DISPOSITION OF PEER REVIEW COMMENTS FOR

TOXICOLOGICAL PROFILE FOR

TETRACHLOROETHYLENE

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Prepared for:

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

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Review comments provided by Reviewer #1:

COMMENT: 1. While the huge data gap on early life risk is indicated in several places, it may not be clear to the reader just how serious this gap may be. In effect, this prominent contaminant has comparatively less information available about risk during critical windows of vulnerability than one expects to encounter for most toxicants of this nature (e.g., trichloroethylene). Section 3.7 has an excellent discussion about potential reason for enhanced early life vulnerabilities. However, the inability to be able to access this due to lack of appropriate studies is less obvious. It is useful and important to stress this point if the data gap is to be filled and more reliable information made available in the future. Simply stated and based on available data, at present we have comparatively little knowledge about the risk for exposure of pregnant women and children. I would urge that this gap be even more prominently identified within the profile.

RESPONSE 1: *The text was revised to emphasize the lack of data on early life risks. A note was added to Section 1 as follows:*

> *It is not known whether children are more susceptible than adults to the effects of tetrachloroethylene. There are very few studies available to answer this question, and many more studies are needed.*

In addition, an introduction to Section 3.12.2 Identification of Data Needs was added, including the following:

> *Data needs by exposure duration and endpoint are discussed below. While the database of toxicity information on tetrachloroethylene is adequate for some endpoints, significant data gaps exist for several endpoints, including: developmental and neurodevelopmental toxicity and immunotoxicity (both developmental and in adult populations).*

COMMENT 2. The gap of information concerning immunotoxicity is made clear in a summary figure (3.6). But what is not stressed is that since the cancers of greatest relevance for exposure to tetrachloroethylene include several immune-derived cancers, non-cancer immune alterations would be an expected outcome of exposure. Very little immune functional data exist for any exposure scenario. The top of pages 124, 143 and 150 are examples where this discussion could be enlarged. It is not just that the Seo et al. studies need to be verified for possible vulnerability for allergic-inflammatory responses, complete immunotoxicity assessment is needed and warranted based on the immune cells as a target for multiple myeloma and lymphoma. Additionally, Seo et al. 2008 emphasizes exacerbated inflammation. This may help to explain some of the adverse outcomes associated with liver, kidney and neurological tissues. The potential for a contribution of tissue inflammation could be mentioned in the section of p.149 lines 31-311 extending to p.150 lines 1-2.

RESPONSE 2: *The text was revised to emphasize the lack of data on immunotoxicity and the available information on tetrachloroethylene-induced inflammation.*

Section 3.5.2, Immune Effects was modified as follows:

> *These data suggest possible mechanisms for tetrachloroethylene-induced perturbation of the immune response to allergens, and exacerbation of inflammation An in vitro study by Kido et al. (2013) also showed effects on pro-inflammatory cytokine gene expression. Significant ($p < 0.05$) increases in the expression of IL-6 and IL-10 mRNA were observed in murine macrophage cells exposed to 800 µg/mL tetrachloroethylene. However, cell viability was significantly diminished at this concentration, and exposure to a higher concentration (1,000 µg/mL) yielded mRNA levels comparable to controls, so a clear dose-response relationship was not demonstrated.*

An introduction to Section 3.12.2 Identification of Data Needs was added, including the following:

Data needs by exposure duration and endpoint are discussed below. While the database of toxicity information on tetrachloroethylene is adequate for some endpoints, significant data gaps exist for several endpoints, including: developmental and neurodevelopmental toxicity, and immunotoxicity (both developmental and in adult populations).

Text in Section 3.12.2 under Chronic-Duration Exposure and Cancer was also revised to point out a need for research into the role of inflammation, as follows:

In addition, research investigating the potential contribution of inflammation to adverse effects of chronic tetrachloroethylene exposure (including cancers as well as liver, kidney, and neurological effects) would be beneficial in light of the data from Seo et al. (2008a) suggesting enhancement of inflammation in rats exposed to this compound.

COMMENT: 3. The different level of conclusions reached in this profile for risk of cancer and the comparison with the NRC 2010 and EPA 2012a reviews could use a clearer explanation. I am concerned the reader will not really understand the basis for this apparent departure from other reviews.

RESPONSE 3. *The text was revised for clarity, as the apparent departure from the NRC (2010) and EPA (2012) conclusions regarding carcinogenicity was not intentional. An introductory sentence was added to Section 3.2.1.7 Cancer as follows: "In humans, tetrachloroethylene exposure may be associated with increased risk of cancer. As discussed further below, the highest quality epidemiological studies suggest an association between tetrachloroethylene exposure and bladder cancer, multiple myeloma, and non-Hodgkin's lymphoma." In addition, further details of the studies suggesting increased risk of non-Hodgkin's lymphoma were added to this section.*

Minor corrections/suggestions for the text:

COMMENT 4: p.35 line 21 – there is an extra dash between Fischer and 344

RESPONSE 4: *Changed to F344 throughout the document.*

COMMENT 5: p.146 line25 – the second work of the sentence "histopathology" should not be capitalized.

RESPONSE 5: *Corrected.*

COMMENT 6: I do suggest rewording the following found on p. 201 lines 12-13 "Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility." Instead, it could read: "Needed child health data to inform age-related susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility."

RESPONSE 6: *Revised as suggested.*

Charge and Chapter Questions and Responses

Please answer the following questions in your review:

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

COMMENT 7: No. The authors have been comprehensive and effective in considering the existing literature relative to children's health. Sadly, the literature is lacking and does little to inform us as to the potential differential risk faced by developing physiological targets during critical windows of development. In particular, early exposure leading to an elevated risk of later-life disease is a massive data gap. What the current literature does suggest is that the neurological system, neurobehavioral endpoints and neurodegenerative risks are a prime consideration with early life exposure. The prior findings, immune system cancer associated with exposed adults (multiple myeloma and lymphoma), suggest that other adverse immune outcomes (*e.g.,* immunotoxicity) are likely. However, studies of comprehensive immunotoxicity assessment with functional analysis and in particular risk of DIT are lacking. While uncertainty factors may be used to cover risk for children, a pollutant of this significance needs relevant Developmental Neurotoxicity (DNT) and Developmental Immunotoxicity (DIT) data as we simply do not know the risk that could exist for these targets during critical windows of development. Developmental data have been important with related pollutants such as trichloroethylene and could well shift our estimations of risk here with tetrachloroethylene. Certainly, the lack of these data is mentioned in the draft profile. However, I recommend that this point be made more overtly in Sections 3.12.2 and 6.81. These are the types of studies that could generate data completely altering our estimates of risk for children. Hopefully, this gap can be filled, in part, through the efforts of ATSTR and NTP.

RESPONSE 7: *The text was revised to emphasize the lack of data on immunotoxicity. An introduction to Section 3.12.2 Identification of Data Needs (Section 6.8.1 pertains to data needs for exposure rather than toxicity) was added, as follows:*

> *Data needs by exposure duration and endpoint are discussed below. While the database of toxicity information on tetrachloroethylene is adequate for some endpoints, significant data gaps exist for several endpoints, including: developmental and neurodevelopmental toxicity, and immunotoxicity (both developmental and in adult populations).*

Charge Q: Are there any general issues relevant to child health that have not been discussed in the profile and should be?

COMMENT 8: No. The landscape is covered in this draft profile. However, as indicated in the prior answer, I think the available data and knowledgebase are quite woeful as relates to children's health needs. This current status needs to be given even more prominence where possible. For a toxicant of this significance, it is unusual to know so little about potential age-, life-stage-related vulnerabilities.

RESPONSE 8: *The text was revised to emphasize the lack of data on early life risks. A note was added to Section 1 as follows:*

> *It is not known whether children are more susceptible than adults to the effects of tetrachloroethylene. There are very few studies available to answer this question, and many more studies are needed.*

An introduction to Section 3.12.2 Identification of Data Needs was added, including the following:

> *Data needs by exposure duration and endpoint are discussed below. While the database of toxicity information on tetrachloroethylene is adequate for some endpoints, significant data gaps exist for several endpoints, including: developmental and neurodevelopmental toxicity, and immunotoxicity (both developmental and in adult populations).*

Charge Q: If you answer yes to either of the above questions, please provide any relevant references.
Chapter 1.
Charge Q: The tone of the chapter should be factual rather than judgmental. Does the chapter present the important information in a non-technical style suitable for the average citizen? If not, suggest alternate wording.
COMMENT 9: Chapter 1 presents a factual representation of the available data. It is written in a manner that provides general accessibility.

RESPONSE 9: *No response required.*

Charge Q: Major headings are stated as a question. In your opinion, do the answers to the questions adequately address the concerns of the lay public? Are these summary statements consistent, and are they supported by the technical discussion in the remainder of the text? Please note sections that are weak and suggest ways to improve them.
COMMENT 10: The most significant concerns of the public may well center on risk for vulnerable subpopulations *(e.g.,* children, pregnant women). There are significant data gaps here. The wording in the report is accurate but it is also likely to produce some dissatisfaction regarding what is not known. For example, the Children and Tetrachloroethylene is accurate but striking in the lack of content. The template probably does not allow for qualifiers (e.g., based on available data) but they might be useful.

RESPONSE 10: *The text was revised to emphasize the lack of data on early life risks. A note was added to Section 1 as follows:*

> *It is not known whether children are more susceptible than adults to the effects of tetrachloroethylene. There are very few studies available to answer this question, and many more studies are needed.*

Charge Q: Are scientific terms used that are too technical or that require additional explanation? Please note such terms and suggest alternate wording.
COMMENT 11: The authors have done an effective job in avoiding use of jargon or terms that fall outside of general use.

RESPONSE 11: *No response required.*

Chapter 2.
Charge Q: Do you agree with those effects known to occur in humans as reported in the text? If not, provide a copy of additional references you would cite and indicate where (in the text) these references should be included.
COMMENT 12: I am in agreement with the health effects reported in Chapter 2.

RESPONSE 12: *No response required.*

Charge Q: 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 13: They may be of concern where data gaps exist. Certainly, the Seo et al. immune studies lack an exact comparative equivalent in humans (e.g., mast cell and basophil-induced inflamamation are not among human assessment measurements.) However, some of the human data that exists support

immune perturbations although either ill-defined or with some limitation to the studies. The fact that immune cell cancers (multiple myeloma, non-Hodgkin's lymphoma) are among significant human cancer concerns provides a greater likelihood that immune cells are a potentially significant target of tetrachloroethylene.

RESPONSE 13: *No response required.*

Charge Q: Have exposure conditions been adequately described? If you do not agree, please explain.
COMMENT 14: Yes they are adequately described.

RESPONSE 14: *No response required.*

Chapter 3.
Toxicity - Quality of Human Studies
Charge Q: 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)? If not, were the major limitations of the studies sufficiently described in the text without providing detailed discussions. If study limitations were not adequately addressed, please suggest appropriate changes.
COMMENT 15: The authors did an excellent job of describing the human studies including the limitations of several studies. The chapter provides a comprehensive listing and analysis of the human studies. No suggested changes are needed.

RESPONSE 15: *No response required.*

Charge Q: Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the profile? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)? Please suggest appropriate changes.
COMMENT 16: No changes are suggested here. The authors did an excellent job of translating the study data to the profile.

RESPONSE 16: *No response required.*

Charge Q: Were all appropriate NOAELs and/or LOAELs identified for each study? 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: The studies appear to have been handled correctly as per identification of NOAELs and LOAELs. The comparative use of these as shown in the figures is appropriate.

RESPONSE: *No response required.*

Charge Q: Were the appropriate statistical tests used in the studies? Would other statistical tests have been more appropriate? Were statistical test results of study data evaluated properly? **NOTE**: As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data.
COMMENT 17: The chapter authors appear to have used a consistent and appropriate measure for evaluating the statistical approaches and results of study data.

RESPONSE 17: *No response required.*

Charge Q: Are you aware of other studies which 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 18: I am not aware of useful existing studies that have been omitted from this section.

RESPONSE 18: *No response required.*

Toxicity - Quality of Animal Studies
Charge Q: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.
COMMENT 19: The authors have done a careful job of describing inherent strengths and weaknesses of animal studies. I did not see a discussion of potential strain effects. However, there is nothing in the table of studies that inherently suggests this is a major issue.

RESPONSE 19: *No response required.*

Charge Q: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?
COMMENT 20: The discussion of animal studies reflects the literature. The predominance of rodent studies is expected. There is some partitioning based on historic model utility. For example, reproductive studies tend to utilize the rat more than the mouse while immune studies are more equally balanced or biased toward the mouse. This only becomes significant when metabolic distinctions might affect extrapolation of results to humans**.**

RESPONSE 20: *No response required.*

Charge Q: Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the text? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)?
COMMENT 21: The authors of the profile did an excellent job of identifying any discrepancies between study data and author's interpretation and/or conclusions of the results and in accurately relaying study limitations identified by authors. I have no concerns in this area.

RESPONSE 21: *No response required.*

Charge Q: Were all appropriate NOAELs and LOAELs identified for each study? Were all appropriate toxicological effects identified for the studies? If not, please explain.
COMMENT 22: Yes. The authors did a very complete job of identifying NOELs and LOAELs in each study and also translating those to information in the table and figures.

RESPONSE 22: *No response required.*

Charge Q: If appropriate, is there a discussion of the toxicities of the various forms of the substance? If not, please give examples of toxicological effects that might be important for forms of the substance.
COMMENT 23: Yes. An appropriate discussion is present. Because there may be more than one route to certain organ toxicities, there are certain data gaps. But these are identified by the authors.

RESPONSE 23: *No response required.*

Charge Q: Were the appropriate statistical tests used in the interpretation of the studies? If not, which statistical tests would have been more appropriate? Were statistical test results of study data evaluated properly? **NOTE**: As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data.
COMMENT 24: The authors have been particularly careful in their handling of statistical analysis. This is reflected in the identification of studies with limitations such as population size.

RESPONSE 24: *No response required.*

Charge Q: Are you aware of other studies that may be important in evaluating the toxicity of the substance? If you are citing a new reference, please provide a copy and indicate where (in the text) it should be included.
COMMENT 25: No. To my knowledge, the database used in the present draft profile is up-to-date and complete regarding the fundamental toxicity of tetrachloroethylene. However, in other sections, I do refer to a new in vitro immune study that likely appeared since the preparation of this draft (Kido et al., 2013). Its primary value is in adding support for the liver and neurological effects seen and additional impetus for potential immune dysfunction in tissues. However, the study also has several weaknesses as are detailed in the answer to the references question.

RESPONSE 25: *The text was revised to add information from Kido et al. (2013) as follows:*

> *An in vitro study by Kido et al. (2013) showed significant ($p < 0.05$) increases in the expression of IL-6 and IL-10 mRNA in murine macrophage cells exposed to 800 µg/mL tetrachloroethylene. However, cell viability was significantly diminished at this concentration, and exposure to a higher concentration (1,000 µg/mL) yielded mRNA levels comparable to controls, so a clear dose-response relationship was not demonstrated.*

Levels of Significant Exposure
Charge Q: Are the LSE tables and figures complete and self-explanatory? Does the "Users Guide" explain clearly how to use them? Are exposure levels (units, dose) accurately presented for the route of exposure? Please offer suggestions to improve the effectiveness of the LSE tables and figures and the "User's Guide."
COMMENT 26: The tables and figures are excellent. The User's Guide is very helpful and the authors have provided a ready and meaningful way to make needed comparisons and identify the most pressing issues. This is an excellent approach.

RESPONSE 26: *No response required.*

Charge Q: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?
COMMENT 27: Yes. I think that the authors have been careful and deliberative in utilizing these categories. Additionally, it is helpful to make these distinctions.

RESPONSE 27: *No response required.*

Charge Q: If MRLs have been derived, are the values justifiable? If no MRLs have been derived, do you agree that the data do not support such a derivation?
COMMENT 28: MRLs were derived and presented in Section 2.3 except for the dermal exposure route. Worksheets were provided in Appendix A. These are helpful. The authors acknowledge that many uncertainties with the MRLs exist and use as an example later-life, allergic-respiratory-asthma risk that could result from either delayed-in-development outcomes or repeated acute exposures (*vs*. a lifetime exposure calculated risk). I agree with these concerns. With the significant uncertainties specified, this is a reasonable approach.

RESPONSE 28: *No response required.*

Evaluation of Text
Charge Q: Have the major limitations of the studies been adequately and accurately discussed? How might discussions be changed to improve or more accurately reflect the proper interpretation of the studies?
COMMENT 29: In general the authors have done an excellent job and should be highly commended. There is one area that I feel would benefit from more explanation. The current profile appears to deviate from the NRC 2010 and EPA 2012a evaluations of tetrachloroethylene and risk of various cancers (and possibly also that of the EPA (as referenced). This is a major point if the CDC is shifting away from the other agency conclusions. Yet, this differing conclusion seems to be only indirectly addressed or discussed only briefly. It would be helpful for readers if this apparent departure in conclusions among recent federal agency-led reviews could be more fully discussed within the cancer section.

RESPONSE 29: *The text was revised for clarity, as the apparent departure from the NRC (2010) and EPA (2012) conclusions regarding carcinogenicity was not intentional. An introductory sentence was added to Section 3.2.1.7 Cancer as follows:* "*In humans, tetrachloroethylene exposure may be associated with increased risk of cancer. As discussed further below, the highest quality epidemiological studies suggest an association between tetrachloroethylene exposure and bladder cancer, multiple myeloma, and non-Hodgkin's lymphoma." Further details of the studies suggesting increased risk of non-Hodgkin's lymphoma were also added.*

Charge Q: Has the effect, or key endpoint, been critically evaluated for its relevance in both humans and animals?
COMMENT 30: As can be expected, not all endpoints have a wealth of both human and animal tetrachloroethylene toxicity data. The authors have done a good job of pointing this out. Some distinctions are made among endpoints that are well-established as biomarkers of specific adverse health vs. other that may not have the same predictive value relative to disease, other vulnerabilities or eroded quality of life. Additionally, the authors do make distinctions where endpoints may not be exactly equivalent or have the same meaning between humans vs. certain animal species. While more could be done in designating biomarker relevancy in this document, it is not an addition I would recommend given the overall goal of the draft profile.

RESPONSE 30: *No response required.*

Charge Q: Have "bottom-line" statements been made regarding the relevance of the endpoint for human health?
COMMENT 31: Many endpoints can be measured. But some endpoints have more known overt relevance to human health than others. In my opinion, the document does a good job of pointing out these distinctions without completely discounting measurements that could be better understood as per relevance in the future and/or might become more relevant in light of additional data. The attention and treatment of this subject is fair.

RESPONSE 31: *No response required.*

Charge Q: 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 32: As a whole the conclusions are sound, clearly stated and reflect the existing database. I believe the Seo et al. 2008 finding of exacerbated inflammation may be as important as the allergic/hypersensitivity component, and this should be mentioned where this information is discussed (pp.149-150). Improper control of tissue inflammation could be a unifying feature that extends to other tetrachloroethylene-induced problems.

RESPONSE 32: *The finding of exacerbated inflammation was added to the text in several places to emphasize this finding.*

COMMENT 33: Information on developmental windows of vulnerability for target organs/systems is almost completely lacking and this needs to be stressed.

RESPONSE 33: *The text of Section 3.7was revised to emphasize the limited data on chilren's susceptibility as follows:*

> *The data available for assessing the potential susceptibility of infants and children to the toxic effects of tetrachloroethylene are very limited.*

COMMENT 34: It is evident that no comprehensive immunotoxicity evaluation (including a range of functional tests) has been performed, to date. This is a major system gap particularly in light of concern of multiple myeloma and lymphoma as possible exposure outcomes.

RESPONSE 34: *The text of Section 3.12.2 Immunotoxicity was revised as follows:*

> *Further study of the immune system effects of tetrachloroethylene is needed, given a) the effects suggested by the studies of Seo et al. (2008a,2012); b) the observation in human epidemiological studies of potential associations between tetrachloroethylene and immune system cancers (multiple myeloma and lymphoma); c) the potential role of enhanced inflammation in the observed effects of tetrachloroethylene on other systems including the liver, kidney, and neurological system; and d) evidence that the related compound trichloroethylene exerts immunotoxic effects. A comprehensive immunotoxicity evaluation, including a range of functional tests, is warranted. .*

Charge Q: Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.
COMMENT 35: Yes this is a strong aspect of the present report. I have no suggestions to make on this point.

RESPONSE 35: *No response required.*

Charge Q: Has the animal data been used to draw support for any known human effects? If so, critique the validity of the support.
COMMENT 36: It seems clear that the neurological system is a major target of tetrachloroethylene induced-toxicity. The animal data, particularly among rodents, supports a potentially broader range of neuro and neurodevelopmental alterations than have been detected in humans. The supposition that human effects may well extend beyond the prominent neuro-involved vision alterations is appropriate given the existing animal data and understanding of metabolic comparisons. I believe the document treats this issue appropriately and have no concerns.

RESPONSE 36: *No response required.*

Toxicokinetics
Charge Q: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.
COMMENT 37: Yes. A lack of information is provided for dermal exposure but this reflects the state of knowledge from the literature.

RESPONSE 37: *No response required.*

Charge Q: Have the major organs, tissues, etc. in which the substance is stored been identified? If not, suggest ways to improve the text.
COMMENT 38: Yes. The tissue/organ discussion includes both transport storage issues as well as target tissue for adverse health effects.
RESPONSE 38: *No response required.*

Charge Q: Have all applicable metabolic parameters been presented? Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.
COMMENT 39: The text presentation on metabolic parameters is quite complete. There is a discussion of the oral route of exposure and the potential metabolic effect of gastrointestinal commensal microbes. This is identified as a data gap and I agree with this suggestion.

RESPONSE 39: *No response required.*

Charge Q: Is there adequate discussion of the differences in toxicokinetics between humans and animals? What other observations should be made?
COMMENT 40: Yes, for example the production of oxalic acid in rats but lack of reporting of oxalic acid with human metabolism is indicated. These species comparisons are appropriately delineated. There is also discussion of possible differential routes to organ-targeted carcinogenicity in rats (e.g., kidney) vs. mice (e.g., liver) based on difference in peroxisome proliferation response. The distinction is made that humans may not follow the mouse liver pattern of carcinogenic risk as a result. This is an appropriate and useful discussion.

RESPONSE 40: *No response required.*

Charge Q: Is there an adequate discussion of the relevance of animal toxicokinetic information for humans? If not, please explain.
COMMENT 41: Yes. Differences are noted particularly between rodent species and humans. There is also a discussion of whether metabolic studies in a species (e.g., primates) more closely resembling the pattern seen in humans is desirable.

RESPONSE 41: *No response required.*

Charge Q: If applicable, is there a discussion of the toxicokinetics of different forms of the substance (e.g., inorganic vs. organic mercury)?
COMMENT: This is less relevant than consideration of some forms of heavy metals.

RESPONSE: *No response required.*

Mechanism of Action
Charge Q: Have all possible mechanisms of action been discussed? If not, please explain.
COMMENT 42: Yes. Some have been given much more emphasis than others. However, the document appears to accurately reflect what is known from the literature.

RESPONSE 42: *No response required.*

Biomarkers of Action
Charge Q: Are the biomarkers of exposure specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?
COMMENT 43: The tests are well-described for tracking exposure and distribution. I have nothing to suggest differently for this section.

RESPONSE 43: *No response required.*

Charge Q: Are there valid tests to measure the biomarker of exposure? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.
COMMENT 44: Yes. Additionally, effective PBPK models have been developed and applied. The section fits well with description in other sections.
RESPONSE 44: *No response required.*

Charge Q: Are the biomarkers of effect specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?
COMMENT 45: As is mentioned in the text, tetrachloroethylene does not produce a toxicant specific disease. As a result, biomarkers of effect are varied and can depend upon the target tissue (among several) that exhibits an effect. The one common feature appears to be inappropriate inflammation. However, that is best described for the liver and kidneys compared with neurological effects. The present text covers the landscape of effects and does so appropriately based on the existing literature.

RESPONSE 45: *No response required.*

Charge Q: Are there valid tests to measure the biomarker of effect? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.
COMMENT 46: At present there appears to be no standardization for measuring a biomarker of effect. There is mention of peroxisome proliferation alterations. But even this may not apply across all target tissues. Under these circumstances the present draft is appropriately worded.

RESPONSE 46: *No response required.*

Interactions with Other Chemicals
Charge Q: 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? If not, please clarify and add additional references.
COMMENT 47: In general, this was not a prominent feature of this profile. The bulk of the consideration of mixed exposures concerned whether outcomes could be attributed to tetrachloroethylene or were potentially related to other chemicals in an exposure mixture. Among the interactions that were considered were mixtures of trichloroethylene and tetrachloroethylene.

RESPONSE 47: *No response required.*

Charge Q: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? If not, please clarify and provide any appropriate references.
COMMENT 47: A detailed consideration of interactive effects appeared to be largely absent from the profile. However, that probably reflects the current state of the literature and a lack of clear mechanistic understanding of the interactions that have been described. Among factors (rather than substances), lean body mass is one where a mechanism for interaction with exposure/absorption seems more obvious.

RESPONSE 47: *The text of Section 3.10 was revised to address the topic of body mass, as follows: The lipophilicity of tetrachloroethylene may also result in higher accumulations of the compound in exposed persons with higher body fat content; conversely, lower body fat may result in higher blood levels of tetrachloroethylene. There are no data on the potential effects of obesity or underweight on tetrachloroethylene pharmacokinetics.*

Populations That are Usually Susceptible
Charge Q: Is there a discussion of populations at higher risk because of biological differences which make them more susceptible? Do you agree with the choices of populations? Why or why not? Are you aware of additional studies in this area?
COMMENT 48: There is a discussion of susceptible subpopulations. One subpopulation that appears to be missing in any discussion would be the obese population. Since toxicant storage appears to favor a lipid environment, there is a question of possible differential risk based on BMI. However, there are probably few to no studies that have addressed this.

RESPONSE 48: *The text was revised to discuss potential vulnerability of obese populations, as follows: The lipophilicity of tetrachloroethylene may also result in higher accumulations of the compound in exposed persons with higher body fat content; conversely, lower body fat may result in higher blood levels of tetrachloroethylene. There are no data on the potential effects of obesity or underweight on tetrachloroethylene pharmacokinetics.*

Methods for Reducing Toxic Effects
Charge Q: Is the management and treatment specific for the substance, or is it general for a class of substances?
COMMENT 49: General supportive care is provided at present. Therefore, it is not substance specific.

RESPONSE 49: *No response required.*

Charge Q: Is there any controversy associated with the treatment? Is it a "well accepted" treatment?
COMMENT 50: There does not appear to be a controversy with the general supportive care. If specific intervention strategies to alter in metabolic pathways were to be performed that might be more controversial.

RESPONSE 50: *No response required.*

Charge Q: Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?
COMMENT 51: Given the current general treatment approaches, the hazards are minimal.

RESPONSE 51: *No response required.*

Charge Q: Are treatments available to prevent the specific substance from reaching the target organ(s), or are the actions general for a class of substances?
COMMENT 52: No treatments of this nature appear to be employed at present beyond the possibility of shifting ventilation rate for inhalation exposure.

RESPONSE 52: *No response required.*

Charge Q: Is there any controversy associated with the treatment? Is it a "well-accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method?
COMMENT 53: Ventilation rate changes are relatively uncontroversial. Their overall impact has some uncertainty.

RESPONSE 53: *No response required.*

Charge Q: Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?
COMMENT 54: It was not evident from the document or literature that specific population-directed treatments are in present use.

RESPONSE 54: *No response required.*

Charge Q: Are there treatments to prevent adverse effects as the substance is being eliminated from the major organs/tissues where it has been stored (e.g., as a substance is eliminated from adipose tissue, can we prevent adverse effects from occurring in the target organ[s])?
COMMENT 55: Any focus is being directed toward possible protection of neurological tissues, the liver and kidney. However, these appear to remain largely theoretical at present.

RESPONSE 55: *No response required.*

Charge Q: Are treatments available to prevent the specific substance from reaching the target organ(s), or are the treatment's actions general for a class of substances?
COMMENT 56: At present, these do not appear to be available.

RESPONSE 56: *No response required.*

Charge Q: Is there any controversy associated with the treatment? Is it a "well accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method?
COMMENT 57: N/A. These are not presently in use.

RESPONSE 57: *No response required.*

Charge Q: Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?
COMMENT 58: Targeted treatment is not currently in general use. As a result this is largely a matter of conjecture. Certainly treatment of children with immature, developing physiological systems has potential risks that are not present in adults. Aged populations could have additional added risks of concern.
RESPONSE 58: *No response required.*

Chapter 4.
Charge Q: Are you aware of any information or values that are wrong or missing in the chemical and physical properties tables? Please provide appropriate references for your additions or changes.
COMMENT 59: To my knowledge the information is presented accurately.

RESPONSE 59: *No response required.*

Charge Q: Is information provided on the various forms of the substance? If not, please explain.
COMMENT 60: Yes. To my knowledge this is complete.

RESPONSE 60: *No response required.*

Chapter 5.
Charge Q: Are you aware of any information that is wrong or missing? If so, please provide copies of the references and indicate where (in the text) the references should be included.
COMMENT 61: I have no corrections to suggest for chapter 5.

RESPONSE 61: *No response required.*

Chapter 6.
Charge Q: 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 62: The text provides a clear picture of substance release through to exposure. I have no suggested changes for this section.

RESPONSE 62: *No response required.*

Charge Q: 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 63: I know of no additional references that should be included on this topic. The most intriguing topic raised in this section involves the potential impact of diverse microbial population.

RESPONSE 63: *No response required.*

Charge Q: 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 64: The text is both complete and clearly presented regarding levels of tetrachloroethylene. I know of no missing studies or data that would alter this section.

RESPONSE 64: *No response required.*

Charge Q: 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 no
COMMENT 65: Yes, the text provides useful information on both general and special populations. I do suggest rewording the following found on p. 201 lines 12-13 "Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility." Instead it could read: "Needed child health data to inform age-related susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility."

RESPONSE 65: *Revised as suggested.*

Chapter 7.
Charge Q: Are you aware of additional methods that can be added to the tables? If so, please provide copies of appropriate references.
COMMENT 66: I am not aware of additional methods. However, these analytical methods falls outside of my general expertise.

RESPONSE 66: *No response required.*

Charge Q: Have methods been included for measuring key metabolites mentioned previously in the text?
COMMENT 67: Yes. I have found no incompatibilities between the previous information and the methods included here.

RESPONSE 67: *No response required.*

Charge Q: If unique issues related to sampling for the substance exist, have they been adequately addressed in the text? What other discussion should be provided?
COMMENT 68: I did not find any problems with this issue. However, sampling methodologies for PERC fall outside of my own expertise.

RESPONSE 68: *No response required.*

Chapter 8.
Charge Q: Are you aware of other regulations or guidelines that may be appropriate for the table? If so, please provide a copy of the reference.
COMMENT 69: This section appears to be both clear in description and complete. The narrative explanation provided just prior to the table is helpful. However, knowledge of the full global spectrum of regulatory activity falls outside of my general expertise.

RESPONSE 69: *No response required.*

Chapter 9.
Charge Q: Are there additional references that provide new data or are there better studies than those already in the text? If so, please provide a copy of each additional reference.
COMMENT 70: One very recent in vitro immune study could be considered for incorporation. Kido *et al.* Ind. Health 51 (3): 319-326. August 2013, http://www.ncbi.nlm.nih.gov/pubmed/23538726
The study provides supporting evidence that tetrachloroethylene may elevate local innate immune cell production of IL-6. Because improperly regulated IL-6 has been associated with both hepatic and neurogenic inflammation, this observation is supportive of the described tetrachloroethylene-associated toxicities. Weaknesses of this study are: 1) that it is an in vitro study performed on a murine macrophage cell line, 2) that the observation of altered cytokine production occurs at a concentration that produced changes in cell viability as well and 3) that there is a lack of evidence of dose response. Therefore, I mention this reference for possible inclusion but it should be noted that its inclusion would not alter the already-specified toxicities in the profile.

RESPONSE 70: *The text was revised to add information from Kido et al. (2013) as follows:*

> *An in vitro study by Kido et al. (2013) showed significant ($p < 0.05$) increases in the expression of IL-6 and IL-10 mRNA in murine macrophage cells exposed to 800 µg/mL tetrachloroethylene. However, cell viability was significantly diminished at this concentration, and exposure to a higher concentration (1,000 µg/mL) yielded mRNA levels comparable to controls, so a clear dose-response relationship was not demonstrated.*

Review comments provided by Reviewer #2:

COMMENT: Although children's health is somewhat outside my expertise, I did conduct a literature search using several common journal databases. The Toxicological Profile seems to adequately reference most of the literature I came acros, with the exception of a review article by Dzubow et al. (2009) entitled "Early Life Stage Exposure and Potential Developmental Susceptibility to Tetrachloroethylene" in Birth Defects Research (Part B). Dzubow et al. provide a quick reference to much of the existing research on early-life exposures to PCE and the article may be of interest to the Toxicological Profile audience.

RESPONSE: *ATSDR agrees that Dzubow et al. (2009) provide a clear review of this topic. ATSDR obtained and reviewed the paper to ensure that the primary literature on early life exposures and effects were adequately captured in the Toxicological Profile. All of the primary studies described by Dzubow et al. (2009) are already cited in the Toxicological Profile.*

Chapter 1

COMMENT: Page 5, Line 14: It is not clear how washing fruits and vegetables will protect against PCE exposures. I believe the existing literature on PCE in foods primarily relate to grains and oils, and to a lesser extent fruits/vegetables. deRaat (2003) provides a summary of PCE concentrations detected in food-stuffs. The contamination of food products appears to occur during storage. Therefore, it seems that storing foods in air tight containers may also help to reduce exposures. Note: Boekhold et al1989 investigates PCE in lettuce. They show that lettuce can uptake PCE from soils and contaminated water, but it is not clear that these concentrations would be reduced by washing.

RESPONSE: *There is literature supporting the presence of tetrachloroethylene in foods, but it does not say how one would get rid of the tetrachloroethlyene in those contaminated foods. The generic statement out of the document, since no supporting literature was located.*

COMMENT: Page 6, Line 1: There is no mention of how families can reduce exposure risks from contaminated groundwater. Assuming that the drinking water exposures will be reduced by bottled water (per the previous sentence in the Toxicological Profile), then exposures from contaminated groundwater would be limited to volatilization of PCE and the possible contamination of indoor air.

RESPONSE: *The statement was amended to: "Please contact local drinking water authorities and follow their advice if you have any concern about the presence of tetracholoroethylene in your tap water". The statement about bottled water was taken out per ADP's request. Likewise, the proper authorities would have to be notified about contaminated groundwater to clean up the site.*

COMMENT: Page 6, Line 2/3: There is no mention of reducing inhalation risks. This should be added. Generally speaking, one way to reduce exposure risks from breathing contaminated indoor air is to ensure indoor air spaces are well ventilated. This is appropriate for vapor intrusion exposures, or vapors that are emitted from consumer products, which are mentioned in Line 2, as well as vapors emitted during showering, which is mentioned in Chapter 3.

RESPONSE: *There is not a section on air, but a sentence was added that said to make sure that the area the person lives in is well ventilated area to reduce risks from breathing contaminated air.*

COMMENT: Page 7, Line 3: USEPA has generated indoor air targets for tetrachloroethylene as part of the Risk Assessment Guidance of Superfund (RAGS) (USEPA 2009). This may not be relevant for this

specific section of the Toxicological Profile, but is does seem relevant to the subject matter. The reference concentration is 0.04 mg/m^3. This reference dose is a referenced in Chapter 8, so it is included in the document, it seemed potentially relevant in this section as well.

RESPONSE: *The statement about the reference concentration as this information is typically provided only in Chapter 8.*

Chapter 2

COMMENT: Page 9, Line 15: I recommend the sentence be edited as:
Tetrachloroethylene is a volatile liquid and when released to surface water or surface soil, it tends to evaporate quickly; however, tetrachloroethylene in the liquid and vapor phases are also mobile in soil and have the potential to leach below the soil surface and contaminate groundwater and .he air space between soil particles.

RESPONSE: *Revised as suggested.*

COMMENT: Page 9, Line 23-27: A reference to substantiate the claim that food levels are low and not considered a primary source of exposure would be useful. In addition, this statement can be made more accurate by adding "general" context because for certain populations it may be possible that food could contribute more substantially to total exposure. However, the main point-exposures are mostly through inhalation of ambient air and ingestion of drinking water of is made in lines 26 and 27. The term ambient air in line 27 is confusing. Different definitions are used, but often ambient air is meant to refer to outdoor air. I think line 27 intends to (and should) collectively refer to indoor AND outdoor concentrations. As I mentioned in my general comment about the lack of conceptual models in Toxicological Profiles, it is difficult to communicate various routes of exposure based on various environmental media without visual aids and a conceptual model framework. This sentence is a good example of that deficiency.

RESPONSE: *There is not a reference for the sentence that states that food levels not considered a primary source of exposure. There is, however, the data in Section 6.4.4 that substantiates this claim. The statement about food exposure was removed because it may be confusing to the reader since there was no measurable number to compare the levels of tetrachloroethlyene in foods to the levels in water and air. The definition of ambient was added in parenthesis. It was intended to mean outdoor air.*

COMMENT: Page 9, line 32. Another sentence about consumer products being a source of PCE in indoor air would be useful. A good reference is USEPA Background Report on VOCs in Residences (2011). Also, see my comments referring to Section 6.4.1.

RESPONSE: *Changes made as suggested; added EPA (2011).*

COMMENT: Page 10, line 2-3. This sentence seems out of place and doesn't directly relate to the preceding information.

RESPONSE: *The statement was removed from this section.*

COMMENT: Page 13, lines 20-22. Additional information describing the "limitations" would be helpful to the reader. The sentences that follow suggest some studies have demonstrated adverse health effects. It is not clear why these studies do not provide basis for conclusions.

RESPONSE: *The text was revised to provide examples of the limitations as follows:*

The available epidemiological data on reproductive and developmental effects of exposure to tetrachloroethylene in occupational settings or in contaminated drinking water suffer from a number of limitations (including lack of measured exposure levels, coexposure to other solvents, lack of control for potential confounders, and small numbers of subjects) and do not provide sufficient basis to draw conclusions.

COMMENT: Page 14, Section 2.3. I read this section expecting different results for the different exposure durations.
I am not a health-scientist. but I think it might be clearer if the section began by saying ...
"An MRL of 0.006 ppm has been derived for acute-, intermediate-, and chronic-duration inhalation exposures."
Then, the discussion of the background studies ... and then a similar statement for oral exposures, followed by a discussion of the background studies.

RESPONSE: *The text of Section 2.3 is structured according to ATSDR guidance and also for clarity. Because the studies that pertain to each exposure duration (and those supporting the use of the same MRL for each duration) differ, it is important to segregate the information by duration.*

Chapter 3
COMMENT: This section appears to reference much of the important literature. I am not a health scientist, so I will not provide scientific critique of the data presented; however, there are several places where the information presented in this Chapter should be echoed in other portions of the document. I have inserted comments for subsequent sections that pertain to similar topics as those referenced in Chapter 3.

RESPONSE: *No response necessary.*

Chapter 4
COMMENT: The peer-review instructions asked reviewers to identify any missing information from the tables and text. I am not aware of any information or values that are missing.

RESPONSE: *No response necessary.*

Chapter 5
COMMENT: Overall, I felt this section was well written and includes pertinent information. The TRI data is presented in a useful manner and the data is appropriately qualified as not being exhaustive.

RESPONSE: *No response necessary.*

Chapter 6

COMMENT: Page 168, Lines 11-27: This paragraph is confusing. The general ideas are presented, but they are a little muddled. PCE is volatile and will rapidly volatilize--when released to the ground surface, some will volatilize and some will infiltrate the ground surface. Since it has a density greater than water, if it is released to water (surface water or groundwater), it could sink beneath the water surface, where it will persist for a longer period of time. In addition, PCE exists as a nonaqueous phase liquid, which complicates its transport in environmental systems. More discussion about the non-aqueous phase should be included.

RESPONSE: *Reworded some statements in this section and mentioned DNAPLs.*

COMMENT: Page 168, Lines 19-20. The sentence that begins "Tetrachloroethylene can seep ... " should be clarified to indicate vapor phase tetrachloroethylene.

RESPONSE: *Vapor-phase was added to the sentence.*

COMMENT: Page 268, Line 24-25: The sentence that begins "It should be noted that ... " seems out of place. Are the chemical analyses typically greater or less than the amount thought to be bioavailable? I tried to find more information about bioavailability in the other sections of this report, but I was not able to. This concept should be further developed.

RESPONSE: *This statement was removed from this section as well as from Section 6.4. Bioavailability relates to the proportion of chemical (parent compound) that is the unchanged in the body after administration by some route. ATSDR believes that the author was attempting to say that the amount of chemical detected is lower than the amount that is available in the environment. No papers that were chemistry related that linked this notion of bioavailability to tetrachloroethylene were located.*

COMMENT: Page 170, Line 16: A sentence should be added to qualify the TRI data as not being exhaustive. There is a footnote in Table 6-1; however the qualification should also appear in the text.

RESPONSE: *There is qualification in the text. Please see page 169, Lines 3-6.*

COMMENT: Page 170, Section 6.2.1: This secti.on is a string of disconnected summaries from the literature. The two paragraphs at the bottom of page 170 are related to vapor intrusion. But, the top paragraph on page 172 is related to "stack" discharges, as well as an isolated sentence about bioformation of PCE by macroalgae (Page 170, lines 18-19). The different types of discharges should be clearly described. It would be difficult for an unfamiliar reader to understand the nature of the PCE releases described.

RESPONSE: *The section was re-organized, with the more technical data was moved to the beginning of the section.*

COMMENT: Page 170, lines 30-34: The reference by Johnston and Gibson (2013) is an example of one study, but many other vapor intrusion sites exist. It might be worth mentioning the EPA vapor intrusion database document (EPA's Vapor Intrusion Database: Evaluation and Characterization of Attenuation Factors for Chlorinated Volatile Organic Compounds and Residential Buildings (EPA 2012). The database (http:/ fwww.epa.gov/oswer/vaporintruslon/vi data.html) shows that PCE has been detected at

several vapor intrusion sites, including the notorious Endicott, NY site, as well as others. Also, Pennell et at (2013) reports an instance where PCE concentrations in sewer gas confounded PCE vapor intrusion characterization efforts at a field site in Boston.

RESPONSE: *The requested studies were added.*

COMMENT: Page 173, Line 25: sentence should be added to qualify the TRI data as not being exhaustive. There is a footnote in Table 6-1; however the qualification should also appear in the text.

RESPONSE: *Please see page 169, Lines 3-6.*

COMMENT: Page 178, Section 6.2.2: The leaching of PeE-containing liners into drinking water supplies lines should be added. Aschengrau et al (2002, 2008 and 2012), summarize exposures in drinking water due to PCE-containing materials in water distribution lines in Cape Cod, MA. References to the work by Aschengrau et al are included in Chapter 3 of this report, but relevant information should also be included in this section (Chapter 6). In addition, Larson et al (1983), which is not currently included in the list of references should be added. Larson et al summarizes leaching of PCE-containing liners into drinking water.

RESPONSE: *Information from Aschengrau et al. (2003, 2013) and Larson et al. (1983) was added.*

COMMENT: Page 178, Lines 29-33: There are several vapor intrusion models that have been developed to predict transport of PCE (and other VOCs) into indoor air spaces. One of the most widely used models is the Johnson and Ettinger Model (1991), as well as 3-D models developed by Abreu and Johnson (2005), and Pennell et al (2009).

RESPONSE: *A section was added describing all three models.*

COMMENT: Page 179, Lines 1-10: There is considerable literature on remediation of chlorinated solvents, including dense non-aqueous phase liquids. The information presented does not adequately describe the state ofthe science. Soil vapor extraction is widely used in the US, as well as the location mentioned in the text. Further, many recent advances in DNAPL remediation have been made. Stroo et al (2012) is a good reference on a state of DNAPL remediation.

RESPONSE: *Significant information on DNAPL soil and groundwater remediation was added.*

COMMENT: Page 179, Line 15: The sentence that begins on line 15 should be modified as follows .... "No evidence of biological transformation of tetrachloroethylene in groundwater was found in this study; however reductive dechlorination is well-known to occur in groundwater systems and is discussed in Section 6.3.2.2"
Then, Section 6.3.2.2. needs to be updated with reductive dechlorination information.

RESPONSE: *Reductive dechlorination information was added.*

COMMENT: Pages 181-184, Sections 6.3.2.2 and 6.3.2.3: These sections include many important findings, but they are disconnected. Some of the most important aspects relate to the fact that PCE is a dense non-aqueous phase liquid (for example the sentence in Lines 32/33 on Page 181 should be expanded) and that PCE can be reductively dechlorinated. A figure showing how the chlorine atom is successively removed (PCE>TCE>DCE>VC>Ethene) might be helpful to a reader. The discussion seems a little confusing because the difference between aerobic degradation and anaerobic degradation is not clearly defined. For instance, lines 1-4 on Page 182 state that PCE biodegradation is unlikely, but then mentions in lines 8 and 9 that biodegradation is a likely in groundwater and soil.

There are few reports of aerobic PCE degradation. Although I could not find a good peer-reviewed source, there is some concern about whether micro-anaerobic zone might be responsible for reported PCE degradation observations in studies investigating aerobic processes. To my knowledge, the first major report of aerobic degradat ion of PCE is by Ryoo et al (2000). The data presented by Ryoo et al appear to be regarded as a quality study and show fairly conclusively that aerobic PCE degradation is possible, although perhaps less likely than anaerobic reductive dechlorination. There is also a report of aerobic degradation via white-rot fungi (Marco-Urrea 2006). The reference to Chang et al (2011) on Page 183 (line 5) appears to be an error. I believe, Chang et al (2011) investigated anaerobic degradation of PCE. As an example of a different way to organize this section, the WHO report on PCE (2006) does a decent job separat ing aerobic vs. anaerobic processes. Generally speaking, the WHO summary seems a bit easier to follow than what is presented in this Toxicological Profile.

RESPONSE: *The section was rearranged and organized as suggested.*

COMMENT: Pages 184-187, Section 6.4.1: As mentioned previously, the term ambient air has not been well-defined in the report. It should be distinguished from indoor air, as well as soil vapor. This section is poorly organized and jumps from study to study without situating the information with context. For instance, Lines 12-13 briefly mention indoor air, but then jumps to concentrations in front of a drying cleaning shop in Lines 15-16, and then back to indoor air in Lines 17-19. There are several studies of indoor air concentrations for PCE. The recent EPA Report of Background VOC concent rations in Residential buildings (2011) provides a summary of many relevant studies related to the detection of PCE in indoor air.

A summary of background sources of PCE for indoor air miglht be relevant here. A couple of articles that would be relevant to the topic are: Sack et al (2001) and Nazaroff and Weschlof (2004). There are additional references that are included in the EPA indoor Air Background Report (2011).

RESPONSE: *Information in this section was revised to include ambient (outdoor) air studies then indoor air studies. The structure for indoor air is as follows: contaminated sites, homes and other establishments above/near dry cleaning shops, background air, soil vapor intrusion and background concentrations. The Levin and Hodgson (2003), Sack et al. (1992), and Won et al. (2000) studies were added.*

COMMENT: Page 184, Line 8: As previously mentioned, the statement that measured PCE concent rations are not indicative of the amount that is bioavailable needs additional discussion and explanation, as well as citations.

RESPONSE: *The statement was removed.*

COMMENT: Page 187, Line 25: After the summary of Johnston and Gibson (2013), it might be useful to reiterate that Pennell et al (2013) detected PCE in sewer gas and that sewer gas appeared to be the source of PCE detected in the indoor air of a residence in the Metro-Boston Area.

RESPONSE: *The statement pertaining to sewer gas emissions was added.*

COMMENT: Page 189, Section 6.4.4: I am not sure which section should include information about building materials containing PCE. However, I do think the topic is relevant to either "air" or "other environmental media". Won et al (2000) report carpet can sorb PCE. Regarding food, a more complete review of food sources of PCE is necessary in this section. DeRaat (2003) provides a summary of PCE concentrations detected in foods. Boekhold et al 1989 investigates PCE in lettuce. They show that lettuce can uptake PCE from soils and contaminated water. The work by Schreiber (1993) published in Risk Analysis might be relevant, although it does not included measured data, rather PBPK modeling. The work by Bagnell and Ellenberger 1977, which is referenced in Chapter 3, and Pellizzari et al (1982), which is referenced in Sect ion 6.5, should also be referenced in this section.

RESPONSE: *Won et al. (2000), as well as other relevant papers, were added to Section 6.4.1.*

COMMENT: Page 190, Lines 6-7: It is not clear to me that ambient (i.e. outdoor) air is the most important route of inhalation. Indoor air exposures appear to be equally, perhaps even more, important. It may be that the term "ambient" air is meant to include indoor and outdoor air. As previously mentioned, the term ambient air should be well-defined at the beginning of the report.

RESPONSE: *Changes made as requested.*

COMMENT: Page 198, Lines 18-22: The work by Won et al (2000) suggests additional understanding of PCE partitioning between indoor air and building materials is warranted, as well as additional understanding of sorption kinetics for these materials.

RESPONSE: *A statement was added.*

COMMENT: Page 199, Lines 11-12: Clarification is needed. Here is a suggestion ...
PCE can be biodegraded under the appropriate conditions in soil and groundwater. However, the non-aqueous phase is quite difficult to treat and persists at many hazardous waste sites.

RESPONSE: *The appropriate statement with references was added.*

COMMENT: Page 199, Lines 18-19: The work by Boekhold (1989) and other studies summarized by DeRaat (2003) suggest that PCE may be present in fruits in vegetables. I believe PCE is thought to contaminate the food during storage; however it seems relevant to point out these studies as indications of additional data needs.

RESPONSE: *A statement on tetrachloroethylene being present in lettuce was added.*

COMMENT: Page 203, Lines 25-26: Given the toxicity of trichloroethylene (TCE), the possibility of its presence in PCE-containing products seems important and warrants mention earlier in the report. Especially given the recent controversial risk-based levels for TCE based on prenatal exposures.

RESPONSE: *A statement was added earlier on page 9.*

COMMENT: Page 207, Section 7.2: Air sampling using summa canisters (Method T0-15) should be highlighted. This is the preferred method for measuring indoor air concentrations during vapor intrusion investigations. Table 7-2 indicates T0-14, which is still used, but T0-15 is becoming more common. Also, Method T0-17, which is a passive sorbent method that should be named in Table 7-2.

RESPONSE: *The appropriate methods were added.*

Chapter 8
COMMENT: This chapter seems to adequately summarize the pertinent information.

RESPONSE: *No response necessary.*

Chapter 9, Pages 222-227:
COMMENT: "Not all references are coded with symbols. Several of the articles appear in the references but are not cited in text."

RESPONSE: *Only those citations noted with an asterisk or plus sign are cited in the text. Citations without symbols are those that were identified in the literature search, reviewed for relevant data, but not cited in the text. No change is necessary.*

Review comments provided by Reviewer #3:

LOAEL calculation

COMMENT 1: This document needs more in-depth discussion of the potential limitations of the calculated LOAEL and MRL described in this document. While it is based on a longer-term study of two years, it is restricted to a worker population with consistent but intermittent exposure. There may be some error in extrapolating this information to a population that is chronically exposed to PCE at low-levels for decades. If faced with indoor air exposed to PCE, it is more likely that susceptible populations, such as the young, elderly or disabled with spend the majority of their time in that environment. While long-term chronic studies of PCE are limited, and should be emphasized as a current information need, some of the studies presented in this profile demonstrate effects at levels below the MRL suggested. In particular, although limited, studies examining long-term residential chronic exposures tend to show lower LOAEL/ NOAEL levels.

For example the Lehmann et al. (2002) study found decreased in IFN-γ-producing T cells in the umbilical cord blood of infants among those from homes with indoor PCE levels of 7.3 $\mu g/m^3$ or greater, which is less than the MRL. Other studies of residential indoor air found that visual contrast sensitivity among adults were noticeable at 0.1-0.3 ppm among adults exposed to PCE in indoor air (Schreiber et al. 2002; Storm et al. 2011). While these studies are limited in terms of sample size, it is important to note that studies, especially ones related to chronic exposure to PCE in indoor air, have found effects levels below that of the Cavalleri et al. (1994) study and should be considered in the development of the MRLs.

RESPONSE 1: *ATSDR agrees that some studies have suggested adverse effects at exposure concentrations below the LOAEL from Cavalleri et al. (1994). All studies that identified reliable LOAELs below the LOAEL used to derive the MRLs were considered, and a discussion of these studies, with identification of limitations that lead to these studies' exclusion from consideration, can be found in the Minimal Risk Level Worksheet for the chronic inhalation MRL. ATSDR considers the differences in susceptibility across the human population using the uncertainty factor for human variability. For the tetrachloroethylene MRLs, an uncertainty factor of 10 for human variability was used. This factor is intended to account for potential differences in susceptibilty between workers in the critical study and other populations (such as the young, elderly, or disabled). In combination with the uncertainty factor of 10 for use of a LOAEL and the modifying factor of 3 for database deficiencies, the MRL of 0.006 ppm is well below the lowest LOAEL identified in the residential exposure studies.*

The study by Lehmann et al. (2002) was not considered for use in deriving MRLs because of its limitations; the text has been revised as follows to clarify these limitations:

> *Levels of 28 VOCs in the homes were measured by continuous passive air sampling during 4 weeks after birth (Lehmann et al. 2002). This study is limited by the fact that exposure measurements occurred after the measurement of outcome (cord blood cytokine-producing T-cells), and indoor levels of tetrachloroethylene likely vary over time based on the presence or absence of recently dry-cleaned materials in the home. In addition, the analyses did not account for potential confounding by coexposure to other VOCs. Thus, the association between indoor tetrachloroethylene and cytokine-producing T-cells in neonates is uncertain.*

Susceptible and environmental justice populations

COMMENT 2: More attention throughout the text needs to address the literature and potential impacts on environmental justice populations in the country, that is, exposure and health effects on minority and low-income populations. Studies that have specifically examined people of color and low-income communities should be noted and differences examined between findings explicitly described for the

different populations. ATSDR should further highlight the need for additional research into effects of PCE exposure on environmental justice populations – as these communities are more likely to face multiple health stressors so the effect of exposure to PCE may be different than in the generally population.

RESPONSE 2: *Three studies explicitly examining race/ethnic or socioeconomic variations in exposure to tetrachloroethylene were identified (Sexton et al., 2005; McDermott et al., 2005; and Storm et al., 2013). Information on exposure differences associated with race/ethnicity was added to Section 6.7. No studies examining differences in susceptibility to tetrachloroethylene toxicity by race/ethnicity or socioeconomic status, or potential interactions between tetrachloroethylene exposure and these variables, were identified. Although several studies examined effects in populations with higher proportions of minority or lower-income subjects, comparisons across studies, unless controlled for other variables affecting the target outcomes, would not be valid. Section 3.12.2 Identification of Data Needs was revised to highlight the need for studies of susceptibility to tetrachloroethylene toxicity as follows: "..research on the potential vulnerability of minority and low-income populations, who may be exposed to multiple health stressors in addition to chemical exposure, would be beneficial."*

COMMENT 3: While this document is a profile of PCE specifically, it is noted several times that PCE is often found in combinations with other chemicals, especially other chlorinated solvents. It is useful and appropriate to emphasize the need for further studies on the interaction of PCE with other chemicals in the human body, which is especially relevant around hazardous waste sites. It would be helpful is the summary of evidence was articulated in section 3.9. This section could also refer to an earlier ATSDR document on chemical mixtures that included PCE.

RESPONSE 3: *The text of Section 3.9 was modified to refer to available ATSDR interaction profiles that included PERC and to provide brief summaries of their conclusions, as follows:*

> *The potential interactions between tetrachloroethylene and other chlorinated solvents are discussed in detail by ATSDR (2004). As concluded by ATSDR (2004), there are no studies available that directly characterize health hazards and dose-response relationships for exposures to mixtures of chlorinated solvents with tetrachloroethylene. The limited available data indicate no evidence for greater-than-additive joint toxic actions on the liver and kidney; there is some evidence tetrachloroethylene may inhibit the effect of trichloroethylene on the liver and kidney (Goldsworthy and Popp 1987; Seiji et al. 1989). Potential interactions between tetrachloroethylene and other common indoor air contaminants (carbon monoxide, formaldehyde, methylene chloride, and nitrogen dioxide) are discussed by ATSDR (2007). While several of these compounds exert toxic effects on the same target sites, there are no data to evaluate potential interactions among them.*

Exposure via air

COMMENT 4: In several places throughout the profile it is noted that ambient air is a dominant exposure pathway and little attention is given to indoor air. More attention is necessary, particularly in the first two chapter that provide a summary and overview of relevance to public health, on PCE in indoor environments. In general, levels of PCE indoors tend to be higher than ambient air and exposure to indoor air is likely to pose a greater public health concern in many cases.

RESPONSE 4: *Changed the profile to focus on and include indoor air.*

Specific comments
Chapter 1
COMMENT 5: In general this section provides an adequate summary of the information to a lay audience. Pictures of the pathways and systems of the body potentially affected would improve the accessibility of this section to multiple audiences. Suggestions for improvement are made below.

RESPONSE 5*: ATSDR will consider this comments in future revisions to the toxicological profile format.*

COMMENT 6: Pg 1 - PCE is found at many NPL sites, as stated by the profile. It is also useful to mention that the scope of PCE contamination in air and water across the country is much greater. These NPL sites only represent a small fraction of the total potential sites of concern.

RESPONSE 6: *Revised as suggested.*

COMMENT 7: Pg 1 - "Even if you're exposed to tetrachloroethylene, you might not be harmed." This sentence could be better phrased as: Exposure to tetrachloroethylene can affect different people in different ways.

RESPONSE 7: *ATSDR will consider this comment in future revisions to the toxicological profile format and boilerplate text.*

COMMENT 8: pg 2, Where is PCE found? – The title may be improved by labeling it as "How PCE enters the environment." Secondly, sources may not be the best descriptor of the first column of the table in this case. This is really how PCE enters the environment (the source is the industrial process, etc.) or how the public may come into contact with PCE. Perhaps this can be better described as possible points of exposure or contact, or exposure pathways. It should be specified that PCE can remain in the groundwater for long periods of time (it doesn't all evaporate).

RESPONSE 8: *ATSDR will consider these comments in future revisions to the toxicological profile format.*

COMMENT 9: Pg 3 Exposure Pathways - Vapor intrusion – the potential for PCE to migrate from the subsurface to indoor air - should be mentioned explicitly in the air category or in its own section. Furthermore, the volatilization of PCE from dry-cleaned or consumer products can be an important source impacting indoor air.

RESPONSE 9: *A statement was added about vapor intrusion on page 2. Adding the information on page 3 was appropriate as the information on page 3 was more focused on health effects rather than the routes of exposure.*

COMMENT 10: Pg 4 - "Tetrachloroethylene exposure may have an <u>adverse</u> effect on the nervous system…"

RESPONSE 10: *Revised as suggested.*

COMMENT 11: Pg 5 - This section is unclear and lacks a clear connection between PCE in indoor air and food: "Tetrachloroethylene can be present in the indoor air of homes and apartments above dry cleaning facilities. However, although tetrachloroethylene has been found in some food, its levels are low. " More appropriate would be to say that PCE in the air has the potential to contaminate food, although the levels found in food are generally low. It also would be appropriate to specify whether PCE uptake is possible through water or soil.

RESPONSE 11: *The change regarding the statement about PCE in food was made. No studies were located specifying whether uptake is possible through water or sol; however, there were some studies about the uptake of PCE into the body, and also a study that briefly mentioned the uptake of PCE into trees.*

COMMENT 12: Pg 6 – Contaminated groundwater or soil. Again, it is relevant to mention the vapor intrusion exposure pathway here. Techniques to decrease exposure include depressurization, increase in the air exchange rate between indoor and outdoor air or vapor barriers.

RESPONSE 12: *Vapor intrusion and techniques information added as suggested.*

COMMENT 13: Pg 6 – Product labels. It is appropriate to mention that storing such items in an outside location or shed would decrease impact on indoor air. Also, dry cleaned clothes can introduce PCE inside buildings.

RESPONSE 13: *The appropriate statements were added to the product labels section.*

COMMENT 14: Pg 6 – More description or resources should be provided for the recommended "safe toxic substance practices"

RESPONSE 14: *ATSDR will consider these comments in future revisions to the toxicological profile format.*

COMMENT 15: Pg 7 – Regulations. The EPA sets the MCL for PCE in drinking water at 5 ppb.

RESPONSE 15: *The MCL and corresponding reference were added to the profile.*

Chapter 2
COMMENT 16: Overall this chapter provides an appropriate summary of the exposure and health effects of PCE and cites relevant research. I have noted by comments about the MRL in the beginning.

RESPONSE 16: *No response required.*

COMMENT 17: Pg 9, line 7-8 – Specify that vast majority to PCE exposure is due to anthropogenic PCE.

RESPONSE 17: *Change made as suggested.*

COMMENT 18: pg 9, line 15 – The description of PCE 'evaporating' is problematic because in lay terms this may be interpreted as the PCE going away or vanishing. More accurate, the PCE can volatile and migrate to ambient air or into buildings.

RESPONSE 18: *Change made as suggested.*

COMMENT 19: Pg 9, line 26-27 – Include language that exposure via indoor air is an important exposure route due to vapor intrusion (at hazardous sites) or consumer products.

RESPONSE 19: *Change made as suggested.*

COMMENT 20: Pg 12, Line 7 – Please qualify substantial. To my knowledge, there are few epidemiological cancer studies for long-term chronic exposures in non-occupational settings, among environmental justice communities or examining the vapor intrusion pathway.

RESPONSE 20: *The text was revied for clarity as follows:*
The epidemiological database examining cancer end points in exposed humans is substantial, including more than 30 cohort or case-control studies, primarily in occupational settings.

COMMENT 21: Pg 12, line 11 – The NRC reports describes 'limited but insufficient evidence.'

RESPONSE 21: *The text was revised to better reflect the conclusions of NRC (2010), as follows:*
NRC (2010) concluded that there was limited evidence from epidemiological studies for an association with esophageal cancer, and insufficient evidence for an association with other cancer types including liver, kidney, cervical, lung, and bladder cancer.

COMMENT 22: pg 13, line 8 – Delete 'are' after mice.

RESPONSE 22: *Revised as suggested.*

Chapter 3
COMMENT 23: Pg 21- line 26-7 – It would be helpful for the read to provide an example of the distinction between a serious and less serious effect.

RESPONSE 23: *Section 3.2 (paragraph 2) of the Profile includes a discussion of serious and less serious effects, with examples.*

COMMENT 24: Section 3.2 – Several of the sections included in the discussion of health effects by routes of exposure would be improved by provided a summary paragraph at the introduction of each route. This would provide the general findings, sources of evidence, the general weight of evidence and the exposure levels of concern. This would provide a better introduction and framing of the topic, rather than starting by describing a specific study.

RESPONSE 24: *Introductory paragraphs were added to several longer sections that lacked them.*

COMMENT 25: Secondly, limitations are described for some but not all studies – what is the rationale? Are limitations described if the study does not meet certain criteria? Does is depend on what the authors discussed in their paper? This should be clarified in the text.

RESPONSE 25: *The text of Section 3.1 was revised for clarity as follows:*

> *Significant study limitations are noted in this chapter if: a) they help to explain disparate findings between studies, b) only one or a few studies are available on a particular endpoint, meaning that the strength of the study is a relatively more important consideration, or c) the limitations create substantial uncertainty in the conclusions.*

COMMENT 26: In many cases the LOAELs and NOAELs are not specifically stated in the text, particularly for human studies. It is useful to explicitly identify these findings for ease of interpretation and comparison.

RESPONSE 26: *All reliable LOAELs and NOAELs are identified in Tables 3-1 and 3-2 and in Figures 3-1 and 3-2. As part of the response to COMMENT 24 above, introductory paragraphs were added to subsections in the Profile; these paragraphs discuss the lowest LOAEL or highest NOAEL in the subsequent section, as recommended by ATSDR guidance.*

COMMENT 27: Pg 27, line 20-21 – This sentence needs citations of the studies to which it refers.

RESPONSE 27: *Citations were added.*

COMMENT 28: Pg 28, line 27 – Why is this effect specific to humans exposed *accidentally*?

RESPONSE 28: *The modifer "accidentally" was removed.*

COMMENT 29: Pg 20, line 20 – misspelling of *However.*

RESPONSE 29: *Spelling corrected.*

COMMENT 30: Pg 32, line 20 – Again, why is this statement restricted to *accidentally* exposed humans?

RESPONSE 30: *The modifier "accidentally" was removed.*

COMMENT 31: Pg 33, line 17-18 – Specify that these findings are among the exposed group.

RESPONSE 31: *Revised as suggested.*

COMMENT 32: Pg 36, line 8-9 – "Therefore, it is unlikely that the observed effect has biological significance.'" Considering this study is only among 60 occupationally exposed women, this statement needs clarified that the findings are limited to this cohort and not general knowledge.

RESPONSE 32: *The text was revised as follows: "it is unlikely that the effect observed in this population has biological significance"*

COMMENT 33: Pg 36, line 14-16 – In the list of the ratios of observed medullary hyperplasia of the adrenal glands and incidence of cortical hyperplasia of the adrenal glands, it would be helpful to clarify that group exposed at 0 ppm is the unexposed or the control group.

RESPONSE 33: *Parentheticals identifying the 0 ppm group as "[control]" were added to the text.*

COMMENT 34: Pg 37, Body Weight Effects – Are they any human studies related to PCE exposure and body weight available?

RESPONSE 34: *The following text was added: "No studies of body weight effects in humans exposed to tetrachloroethylene were identified in the available literature."*

COMMENT 35: Pg 38, line 5 – The description of "five vapor concentration determinations" is not clear. Is this referring to air samples?

RESPONSE 35: *The text was clarified as follows: "…five vapor concentration measurements obtained by sampling various sites in each shop."*

COMMENT 36: Pg 38, line 28 – There is no evidence of increase allergies based on what exposure levels?

RESPONSE 36: *The text was revised for clarity as follows:*

> *Lehmann et al. (2001) measured indoor concentrations of several VOCs in the bedrooms of 3-year-old children and assessed their association with serum IgE antibodies to food, indoor, and outdoor allergens. The 25th, 50th, and 75th percentile concentrations of tetrachloroethylene were 0.87, 2.54, and 5.09 μg/m^3, respectively. While there were significant associations between some VOCs and sensitization to food allergens (eggs or milk), there was not a significant association between indoor tetrachloroethylene levels and food allergies. Further, there was no evidence for increased indoor (e.g., pet) or outdoor (e.g., pollen) allergen sensitization with higher levels of any VOC (Lehmann et al. 2001).*

COMMENT 37: Pg 39, line 1 – Replace 'as' with 'at.'

RESPONSE 37: *Revised as suggested.*

COMMENT 38: Pg 38 , line 10 - Delete 'n=6' because it is repetitive.

RESPONSE 38: *Deleted as suggested.*

COMMENT 39: Pg 43, line 4-6 – In regard to the Benignus et al. (2009) study, could this observed effect also be related to the chronic effect of residential low-level exposure compared to the more intermittent and likely shorter term of occupational exposures? This finding is very interesting and contributes to growing understanding that timing of exposure is important (that is, for example, 100 ppm for one hour does not produce the same effects at 10 ppm for 10 hours). This finding is also important in light of the reliance on occupational data among studies of PCE in humans.

RESPONSE 39: *The text was revised to add information on other explanations postulated by Benignus et al. (2009), as follows:*

> *Other possible explanations suggested by the authors included: 1) the potential greater susceptibility of residents compared with workers, due to the "healthy-worker" effect or due to differences in age or gender between the two populations; and 2) differences in exposure scenario (i.e., residents are exposed to lower concentrations but more continuously and over longer periods than workers, and workers' time away from work provides greater opportunity for elimination of tetrachloroethylene from the body).*

COMMENT 40: Pg 44, line 2-3 – The profile states that 'no significant difference were observed.' It is unclear among whom were no significant difference observed– among the 14 people in the study? How were the people classified in terms of exposure to draw this conclusion?

RESPONSE 40: *The text was revised for clarity as follows:*

> *In a study comparing 14 persons living above or next to dry cleaning facilities for 1–30 years with 23 controls with no history of solvent exposure, no significant differences were observed in the absolute values of tests of a neurological battery (pattern reversal visual-evoked potentials continuous performance test, hand-eye coordination, finger tapping, simple reaction time, visual memory) (Altmann et al. 1995).*

COMMENT 41: Pg 45, line 2-5 – How many participants in the Schrieber et al. (2002) study? How was the 'no effect' measured?

RESPONSE 41*: The text was revised for clarity as follows:*

> *Color discrimination (measured by Lanthony D-15 test) was not significantly affected in 4 children or 13 adults exposed to concentrations up to 0.3 ppm tetrachloroethylene for an average of 4–5 years; exposure resulted from living in residential buildings that also housed dry cleaning facilities (Schreiber et al. 2002). The mean color confusion index score of the exposed persons (1.33) was higher than that of age- and sex-matched controls (1.20), but the difference was not statistically significant by two-tailed matched-pair analysis (Schreiber et al. 2002).*

COMMENT 42: pg 55, line 2-4 - Specify that this LOAEL and NOAEL listed is for rats.

RESPONSE 42: *The text was revised to specify that the LOAEL and NOAEL are for rats.*

COMMENT 43: Section 3.2.1.6 – It may be useful to include these two studies looking at occupational exposures to CVOCs and birth defects – it is not specific to PCE but is informative:

Gilboa, et al. 2012. Association between maternal occupational exposure to organic solvents and congenital heart defects, National Birth Defects Prevention Study, 1997–2002. *doi:10.1136/oemed-2011-100536*

Desrosiers, et al. 2012. Maternal occupational exposure to organic solvents during early pregnancy and risks of neural tube defects and orofacial clefts. *doi:10.1136/oemed-2011-100245*

RESPONSE 43: *These studies examine effects associated with exposure to chlorinated solvents as a class, rather than with tetrachloroethylene in particular. ATSDR agrees that the literature on exposures to organic and/or chlorinated solvents may provide information pertinent to the effects of PCE. However, because of the large number of studies of chlorinated solvents (on birth defects and a wide range of other health endpoints) and the challenges involved in discriminating between effects attributable to PCE and those attributable to other compounds, this body of literature was not included in the Toxicological Profile.*

COMMENT 44: pg 58, line 20 – Again, suggest the phrase "limited evidence."

RESPONSE 44: *The text was revised to better reflect the conclusions of NRC (2010), as follows: NRC (2010) concluded that there was limited evidence from epidemiological studies for an association with esophageal cancer, and insufficient evidence for an association with other cancer types including liver, kidney, cervical, lung, and bladder cancer.*

COMMENT 45: pg 60, line 20-21 – Please specify the exposures to which these ratios refer.

RESPONSE 45: *Exposure concentrations corresponding to the incidences were added to the text.*

COMMENT 46: pg 65, line 23-26 – Please provide evidence for this statement that the liver is not a target organ in humans. Does the body of evidence suggest this or is there simply a lack of specific studies?

RESPONSE 46: *The text was revised for clarity as follows: "There is little information on the potential hepatic effects in humans exposed orally to tetrachloroethylene. Available information is limited to a single case report of…"*

COMMENT 47: pg 70, line 6 – The statement that there is "no evidence" would be better phased as "no conclusive evidence" since stopping the exposure is potentially correlated with improvement of the symptoms.

RESPONSE 47: *Revised as suggested.*

COMMENT 48: pg 77 – Camp Lejeune is discussed twice on the page – it is not clear if these are two different studies. The data presented is different. This should be clarified and these studies should be sequentially and cited. Likewise, the studies from Cape Cod should be placed together.

RESPONSE 48: *Citations in the first discussion of Camp Lejeune were edited for clarity. The second discussion of the Camp Lejeune study was deleted; it was inadvertently included from an unpublished*

version of the Sonnenfeld et al. (2001) study. The paragraphs describing studies of the Cape Cod cohort were combined.

COMMENT 49: pg 78, line 17 – This sentence and transition is awkward. Rephrase.

RESPONSE 49: *The text was revised for clarity as follows:*

Increased numbers of postnatal deaths, and increased micro/anophthalmia were observed in offspring of rats treated by gavage with 900 mg/kg/day tetrachloroethylene in corn oil on gestation days 6–19 (Narotsky and Kavlock 1995). This dose also resulted in maternal toxicity (ataxia and body weight gain approximately 25% less than controls).

COMMENT 50: pg 79, line 17 - Possible associations cannot be evaluated *independently* for PCE. Associations can be drawn for PCE along with other co-contaminants as a mixture.

RESPONSE 50: *The text was revised for clarity as follows:*

In addition, this population had coexposure to trichloroethylene and other solvents, so identification of effects attributable to tetrachloroethylene is not possible.

COMMENT 51: pg 79 – Again, I would suggest grouping the studies coming from one location together.

RESPONSE 51: *The text was reorganized such that studies of the same cohort are discussed together.*

COMMENT 52: Section 3.2.3.5 and 3.2.3.6 need some text even to state that no studies were located

RESPONSE 52: *Statements indicating that no studies were located were added to both subsections.*

COMMENT 53: pg 130, 3.8.1 Biomonitoring – It would be helpful to include information about the time period of exposure representative by the breath analysis (e.g. past day, past week, etc.)

RESPONSE 53: *Depending upon the conditions of exposure (continuous, intermittent, acute, chronic), the concentration of tetrachloroethylene in exhaled breath may reflect an equilibrium concentration associated with ongoing exposure to a fairly steady air concentration or may reflect a recent acute exposure. Thus, it is difficult to state unequivocally what time period is reflected by a breath analysis result. No change to the text was made.*

COMMENT 54: pg 131, line 29-31 – As described above, it is important to include any other studies or information regarding differences by race or ethnicity.

RESPONSE 54: *ATSDR agrees that information on susceptibility by race or ethnicity is important, and any studies including such information are discussed in the profile. No change to the text was made.*

COMMENT 55: Section 3.10 – This section should specific refer to environmental justice considerations. Lack of information related to racial and ethnic differences or environmental justice communities should be raised in the 3.12.2 section on the identification of data needs.

RESPONSE 55: *The text was revised to emphasize the lack of data on environmental justice considerations. An introduction to Section 3.12.2 Identification of Data Needs was added, including the following:*

> *Data needs by exposure duration and endpoint are discussed below. While the database of toxicity information on tetrachloroethylene is adequate for some endpoints, significant data gaps exist for several endpoints, including: developmental and neurodevelopmental toxicity and immunotoxicity. In addition, additional in vivo or in vitro research on interactions between tetrachloroethylene and other constituents of commonly-encountered chemical mixtures is needed. Tetrachloroethylene frequently occurs in conjunction with other chlorinated solvents in water from hazardous waste sites (ATSDR 2004) and in conjunction with other indoor air contaminants (ATSDR 2007); however, few data are available on the toxicity of these mixtures. Finally, research on the potential vulnerability of minority and low-income populations, who may be exposed to multiple health stressors in addition to chemical exposure, would be beneficial.*

COMMENT 56: Figure 3-6 - I recommend adding an additional table to this figure to summarize studies that have specifically looked at a susceptible population (youth, elderly, people of color, poor, etc.)

RESPONSE 56: *ATSDR will consider this comments in future revisions to the toxicological profile format.*

COMMENT 57: Section 3.12.2 – For the reader it would be helpful to summarize the recommendations or have bullet points at the beginning of end of each of the subsection. As is, it is difficult to locate the summary of existing literature from the specific recommendations being made by this body. Also, is the recognition of the lack of data in a specific area a recommendation for future work?

RESPONSE 57: *The introduction to this section was revised to offer a general summary of data needs and specific recommendations for research, as follows:*

> *While the database of toxicity information on tetrachloroethylene is adequate for some endpoints, significant data gaps exist for several endpoints, including: developmental and neurodevelopmental toxicity, and immunotoxicity (in both developmental and in adult populations). Data needs by exposure duration and endpoint are discussed in further detail below; specific research recommendations include the following:*
>
> - *Studies of immunotoxicity and immune function in developing and adult animals and/or in human populations exposed to tetrachloroethylene for intermediate and chronic durations;*
> - *Additional studies of developmental and neurodevelopmental endpoints in humans or animals exposed to tetrachloroethylene;*
> - *Additional oral bioassays evaluating chronic effects and cancer in animals.*
> - *Studies of tetrachloroethylene effects in humans or animals exposed dermally.*
>
> *In addition, in vivo or in vitro research on interactions between tetrachloroethylene and other constituents of commonly-encountered chemical mixtures is needed. Tetrachloroethylene frequently occurs in conjunction with other chlorinated solvents in water from hazardous waste sites (ATSDR 2004) and in conjunction with other indoor air contaminants (ATSDR 2007); however, few data are available on the toxicity of these mixtures. Finally, research on the*

potential vulnerability of minority and low-income populations, who may be exposed to multiple health stressors in addition to chemical exposure, would be beneficial.

COMMENT 58: pg 142, line 3-4 – Please clarify the statement that "people living near hazardous waste site may be potentially exposed for brief periods." It seems like chronic exposure would be of most concern. Do this suggest that these populations can face acute high exposures (in addition to chronic exposures)?

RESPONSE 58: *The text was revised for clarity as follows:*

Populations living near hazardous waste sites may experience acute-duration exposures to tetrachloroethylene via inhalation, oral, or dermal routes as a result of occasional, intermittent, or other types of accidental releases.

COMMENT 59: pg 142, line 32-33 - This recommendation is important, but also emphasize the need for such studies among environmental justice communities.

RESPONSE 59: *The text discussing data needs in human populations was revised to address this recommendation as follows:*

In addition, studies of tetrachloroethylene effects in potentially susceptible populations, including minority and low-income populations who may be exposed to multiple health stressors in addition to chemical exposure, may serve to inform or refine the MRL.

COMMENT 60: pg 152, line 29-32 – Additionally studies are needed to consider low-level chronic exposure via vapor intrusion (in addition to the mentioned drinking water).

RESPONSE 60: *Revised as suggested.*

COMMENT 61: pg 154, line 29 – The statement "trichloroethylene, which can contaminate tetrachloroethylene, " is unclear as written.

RESPONSE 61*: The text was revised as follows:*

Research to determine if trichloroethanol is a metabolite of tetrachloroethylene, or is produced from trichloroethylene (a contaminant of tetrachloroethylene), would also be useful.

COMMENT 62: 3.12.3 – Does this provide an exhaustive list of ongoing studies or reflective of NIEHS funded studies?

RESPONSE 62: *The list of ongoing studies is obtained from NIH Reporter (2013) and reflects NIH-funded studies only. The text was revised for clarity as follows:*
"Ongoing studies funded by NIH and pertaining to tetrachloroethylene are shown in Table 3-9."

LSE Tables and Figures

COMMENT 63: These figures attempt to summarize and convey a significant amount of information, but could be improved for ease of interpretation. The difference between animal and human studies should be more apparent. Perhaps including a caption that says circles represent animal studies and

triangles represent human studies – or making the size of the triangles larger. Also, this information should be presenting first, before the list of the codes for the various animals. It is difficult to distinguish the various columns. This could be improved by adding light background shading to every other column.

RESPONSE 63: *ATSDR will consider these comments in future revisions to the toxicological profile format. An explanation of how to use the LSE figure is included in Appendix B of the profile.*

COMMENT 64: The y-axis could be better labeled – such as "expose dose to PCE (in ppm)."

RESPONSE 64: *See response above.*

COMMENT 65: The link between the numbers on the Figure and the Table should be made clear.

RESPONSE 65: *See response above.*

Chapter 4
COMMENT 66: This section appears adequate and complete.

RESPONSE 66: *No response required.*

Chapter 5
COMMENT 67: pg 164, Table 5-1 – Just considering the prevalence of dry cleaning facilities in the U.S., this table seems to vastly underestimate the number of facilities producing, processing of using PCE. It is later stated that approximately 28,000 dry cleaners use PCE. Please clarify this table.

RESPONSE 67: *Only certain industrial facilities are required to report. The TRI is not an exhaustive list.*

Chapter 6
COMMENT 68: pg 168, line 5-9 – It would be useful to describe the approximate number of sites across the U.S. with PCE contamination, even if not a superfund site.

RESPONSE 68: An approximate number was not identified in the literature. However, a statement was added that tetrachloroethylene is one of the more frequently detected VOCs. There were studies for individual contaminated sites, but no studies that actually gave an approximate value for the amount of contaminated sites.

COMMENT 69: pg 168 , line 18 - It should be clarified that PCE can last for decades in the groundwater.

RESPONSE 69: *Revised as suggested.*

COMMENT 70: pg, 168 – line 17-28. There is no need to distinguish between vapor intrusion and soil vapor intrusion. There are several corrections needed in the description. First, vapor intrusion is not limited to commercial buildings and in fact the majority of the studies are in residential homes. Second,

contaminants can enter through the foundation of the building – it does not necessarily need to be a home with a basement. While pressure differentials are believe to be the driving force behind vapor intrusion, diffusion is also a process by which contaminants enter the home.

RESPONSE 70: *Revised as suggested.*

COMMENT 71: Figure 6-1. Incomplete legend. Difficult to read.

RESPONSE 71: *The figure was enlarged and the legend was revised.*

COMMENT 72: Section 6.2.1 Air – Suggest separating discussion of ambient air from indoor air exposure.

RESPONSE 72: The section was rearranged so that discussions on industrial emissions and ambient air were discussed first. Indoor air was discussed subsequently.

COMMENT 73: Pg 170, line 30 – Revise: "In Texas, indoor *air in* homes of communities that sit above…"

RESPONSE 73: *Revised as suggested.*

COMMENT 74: pg 169, line 33-34 - Replace "with the occurrence of winter, and with homes" with "during winter, and in homes without air conditioners"

RESPONSE 74: *Revised as suggested.*

COMMENT 75: There are additional studies on PCE vapor intrusion to be considered for inclusion in the profile, such as:

> Folkes, D., Wertz, W., Kurtz, J., & Kuehster, T. (2009). Observed spatial and temporal distributions of CVOCs at Colorado and New York vapor intrusion sites. *Groundwater Monitoring & Remediation*, *29*(1), 70-80.
>
> McDonald, G. J., & Wertz, W. E. (2007). PCE, TCE, and TCA vapors in subslab soil gas and indoor air: A case study in upstate New York. *Ground Water Monitoring & Remediation*, *27*(4), 86-92.

RESPONSE 75: *Papers were reviewed and added.*

COMMENT 76: Section 6.2.2 Water - Include information about the frequency of detection of PCE among drinking water systems in the US. (Some of the information is presented in a subsequent section)

RESPONSE 76: *A statement was added regarding water supplies.*

COMMENT 77: pg 176, line 1-5 - Concentrations of PCE in groundwater aquifer have been found at levels exceeding 50,000 ppb despite its high volatility and PCE can persist in groundwater for decades. The statement regarding the non-impact of aquatic ecosystems may be an overgeneralization and needs clarification, including the exposure levels evaluated.

RESPONSE 77: The statement was revised. There were no additional clarifications made in the NICNAS document about the impact of tetrachloroethylene in the groundwater. That statement was separated out, and kept it in the profile.

COMMENT 78: pg 176, line 20. The statement "When released to the soil, tetrachloroethylene is evaporated into the atomposhpere " is not factual. PCE can (and often does) migrate into the groundwater or surface water or intrude into buildings and homes. It also can stay in the soil for long periods of time. Atmosphere is misspelled.

RESPONSE 78: *Revised as suggested.*

COMMENT 79: Table 6-3 – An unnecessary number of decimal places are used and makes the table difficult to read.

RESPONSE 79: *Revised as suggested.*

COMMENT 80: Pg 187, line 20-21 - Revise to: These levels are much higher than the *average* U.S. indoor *residential* air concentrations measured by the EPA.

RESPONSE 80: *Revised as suggested.*

COMMENT 81: pg 188, line 32-33 – It seems that the mass of PCE described here needs an associated measure of volume or soil weight.

RESPONSE 81: *Original source was consulted; the units are correct.*

COMMENT 82: pg 189, line 9-17 – It is also appropriate to mention that this level is below the MRL recommended by ATSDR.

RESPONSE 82: *Revised as suggested.*

COMMENT 83: Section 6.5 – Indoor air is also a potentially important exposure pathway – as noted by the study cited.

RESPONSE 83: *Revised as suggested.*

COMMENT 84: Pg 194, line 17-18 – An additional study that considered PCE in indoor air due to volatilization from consumer products is:

Dawson, H. E., & McAlary, T. (2009). A compilation of statistics for VOCs from post-1990 indoor air concentration studies in North American residences unaffected by subsurface vapor intrusion. Ground Water Monitoring & Remediation, 29(1), 60-69.

RESPONSE 84: *Papers were reviewed and added.*

COMMENT 85: pg 194, line 20-27 - This paragraph is better suited in the section on water.

RESPONSE 85: *Moved the study description to Section 6.4.2.*

COMMENT 86: pg 196, line 31 - Replace "though" with "if."

RESPONSE 86: *Revised as suggested.*

COMMENT 87: Section 6.7 - Include environmental justice considerations, both in terms of likelihood of exposure as well as in terms of health effects. Also, this section should discuss cumulative exposures and potential of these populations to deal with multiple exposures from multiple pathways over a lifetime.

RESPONSE 87: *Two papers were added to discuss minority populations; no information was located on the ability of the populations to deal with the multiple exposures.*

COMMENT 88: pg 199, section 6.8.1 – More studies are needed on environmental fate of subsurface PCE, particular in regard to vapor intrusion.

RESPONSE 88: *Revised as suggested.*

COMMENT 89: pg 200, subsection Exposure Levels in Humans – There are needs for studies that focus on nonwhite populations and other ethnicities.

RESPONSE 89: *Revised as suggested.*

Chapter 7 and 8
COMMENT 90: No additional comments.

RESPONSE 90: *No response required.*

Chapter 9
COMMENT 91: Refer to specific additional studies cited above.

RESPONSE 91: *No response required.*

Unpublished study
COMMENT 92: This study seems appropriate to include in this profile review. However, I am not an expert in toxicology and cannot comment on specifics of the experimental design.

RESPONSE 92: *ATSDR assumes that the Reviewer is referring to JISA (1993), which is included in the draft toxicological profile.*