 5.5.2—Grimvall et al. (1991) measured 2,4,6-TCP in unpolluted surface waters in remote areas of southern Sweden and in pulp bleaching plant recipient waters, Lake Vattern and the Baltic Sea—the Reviewer commented " The appropriate term is 'receiving waters'."

RESPONSE: *The text in Section 5.5.2 was corrected as indicated.*

Grimvall et al. (1991) measured 2,4,6-TCP in unpolluted surface waters in remote areas of southern Sweden and in pulp bleaching plant receiving waters, Lake Vattern and the Baltic Sea.

COMMENT 55: Referring to the statement in Section 5.5.2—Consequently, several investigators have detected these chemicals downstream of wastewater discharge points—the Reviewer commented " 'Consequently' this implies causation. Was any measurement made of influent? Why couldn't industrial discharge to a municipal WWTP be the cause?"

RESPONSE: *The text in Section 5.5.2 was revised to remove the term "consequently" as data to demonstrate causation are not available.*

Several investigators have detected these chemicals downstream of wastewater discharge points.

COMMENT 56: Referring to statement in Section 5.6—The average fat concentrations of combined 2,3,4,6-TeCP and 2,3,5,6-TeCP and of 2,3,4,5-TeCP in autopsy specimens were 22 and 6 ng/g respectively in Kingston, Ontario, which is near the Great Lakes, relative to 7 ng/g for 2,3,4,6-TeCP, 2,3,5,6-TeCP, and 2,3,4,5-TeCP in tissue from persons living in Ottawa (Williams et al. 1984)—the Reviewer commented "Kingston, ON is a port city on Lake Ontario. Saying it's 'near the Great Lakes' is an understatement."

RESPONSE: *The text in Section 5.6 was revised to indicate Kingston's location on Lake Ontario.*

The average fat concentrations of combined 2,3,4,6-TeCP and 2,3,5,6-TeCP and of 2,3,4,5-TeCP in autopsy specimens were 22 and 6 ng/g respectively in Kingston, Ontario, which is on Lake Ontario, relative to 7 ng/g for 2,3,4,6-TeCP, 2,3,5,6-TeCP, and 2,3,4,5-TeCP in tissue from persons living in Ottawa (Williams et al. 1984).

COMMENT 57: Referring to the statement in Section 5.6—Potential exposure to chlorophenols tends to be limited because of the pronounced odor and taste imparted by the presence of these substances—the Reviewer commented "Taste and odor thresholds are very subjective and variable among the population."

RESPONSE: *The following sentence was added after the statement in Section 5.6:*

While taste and odor thresholds do vary across the population, low concentrations of chlorophenols can be detected by most people.

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 58: I do not.

RESPONSE: *No response needed.*

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

COMMENT 59: I would argue that the greatest data need is on developmental effects in humans. I would also argue that knowing where in the body precursor molecules are transformed to chlorophenols is important as this is another route of exposure to chlorophenols.

RESPONSE: *A sentence was added to Section 6.2, Identification of Data Needs, regarding the need for additional epidemiological data on developmental effects in humans. ATSDR agrees that biotransformation to one of the subject chlorophenols represents exposure to the chlorophenol. However, any effects seen in humans after exposure to a compound that is metabolized to a chlorophenol may be attributable to the parent compound, the chlorophenol metabolite, or to another metabolite.*

More epidemiological studies of developmental effects in humans exposed to chlorophenols would be beneficial as well.

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

COMMENT 60: I do not sense any bias.

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 61: I would include REACH regulations on chlorophenols: https://echa.europa.eu/substance-information/-/substanceinfo/100.042.432

RESPONSE: *The focus of Chapter 7 is U.S. regulations and guidelines, with the exception of the International Agency for Research on Cancer (IARC) cancer classifications and World Health Organization (WHO) air and water guidelines; international regulations and guidelines are not included in Table 7-1.*

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

COMMENT 62: No.

RESPONSE: *No response needed.*

Appendices

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

COMMENT 63: As stated earlier, Appendix A is mislabeled Appendix B and has the page numbering incorrect as well. Subsequent appendices are then off by one letter as well. The page numbering for Appendix B also goes from C-1 to B2 and then continues correctly.

RESPONSE: *All Appendix labels and page numbering were corrected.*

Peer Review Comments on Unpublished Studies

<u>Unpublished Study:</u> BSRC. 2011. Simplified reproductive toxicity testing of oral p-chlorophenol dosage using rats. Biosafety Research Center. Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare of Japan. Test No: C539 (115-222).

General Comment From Peer Reviewer #1

COMMENT: This is a sound well planned study to assess the reproductive toxicity of p-chlorophenol (4-chlorophenol) where pertinent details are amply documented and followed GLP guidelines.

ATSDR Charge Questions Reviewer Comments and Responses

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIWER #1 COMMENT: Yes. Pertinent details of animal care, feed, dosing etc. have been provided.

PEER REVIWER #2 COMMENT: This unpublished BSRC (2011) study was performed to GLP and OECD guidelines. The report was logically presented and did not create any concern regarding the design or conduct of the study, thus it should be cited and utilized in this Toxcological Profile of Chlorophenols.

PEER REVIWER #3 COMMENT: Yes, the study had ample numbers of animals (52 male and 60 female) and good animal care.

QUESTION: Did the study account for competing causes of death?

PEER REVIWER #1 COMMENT: Yes. Death as reported in highest dose group (1,000 mg/kg) among both male and females had problems which are attributed to irritant properties of p-chlorophenol and its impact on central nervous system.

PEER REVIWER #2 COMMENT: YES.

PEER REVIWER #3 COMMENT: They had some "unknown" causes of death that they couldn't account for. For the other deaths, they were coincident with symptoms consistent with exposure to the test compound.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIWER #1 COMMENT: Yes. Three doses ranging 4-1,000 mg/kg were used for oral feeding dissolved in corm oil.

PEER REVIWER #2 COMMENT: YES.

PEER REVIWER #3 COMMENT: Both the 28-day and 2-week trials contained four dosage levels (albeit different levels between trials). Given the results of toxicity, I would have like to see more levels between the 200 and 1,000 mg/kg levels in the 2-week trial.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIWER #1 COMMENT: Well-designed study to examine the reproduction and ontogenesis of p-chlorophenol in rats.

PEER REVIWER #2 COMMENT: NOT APPLICABLE.

PEER REVIWER #3 COMMENT: While the results are not negated, I think more accurate results would have been obtained with more levels.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIWER #1 COMMENT: Yes.

PEER REVIWER #2 COMMENT: YES.

PEER REVIWER #3 COMMENT: Yes.