

**DISPOSITION OF PEER REVIEW COMMENTS FOR
TOXICOLOGICAL PROFILE FOR TETRACHLOROETHYLENE**

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

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Peer reviewers for the cancer sections of the fourth draft of the post-public comment Toxicological Profile for Tetrachloroethylene were:

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NOTE: Peer reviewer comments are written next to “COMMENTS:” in unformatted text. Any italicized text following the comment is added for clarification purposes. Any page and line numbers that were added by the Reviewers have been kept, but often will not align with the appropriate text.

Comments Provided by Peer Reviewer #1

General Comments

COMMENT: This document describes the toxicological profile of tetrachloroethylene, as developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The document is generally well-written and presents a detailed summary of the literature concerning the health effects associated with exposure to tetrachloroethylene. Nevertheless, I am presenting a few suggestions for improving the presentation of these data, particularly with focus on cancer epidemiology. I have commented directly in the document and also present a summary below.

RESPONSE: *No response needed. Specific comments are addressed below.*

COMMENT: EPA 2012: please provide the web link:
https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0106tr.pdf.

RESPONSE: *The citation in the reference section was revised to include the URL.*

COMMENT: NTP 2014: I cannot access the link provided <http://ntp-server.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf>.

RESPONSE: *The link was corrected in the reference section; please note that this reference was updated to the 14th Report on Carcinogens (NTP 2016).*

COMMENT: In addition to the narrative text presented, it would be useful to see the epidemiological data presented in tables. Such tables are freely available on the IARC Monographs website <http://monographs.iarc.fr/ENG/Monographs/vol106/mono106-002.pdf> and in Appendix B of the EPA 2012 report (e.g. Table B-1, B-2, B-3) https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0106tr.pdf.

RESPONSE: *This comment pertains to the cancer sections of the profile (Section 3.2.1.7, Inhalation Cancer; Section 3.2.2.7, Oral, Cancer). ATSDR has substantially revised the cancer sections in this profile. For all studies, Tables 3-2 and 3-5 have been added to include additional information on study type (cohort, case-control, pooled case-control, meta-analysis), population type (specific occupations), type of exposure estimate (quantitative, semi-quantitative), methods used to determine or estimate exposure, confounders, and study strengths and limitations. In addition, study results for each cancer type are displayed in forest plots (Figures 3-2 through 3-15; Figures 3-17 through 3-19). The plots include information on population size, exposure type (general or specific occupations), type of risk estimate (e.g., standardized mortality ratio [SMR], standardized incidence ratio [SIR], odds ratio [OR]), and central risk estimates with 95% confidence intervals (CIs).*

COMMENT: It could be helpful for the general reader to have the narrative text written in a more synthetic style that presents the overall story of the association between tetrachloroethylene and a particular cancer.

RESPONSE: *This comment pertains to the cancer sections of the profile (Section 3.2.1.7, Inhalation Cancer; Section 3.2.2.7, Oral, Cancer). The revised cancer section does not include separate sections for each cancer types; rather, data (risk estimates and 95% CIs) are displayed in forest plots (Figures 3-2 through 3-15; Figures 3-17 through 3-19) for each cancer type. ATSDR does not conduct weight-of-evidence assessments for cancer. Conclusions regarding associations between tetrachloroethylene and specific cancer types are taken from EPA (2012a), National Research Council (NRC 2010), and International Agency for Research on Cancer (IARC 2014). These conclusions are included in the introductory paragraph to the “Epidemiological Studies” section. The reader is also directed to these references for more extensive discussions of the literature databases for each cancer type.*

COMMENT: For each cancer, it would be helpful to have an opening statement of the potential confounders to be considered. With the current text, it is not possible to determine if the studies cited were designed or analyzed appropriately; it is currently not possible to determine if major study limitations were sufficiently addressed. This could lead to inconsistencies in reported findings between studies.

RESPONSE: *In reference to the cancer sections of the profile (Section 3.2.1.7, Inhalation Cancer; Section 3.2.2.7, Oral, Cancer), ATSDR has substantially revised the cancer sections in this profile. Tables 2-3 and 3-5 present information on the confounders and strengths and limitations for each study were added to the profile.*

COMMENT: Do the epidemiological data need to be presented by exposure route, as this could overlap across studies? It would be more helpful to present the data by cancer and then stratify the findings by exposure route (if warranted)

RESPONSE: *Prior to 2018, ATSDR Guidance for the Preparation of Toxicological Profiles has the profile organized to discuss toxicity information discussed by route of exposure. ATSDR has recently revised the toxicological profile format; in newly developed profiles, data for different routes of exposure are combined for each toxicological endpoint, including cancer.*

COMMENT: “No association” is written several times in the text, but risk estimates above 1 are presented. For example, please see kidney cancer (pg 67, line 3, 12, 17, 20, 29, 32). It appears that the statement of “no association” is based on statistical significance (e.g. the confidence interval does not include 1, $p < 0.05$). It would be more appropriate to report the risk estimate and confidence interval and describe the overall coherence of findings. When synthesizing the overall body of literature on a particular cancer, it is important to keep in mind that individual studies may have been underpowered to detect an effect and if they could be combined into a single summary through a meta-analysis, the overall meta-risk estimate may be statistically significant.

RESPONSE: *This comment refers to the cancer sections of the profile (Section 3.2.1.7, Inhalation Cancer; Section 3.2.2.7, Oral, Cancer). The cancer sections of the profile have been substantially revised. Terms such as “no association” and statements regarding statistical significance have been removed from the cancer sections of the profile. Central risk estimates (with 95% CIs) for each study are now displayed graphically for each cancer type. In addition, study strengths and limitations for each study are now included in Tables 3-2 and 3-5.*

COMMENT: Why is the EPA document cited but not also the IARC and NTP reviews on tetrachloroethylene? I have noted this in the text.

RESPONSE: A detailed discussion of the IARC (2014) and National Toxicology Program (NTP 2016) reviews have been added to Section 3.2.1.7 (Inhalation, Cancer). The following text was added:

“A large number of cohort and case-control studies have assessed possible associations between exposure to tetrachloroethylene and cancer, with comprehensive reviews conducted by NRC (2010), EPA (2012a), and IARC (2014). The NRC (2010) concluded that there was suggestive evidence for an association between tetrachloroethylene exposure and lymphoma, despite weak and sometimes inconsistent data; 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. EPA (2012a) evaluated the studies reviewed by NRC (2010) plus 27 additional studies that were not included in the NRC (2010) review. The EPA (2012a) Toxicological Review concluded that epidemiological data support a pattern of association between tetrachloroethylene exposure and bladder cancer, multiple myeloma, and non-Hodgkin’s lymphoma. EPA (2012a) also concluded that epidemiological studies suggest possible associations with other cancers (esophageal, kidney, lung, liver, cervical, and breast cancer), but the data on these cancers were more limited and/or inconsistent. IARC (2014) concluded that “positive associations have been observed for cancer of the bladder” in humans. For additional details and reviews of these and other epidemiological studies assessing the potential carcinogenicity of tetrachloroethylene, the EPA Integrated Risk Information System (IRIS) Toxicological Review for Tetrachloroethylene (EPA 2012a), IARC (2014), and NRC (2010) may be consulted.”

In Section 3.2.2.7 (Oral, Cancer), the reader is directed to Section 3.2.1.7.

“Cancer classifications for tetrachloroethylene by the HHS (NTP 2016), IARC (2014), and EPA (2012a) are reviewed in Section 3.2.1.7 (Inhalation, Cancer). Conclusions made in comprehensive reviews (EPA 2012a; IARC 2014; NRC 2010) regarding associations between tetrachloroethylene exposure and specific cancer types also are summarized. For additional details and reviews of these and other epidemiological studies assessing the potential carcinogenicity of tetrachloroethylene, the EPA IRIS Toxicological Review for Tetrachloroethylene (EPA 2012a), IARC (2014), and NRC (2010) may be consulted.”

COMMENT: For the bladder cancer section, it would be helpful to start with the Vlaanderen 2014 meta-analysis as it quantitatively (and qualitatively) summarizes the results of all the studies.

RESPONSE: This comment refers to the subsection on bladder cancer in Section 3.2.1.7 (Inhalation, Cancer). ATSDR has substantially revised the cancer sections in this profile. The discussion of epidemiological cancer data is no longer divided by cancer type. Studies assessing bladder cancer, including Vlaanderen et al. (2014), are displayed graphically in a forest plot (Figure 3-2), with study details provided in the plots and in a new table that summarized the studies (Table 3-2). Data from the Vlaanderen et al. (2014) meta-analysis are presented first in the forest plot (Figure 3-2).

Annotated Comments on the Profile

FOREWORD

COMMENT: “most informative” could be another synonym for “key”. One could transparently describe what would constitute an informative study for evaluating exposure to tetrachloroethylene and the outcome.

RESPONSE: *In reference to the second paragraph 2 of the Foreword to the profile, the sentence was revised as follows:*

*“Each peer-reviewed profile identifies and reviews the **most informative (i.e., key)** literature that describes a substance’s toxicologic properties.”*

COMMENT: In the IARC Monographs program, we provide an exhaustive document/review of the cancer studies in humans and animals. This could be helpful also for your work.

RESPONSE: *This comment is a general comment on the profile, made in Chapter 1, subsection “How can tetrachloroethylene affect my health?” Conclusions of the IARC (2014) document have been added to the cancer sections (Sections 3.2.1.7 and 3.2.2.7) of the profile. In addition, in Section 3.2.1.7 (Inhalation Cancer), the reader is directed to consult to the IARC (2014) document for a more detailed and comprehensive review of the literature.*

COMMENT (page 7, line 13-14): This is a very effective means of disseminating information. Thank you ATSDR – I use this resource often! *In reference to: Chapter 1: Public Health Statement: “It explains a substance’s relevant toxicologic properties in a nontechnical, question and answer format”*

RESPONSE: *No response needed.*

COMMENT: For the epidemiologic studies, there could be multiple routes of exposure leading to a cancer outcome. This format could lead to overlap in the presentation of studies. Is route of exposure needed for the assessment of human studies?

RESPONSE: *This is a general comment (written in the Quick Reference for Health Care Providers) regarding the discussion of health effects by route of exposure. The current format of the profile is to discuss all data (in humans and experimental animals) by route of exposure. ATSDR has recently (2018) revised the format of toxicological profiles and future profiles will no longer divide the discussion of health effects by route of exposure. In the Quick Reference for Health Care Providers for the tetrachloroethylene profile, the following sentence was added under Chapter 3: Health effects.*

“Note that for epidemiological studies, there could be multiple routes of exposure.”

COMMENT: I assume that acute effects are not the focus here. Please add bladder as the IARC review (vol 106) found limited evidence for carcinogenicity for bladder cancer associated with tetrachloroethylene exposure. This finding is in agreement with the USEPA IRIS review.

RESPONSE. *The Reviewer is referring to Chapter 1, How can tetrachloroethylene affect my health? Regarding the portion of the comment on acute effects, the following was added to the beginning of the second paragraph:*

“If you are exposed for short periods of time (a few hours to less than 14 days), tetrachloroethylene may cause effects on your health.”

Regarding adding bladder cancer, in the 5th paragraph of this section, bladder cancer conclusions of EPA (2012a), NTP (2016), and IARC (2014) were already noted in Chapter 1 (under subsection: How can tetrachloroethylene affect my health?). Additional more specific details on these assessments are provided in Section 3.2.1.7 (Inhalation, Cancer).

COMMENT: The Reviewer noted “This qualifier is not needed as uncertainty is conveyed by “may”” and suggested the following revisions (insertions noted in red and deletions noted in strikeout): Studies in humans suggest that exposure to tetrachloroethylene ~~might~~ **may** lead to a higher risk of getting bladder cancer, multiple myeloma, or non-Hodgkin’s lymphoma, ~~but the evidence is not very strong.~~

RESPONSE: *In the How can tetrachloroethylene affect my health? subsection of Chapter 1, the revision was made as suggested. “Studies in humans suggest that exposure to tetrachloroethylene may lead to a higher risk of getting bladder cancer, multiple myeloma, or non-Hodgkin’s lymphoma.”*

COMMENT: Why was only NTP Cited? I could not access the NTP report. The Reviewer suggested the following insertion “IARC has classified tetrachloroethylene as *probably carcinogenic to humans* (Group 2A) (IARC 2014). The USEPA has characterized tetrachloroethylene as “likely to be carcinogenic in humans by all routes of exposure.” (EPA 2012a)”

RESPONSE: *The comment refers to the introduction of Section 3.2.1.7 (Inhalation, Cancer). The cancer section has been substantially revised. The IARC (2014) and EPA (2012a) cancer classifications have been added as follows:*

“IARC (2014) has classified tetrachloroethylene as ‘probably carcinogenic to humans’ based on limited evidence in humans and sufficient evidence in animals (Group 2A). EPA (2012a) has characterized tetrachloroethylene as “likely to be carcinogenic in humans by all routes of exposure.”

In addition, NTP (2014) was updated to the 14th Report on Carcinogens (NTP 2016) and the citation and link were updated in the reference section.

COMMENT: Regarding the statement—however, it is important to note that interpretations of study results may be confounded by concomitant exposure to other chemicals (NRC 2010)—the Reviewer commented “Could smoking also be an important confounder? Smoking causes bladder cancer and those occupationally exposed to tetrachloroethylene may also smoke more.”

RESPONSE: *This comment refers to Section 3.2.1.7 (Inhalation, Cancer). The cancer section has been substantially revised, and the sentence noted above was deleted. Table 3-2 was created and the following text was added:*

“Table 3-2 provides an overview of selected epidemiological studies, including information on study types (cohort, case-control), study populations (specific industries or general worker populations),

exposure assessments (qualitative versus semi-quantitative, assessment methods), consideration of confounders, and study strengths and limitations.”

“The potential influence of confounding factors is an important consideration in the interpretation of these epidemiological studies. As shown in Table 3-2, confounders were not consistently addressed across studies. Studies by Neta et al. (2012) and Vizcaya et al. (2013) provided the most comprehensive assessment of confounders, with other studies considering several confounders (Christensen et al. 2013; Hadkhale et al. 2017; Lipworth et al. 2011; Mattei et al. 2014; Silver et al. 2014). However, other studies considered only a few confounders or did not assess any confounders. For assessments of the carcinogenic potential of tetrachloroethylene, it is important to consider the potential influence of exposure to other solvents and chemicals, including smoking tobacco, an important confounder for bladder and lung cancer (EPA 2012a; Guyton et al. 2014). Studies by Christensen et al. (2013), Mattei et al. (2014), Neta et al. (2012), and Vizcaya et al. (2013) considered both smoking and exposure to solvents and other chemicals. Other studies considered smoking (Dosemeci et al. 1999; Lynge et al. 2006; Pesch et al. 2000a, 2000b; Selden and Ahlborg 2011) or exposure to solvents and other chemicals (Hadkhale et al. 2017; Lipworth et al. 2011; Silver et al. 2014; Talibov et al. 2017).”

COMMENT: A summary of the animal cancer bioassays are considered here. Should the mechanistic evidence also be briefly summarized?

RESPONSE: *The comment refers to the beginning of the discussion of animal studies in Section 3.2.1.7 (Inhalation, Cancer). Mechanisms of action are discussed in Section of 3.5.2 (Mechanisms of Toxicity). The cancer mechanistic data are discussed under specific subsections on individual organs. The following text was added in Section 3.5.2:*

“Results indicate that epigenetic mechanisms may be involved in the development of tetrachloroethylene-induced toxicity.”

“Several mechanisms may contribute to hepatic carcinogenicity of tetrachloroethylene, including genotoxicity, changes in mitochondrial transcription, effects on transporter pathways, oxidative stress, and PPAR α activation. Evidence for possible involvement of DNA hypomethylation in hepatic carcinogenesis comes from observations made in mice administered trichloroacetic acid or dichloroacetic acid (EPA 2012a; Guyton et al. 2014; IARC 2014, NRC 2010). Evidence for possible involvement of oxidative stress comes from studies conducted in mice in which antioxidants were shown to protect against hepatotoxicity of tetrachloroethylene and in vitro studies of showing altered expression of genes that are activated by reactive oxygen species (EPA 2012a).”

“Several mechanisms may contribute to the renal carcinogenicity of tetrachloroethylene, including genotoxicity or cytotoxicity related to or unrelated to α -2u-globulin accumulation in the proximal tubule epithelium. Peroxisome proliferation may also be a contributing factor (EPA 2012a; Guyton et al. 2014; IARC 2014, NRC 2010).”

“Wang et al. (2017) suggested that lipid-derived aldehydes (e.g., malondialdehyde [MDA]) may be involved in the development of tetrachloroethylene-induced autoimmunity. Following exposure of mice to drinking water containing 0.5 mg/mL tetrachloroethylene for 12–24 weeks, isolated splenocytes stimulated with MDA-mouse serum protein adducts showed an increased in Th17 cell (an effector T-cell type) proliferation and increase of IL-17 into culture media.”

“Genotoxic Effects. Genotoxic effects produced by tetrachloroethylene are thought to be the result of reactive metabolic intermediates of metabolism of tetrachloroethylene (Cichoki et al. 2016; EPA 2012a;

IARC 2014; NRC 2010). Evidence for genotoxicity of tetrachloroethylene metabolites comes from numerous in vitro studies that have found that metabolic activation (e.g., S9 fraction) is required or greatly enhances genotoxicity. Studies of the genotoxicity of tetrachloroethylene metabolites suggest that genotoxicity may involve tetrachloroethylene epoxide, trichloroacetyl chloride, and metabolites formed in the glutathione conjugation pathway.”

COMMENT: The NTP and IARC also summarized a large number of epidemiologic studies. Should this be stated? IARC reviewed all studies on the association between tetrachloroethylene and cancer. Any exclusions were clearly noted in the narrative, along with a rationale.

RESPONSE: *The comment above refers to the overview discussion of the epidemiological studies in Section 3.2.1.7 (Inhalation, Cancer). Conclusions of the NTP (2016) cancer assessment were added to Section 3.2.1.7. In addition, the following statements were added:*

“A large number of cohort and case-control studies have assessed possible associations between exposure to tetrachloroethylene and cancer, with comprehensive reviews conducted by the NRC (2010), EPA (2012a), and IARC (2014).”

“For additional details and reviews of these and other epidemiological studies assessing the potential carcinogenicity of tetrachloroethylene, the EPA Integrated Risk Information System (IRIS) Toxicological Review for Tetrachloroethylene (EPA 2012a), IARC (2014), and NRC (2010) may be consulted.”

COMMENT: Should it be stated how this selection was performed? What criteria were needed to judge an epidemiologic study as adequate quality?

RESPONSE: *The comment above refers to the introduction to Section 3.2.1.7 (Inhalation, Cancer), discussing selection of epidemiological cancer studies included in the profile. The following information was added:*

“Studies were selected based on the following considerations: studies that EPA (2012a) relied upon to support conclusions regarding associations between tetrachloroethylene exposure and specific cancer types; studies that EPA (2012a) considered to have higher quality exposure assessments; and studies published after EPA (2012a), with higher quality exposure assessments (as defined by EPA 2012a). EPA (2012a) considered higher quality exposure assessments to include the following: biological monitoring data; use job-exposure matrix (JEM) based on historical data or job title and/or tasks; and use of union records or other data for specific jobs/tasks (Guyton et al. 2014).”

COMMENT: The IARC and NTP reviews can also be consulted.

RESPONSE: *In reference to the introduction to Section 3.2.1.7 (Inhalation, Cancer), information from the IARC (2014) and NTP (2016) reviews have been included in the revised cancer section as follows:*

“A large number of cohort and case-control studies have assessed possible associations between exposure to tetrachloroethylene and cancer, with comprehensive reviews conducted by NRC (2010), EPA (2012a), and IARC (2014). The NRC (2010) concluded that there was suggestive evidence for an association between tetrachloroethylene exposure and lymphoma, despite weak and sometimes inconsistent data; 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. EPA (2012a) evaluated the studies reviewed by NRC (2010) plus 27 additional studies that were not included in the NRC (2010) review. The EPA (2012a) Toxicological Review concluded that epidemiological data support a pattern of association between tetrachloroethylene exposure and bladder cancer, multiple myeloma, and non-Hodgkin's lymphoma. EPA (2012a) also concluded that epidemiological studies suggest possible associations with other cancers (esophageal, kidney, lung, liver, cervical, and breast cancer), but the data on these cancers were more limited and/or inconsistent. IARC (2014) concluded that "positive associations have been observed for cancer of the bladder" in humans. For additional details and reviews of these and other epidemiological studies assessing the potential carcinogenicity of tetrachloroethylene, the EPA Integrated Risk Information System (IRIS) Toxicological Review for Tetrachloroethylene (EPA 2012a), IARC (2014), and NRC (2010) may be consulted."

COMMENT: The Reviewer noted "You could report the meta-analysis first since it summarizes nearly all of the literature." and suggested the following insertion "All epidemiological studies that reported on the association between bladder cancer and occupational exposure to tetrachloroethylene or in workers in the dry-cleaning industry, except one recent study (Hadkhale et al 2017), were reviewed and summarized in a meta-analysis (Vlaanderen et al. 2014). A random-effects meta-analysis of dry cleaning workers (139 exposed cases from seven studies) showed an increased risk of bladder cancer, with a meta-relative risk of 1.47 (95% CI 1.16–1.85). It is notable that the findings were consistent and there was no heterogeneity in the findings between studies overall or by study design ($I^2=0\%$). This study noted that although dry cleaners incur mixed exposures, tetrachloroethylene could be responsible for the excess risk of bladder cancer because it is the primary solvent used and it is the only chemical commonly used by dry cleaners that is currently identified as a potential bladder carcinogen. Relatively crude approaches in exposure assessment in the studies of "tetrachloroethylene-exposed workers" may have attenuated the relative risks."

RESPONSE: *The comment above refers to the Bladder Cancer Subsection of Section 3.2.1.7 (Inhalation, Cancer). The cancer section has been substantially revised and subsections have been removed. Results of cancer studies are now displayed in forest plots (risk estimates and CIs) for each cancer type (Figures 3-2 through 3-15). The following text was added:*

"Exposure assessment methods are listed in Table 3-2. It is important to note that none of the exposure assessments included individual monitoring data or rigorous monitoring of tetrachloroethylene concentrations in individual workplaces. A few case-control studies provided semi-quantitative estimates for cumulative exposure, based on JEM, with estimates of average exposure per specific occupation (Gold et al. 2010, 2011; Hadkhale et al. 2017; Talibov et al. 2017; Vlaanderen et al. 2013). The remaining studies provided qualitative descriptions of exposure (e.g., exposed/not exposed, probable, substantial, low-moderate-high) based on JEM and/or occupational history from union records, census records, and/or participant questionnaires. For most study participants, it is likely that exposure included other solvents or chemicals. For workers in the dry cleaning industry, exposure is primarily to tetrachloroethylene (Vlaanderen et al. 2014)."

COMMENT: Why is the EPA document cited but not also the IARC and NTP reviews on tetrachloroethylene? Here and throughout this document?

RESPONSE: *The comment above refers to the Bladder Cancer subsection of Section 3.2.1.7 (Inhalation, Cancer). The cancer section has been substantially revised and subsections on cancer types have been*

eliminated from the profile. Information from the IARC (2014) and NTP (2016) reviews has been included in the revised text as follows:

“A large number of cohort and case-control studies have assessed possible associations between exposure to tetrachloroethylene and cancer, with comprehensive reviews conducted by NRC (2010), EPA (2012a), and IARC (2014). The NRC (2010) concluded that there was suggestive evidence for an association between tetrachloroethylene exposure and lymphoma, despite weak and sometimes inconsistent data; 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. EPA (2012a) evaluated the studies reviewed by NRC (2010) plus 27 additional studies that were not included in the NRC (2010) review. The EPA (2012a) Toxicological Review concluded that epidemiological data support a pattern of association between tetrachloroethylene exposure and bladder cancer, multiple myeloma, and non-Hodgkin’s lymphoma. EPA (2012a) also concluded that epidemiological studies suggest possible associations with other cancers (esophageal, kidney, lung, liver, cervical, and breast cancer), but the data on these cancers were more limited and/or inconsistent. IARC (2014) concluded that “positive associations have been observed for cancer of the bladder” in humans. For additional details and reviews of these and other epidemiological studies assessing the potential carcinogenicity of tetrachloroethylene, the EPA Integrated Risk Information System (IRIS) Toxicological Review for Tetrachloroethylene (EPA 2012a), IARC (2014), and NRC (2010) may be consulted.”

COMMENT: The strengths and limitations of the individual studies are not noted here or in the rest of the document. A summary of the IARC Working Group’s assessment of individual studies can be found in the text and tables <http://monographs.iarc.fr/ENG/Monographs/vol106/index.php>. In reference to paragraph 1: “EPA (2012a)”.

RESPONSE: *This comment refers to the Bladder Cancer subsection of Section 3.2.1.7 (Inhalation, Cancer); as previously noted, the cancer section has been substantially revised and subsections on cancer types have been eliminated from the profile. Table 3-2 was added to Section 3.2.1.7 and this includes study strengths and limitations for all epidemiological inhalation cancer studies included in the profile.*

COMMENT: What are the criteria that constitute a high-quality exposure assessment?

RESPONSE: *This comment refers to the Bladder Cancer subsection of Section 3.2.1.7 (Inhalation, Cancer). As previously noted, the cancer section has been substantially revised and subsections on cancer types have been eliminated from the profile. The following information regarding higher quality exposure assessments was added to the profile:*

“Studies were selected based on the following considerations: studies that EPA (2012a) relied upon to support conclusions regarding associations between tetrachloroethylene exposure and specific cancer types; studies that EPA (2012a) considered to have higher quality exposure assessments; and studies published after EPA (2012a), with higher quality exposure assessments (as defined by EPA 2012a). EPA (2012a) considered higher quality exposure assessments to include the following: biological monitoring data; use job-exposure matrix (JEM) based on historical data or job title and/or tasks; and use of union records or other data for specific jobs/tasks (Guyton et al. 2014).”

COMMENT: The Reviewer suggested the deletion of the following statement “A random-effects meta-analysis of dry cleaning workers (139 exposed cases from seven studies) showed an increased risk of bladder cancer, with a meta-relative risk of 1.47 (95% CI 1.16–1.85) (Vlaanderen et al. 2014).”

RESPONSE: *Regarding discussion of the Vlaanderen et al. (2014) study in the Bladder Cancer section of Section 3.2.1.7 (Inhalation, Cancer), the cancer section has been substantially revised. The statement noted in the comment above was deleted. Results of this study are presented in a forest plot (Figure 3-2).*

COMMENT: The Reviewer commented “It would be helpful to cite the number of exposed cases” and suggested the following revisions (insertions noted in red and deletions noted in strikeout): No increased risk of bladder cancer was observed in a case-control study of workers in Montreal, Canada for workers who had any tetrachloroethylene exposure (OR 0.5; 95% CI 0.1–3.0) or “substantial” tetrachloroethylene exposure (OR 0.9; 95% CI 0.1–7.3; Christensen et al. 2013); however, ~~the number of~~ **there were few exposed** cases of bladder cancer ~~was very low~~.

RESPONSE: *This comment refers to the Bladder Cancer subsection of Section 3.2.1.7 (Inhalation, Cancer). Section 3.2.1.7 (Inhalation, Cancer) was substantially revised and the referenced sentence was deleted. In the revised section, study results are now displayed in forest plots. All forest plots (Figures 3-2 through 3-15) include the number of cases or cancer incidence for all studies.*

COMMENT: You should qualify the criteria for this. Consider saying studies where the exposure assessment was informative. This same comment applies throughout the document when non-specific wording is used.

RESPONSE: *The comment above is in reference to discussion of criteria for selecting studies to include in the profile noted in the non-Hodgkin’s lymphoma subsection of Section 3.2.1.7 (Inhalation, Cancer). Section 3.2.1.7 (Inhalation, Cancer) was substantially revised and subsections for each cancer type were removed. Criteria for higher quality exposure (e.g., reliable exposure) assessments was added in the following text:*

“Studies were selected based on the following considerations: studies that EPA (2012a) relied upon to support conclusions regarding associations between tetrachloroethylene exposure and specific cancer types; studies that EPA (2012a) considered to have higher quality exposure assessments; and studies published after EPA (2012a), with higher quality exposure assessments (as defined by EPA 2012a). EPA (2012a) considered higher quality exposure assessments to include the following: biological monitoring data; use job-exposure matrix (JEM) based on historical data or job title and/or tasks; and use of union records or other data for specific jobs/tasks (Guyton et al. 2014).”

COMMENT: Again, why is only the EPA report cited here and not also IARC and NTP?

RESPONSE: *In reference to Section 3.2.1.7 Cancer, subsection on Multiple Myeloma, the cancer section has been substantially revised and cancer type subsections have been removed. The IARC (2014) and EPA (2012a) cancer classifications have been added as follows:*

“IARC (2014) has classified tetrachloroethylene as ‘probably carcinogenic to humans’ based on limited evidence in humans and sufficient evidence in animals (Group 2A). EPA (2012a) has characterized tetrachloroethylene as “likely to be carcinogenic in humans by all routes of exposure.”

COMMENT: The Reviewer suggested the following revisions (insertions noted in red and deletions noted in strikeout): The risk of cancers types (e.g., not other than bladder, non-Hodgkin's lymphoma, or multiple myeloma) in tetrachloroethylene-exposed workers has been investigated in a large number of epidemiological studies.

RESPONSE: *The comment above refers to Section 3.2.1.7 Cancer, Other Cancer End Points. In revision of this Section 3.2.1.7, the referenced sentence was deleted from the profile.*

COMMENT: The Reviewer suggested the following revisions (insertions noted in red and deletions noted in strikeout): ~~A comprehensive review of the epidemiological literature is impractical due to the large number of studies. Therefore,~~ The epidemiological data reviewed below were selected from studies that EPA (2012a) identified as having used a relatively high quality exposure assessment approach for tetrachloroethylene exposure ~~as being informative for assessing cancer outcomes associated with exposure to tetrachloroethylene (e.g., studies with~~ high-quality exposure-assessment).

RESPONSE: *The comment above is in reference to the Other Cancer Types subsection of Section 3.2.1.7 (Inhalation, Cancer). Section 3.2.1.7 (Inhalation, Cancer) was substantially revised and subsections for each cancer type were removed. Criteria for higher quality exposure (e.g., reliable exposure) assessments was added in the following text:*

“Studies were selected based on the following considerations: studies that EPA (2012a) relied upon to support conclusions regarding associations between tetrachloroethylene exposure and specific cancer types; studies that EPA (2012a) considered to have higher quality exposure assessments; and studies published after EPA (2012a), with higher quality exposure assessments (as defined by EPA 2012a). EPA (2012a) considered higher quality exposure assessments to include the following: biological monitoring data; use job-exposure matrix (JEM) based on historical data or job title and/or tasks; and use of union records or other data for specific jobs/tasks (Guyton et al. 2014).”

COMMENT: The quality for high quality should be qualified for transparency

RESPONSE: *Referring to the Other Cancer Types subsection of Section 3.2.1.7 (Inhalation, Cancer), criteria for higher quality exposure (e.g., reliable exposure) assessments was added in the following text:*

“Studies were selected based on the following considerations: studies that EPA (2012a) relied upon to support conclusions regarding associations between tetrachloroethylene exposure and specific cancer types; studies that EPA (2012a) considered to have higher quality exposure assessments; and studies published after EPA (2012a), with higher quality exposure assessments (as defined by EPA 2012a). EPA (2012a) considered higher quality exposure assessments to include the following: biological monitoring data; use job-exposure matrix (JEM) based on historical data or job title and/or tasks; and use of union records or other data for specific jobs/tasks (Guyton et al. 2014).”

COMMENT: Risk estimates are above 1, although not statistically significant. Consistency and coherence across the overall body of literature is more crucial to capture in such a review. Therefore I suggest simply reporting the risk estimates and Cis with no reference to statistical significance. Then summarize the overall findings which appears to show no association between tetrachloroethylene exposure and kidney cancer.

RESPONSE: *The comment above is in reference to Section 3.2.1.7 Inhalation, Cancer, Kidney Cancer. In revision of Section 3.2.1.7 (Inhalation, Cancer), this subsection was deleted. Risk estimates and CIs for each study for each cancer type are displayed on forest plots (Figures 3-2 through 3-15). No reference to statistical significance of results is included. ATSDR has relied upon EPA (2012a), NRC (2010), and IARC (2014) conclusions regarding associations between tetrachloroethylene and specific cancer types. These conclusions are summarized in the introductory paragraph to the “Epidemiological Studies” section. The reader is also directed to these references for more extensive discussions of the literature databases for each cancer type.*

COMMENT: The Reviewer suggested the following revision (insertions noted in red and deletions noted in strikeout): ~~note only two observations of kidney cancer based on 2 exposed~~ kidney cancer cases]. The Reviewer also noted “Use this type of wording throughout the document”

RESPONSE: *The comment above in is reference to Section 3.2.1.7 Inhalation, Cancer, Kidney Cancer. In revision of Section 3.2.1.7 (Inhalation, Cancer), this subsection was deleted. The numbers of cases in case-control studies or incidence data from cohort studies have been added for each study and are included in the forest plots (Figures 3-2 through 3-15) for each cancer type.*

COMMENT: See previous comment

RESPONSE: *The comment above in is reference to Section 3.2.1.7 Inhalation, Cancer, Kidney Cancer. In revision of Section 3.2.1.7 (Inhalation, Cancer), this subsection was deleted. The numbers of cases in case-control studies or incidence data from cohort studies have been added for each study and are included in the forest plots (Figures 3-2 through 3-15) for each cancer type.*

COMMENT: CLL is now considered as a NHL under the new WHO classification (Swerdlow et al). Consider moving this under NHL.

Swerdlow SH, et al (editors). WHO classification of tumours of haematopoietic and lymphoid tissues. 4th edition. 2008. International Agency for Research on Cancer (IARC), Lyon, France

Further reading (not to be cited): <https://www.lymphomas.org.uk/about-lymphoma/types/non-hodgkin-lymphoma/chronic-lymphocytic-leukaemia-ctl-incl-small-lymphocytic>.

RESPONSE: *The comment refers to Section 3.2.1.7 (Inhalation, Cancer, Leukemias/Lymphoma [Excluding Non-Hodgkin’s Lymphoma and Multiple Myeloma]). No change was made in response to this comment. The World Health Organization (WHO) classification of lymphoid tumors, including classification of chronic lymphocytic leukemia (CLL), was updated in 2016. This revision was recently reviewed by Swerdlow et al. (2016; The 2016 Revision of the World Health Organization classification of lymphoid neoplasms. 127(20): 2375-2390). In the revised classification, CLL is classified as a “mature B-cell lymphoid neoplasm.”*

COMMENT: This is not true. The increase was not statistically significant. Several other studies show an increased risk of liver cancer. I suspect some of the analyses reported here may have been underpowered – thus it could be helpful to include the number of exposed cases and also some indication of what the most informative studies were.

This is a general comment that applies throughout the document. See comment above on reporting the risk estimates, CIs, and exposed cases and then summarizing the overall body of evidence by cancer

RESPONSE: *In reference to the statement—Selden and Ahlborg 2011 [SMR 2.14; 95% CI 0.92–4.21]) did not observe increased risks of liver cancer—in Section 3.2.1.7 (Inhalation, Cancer, Liver Cancer), subsections on individual cancer types were deleted. Risk estimates and CIs for each study for each cancer type are now displayed on forest plots (Figures 3-2 through 3-15). No reference to statistical significance of results is included. ATSDR has relied upon EPA (2012a), NRC (2010), and IARC (2014) conclusions regarding associations between tetrachloroethylene and specific cancer types. These conclusions are summarized in the introductory paragraph to the “Epidemiological Studies” section. The reader is also directed to these references for more extensive discussions of the literature databases for each cancer type. In addition, Table 3-2 has been included that reviews study strengths and limitations for all studies.*

COMMENT: The Reviewer suggested the following revisions (insertions noted in red and deletions noted in strikeout): ~~No~~ Inconsistent results were reported for the association between tetrachloroethylene exposure and rectal cancer ~~were observed~~ in several cohort (Andersen et al. 1999; Blair et al. 2003; Boice et al. 1999; Calvert et al. 2011; Lipworth et al. 2011; Pukkala et al. 2009; Selden and Ahlborg et al. 2011) and case-control (Christensen et al. 2013) studies.

RESPONSE: *In reference to the discussion of studies on rectal cancer (Section 3.2.1.7 Inhalation, Cancer, Rectal Cancer), this subsection was deleted. ATSDR has relied upon EPA (2012a), NRC (2010), and IARC (2014) conclusions regarding associations between tetrachloroethylene and specific cancer types. These conclusions are summarized in the introductory paragraph to the “Epidemiological Studies” section. The reader is also directed to these references for more extensive discussions of the literature databases for each cancer type. In addition, Table 3-2 has been included that reviews study strengths and limitations for all studies.*

COMMENT: The Reviewer suggested the following revisions (insertions noted in red and deletions noted in strikeout): A study examining the association between prenatal and early childhood exposure to tetrachloroethylene in drinking water and cancer is ~~reviews~~ reviewed in Section 3.2.2.7 (Aschengrau et al. 2015).

RESPONSE: *This statement in Section 3.2.2.6 (Oral, Developmental Effects) was substantially revised and the referenced statement was deleted.*

COMMENT: The Reviewer suggested the following revisions (insertions noted in red): The epidemiological data on cancers among humans exposed to tetrachloroethylene orally is much more limited than the inhalation data due to **small** numbers of studies and small cohort sizes. The Reviewer also commented “Again, it would be important to have an indication of potential confounders by cancer sites reviewed (eg, smoking for bladder or lung cancers). A paper by Coglianò et al in JNCI is useful for this exercise.”

RESPONSE: *In reference to Section 3.2.2.7 (Oral, Cancer), this section has been substantially revised and the referenced sentence was deleted. The section now follows the same format as the revised Section 3.2.1.7 (Inhalation, Cancer). For all epidemiological studies reviewed in Section 3.2.2.7, Table 3-5 was added and includes study details. The following sentence was added regarding confounding of smoking for bladder and lung cancers:*

“In addition, tobacco smoke should be considered as an important confounder for bladder and lung cancer (EPA 2012a; Guyton et al. 2014).”

COMMENT: The Reviewer suggested the following revisions (insertions noted in red and deletions noted in strikeout): An early case-control study was ~~completed~~ **conducted** to examine the relationship between bladder cancer, kidney cancer, and leukemia among residents of Cape Cod with exposure to tetrachloroethylene in public drinking water

RESPONSE: *In reference to Section 3.2.2.7 (Oral, Cancer), this section has been substantially revised and the referenced sentence was deleted.*

COMMENT: For the Cape Cod studies, the ecological exposure assessment should be mentioned along with its implication for interpretation.

RESPONSE: *In response to the comment on Section 3.2.2.7 (Oral, Cancer), as noted in the response above, the oral cancer section has been substantially revised. In revision of Section 3.2.2.7, Table 3-5 was added and this details exposure assessment methods for all oral epidemiological cancer studies. The table also includes discussion of study strengths and limitations.*

COMMENT: What was the study design? Was the exposure misclassification differential or non-differential? Which direction would this bias the risk estimate?

RESPONSE: *In reference to Section 3.2.2.7 (Oral, Cancer), this section has been substantially revised to follow the same format as the revised Section 3.2.1.7 (Inhalation, Cancer). For all epidemiological studies reviewed in Section 3.2.2.7, study details are in Table 3-5. Information in this table includes study type, population studied, exposure methodology, confounders considered, and study strengths and limitations, including bias due to misclassification.*

COMMENT: Regarding the statement “Study details are described in Section 3.2.2.6,” the Reviewer commented “Study details are presented for many studies here. For consistency you could present details for all studies cited here.”

RESPONSE: *In reference to Section 3.2.2.7 (Oral, Cancer), this section has been substantially revised to follow the same format as the revised Section 3.2.1.7 (Inhalation, Cancer). For all epidemiological studies reviewed in Section 3.2.2.7, study details are in Table 3-5. Information in this table includes study type, population studied, exposure methodology, confounders considered, and study strengths and limitations. Results are now presented in forest plots (Figures 3-17 through 3-19), which include information regarding population size, risk estimates, and CIs.*

COMMENT: Regarding the NTP (2014) reference in Chapter 9, the Reviewer commented “This link does not work for me. 13th edition is listed, but the link is for ROC 12?”

RESPONSE: *The NTP (2014) citation was for a previous version of the Report on Carcinogens. This has been updated to the 14th edition of the Report on Carcinogens (NTP 2016); the link was also updated.*

Comments provided by Peer Reviewer #2

COMMENT: The ATSDR is to be commended for the draft Toxicological Profile on perchloroethylene (PERC). The data concerning health hazards of PERC are both numerous and complex, and ATSDR has done an admirable job of compiling information relevant to cancer in humans and in experimental systems, as well as non-cancer effects (notably, neurotoxicity). Major comments for consideration during the finalization of the draft Toxicological Profile are detailed below, focused on (as requested) the cancer sections.

RESPONSE: *No response needed.*

COMMENT: Concerning the presentation of epidemiological studies, some additional information is needed to achieve accuracy and consistency with other published reviews and the more recently published studies. In particular, the ATSDR nicely introduces the characterization of the study quality assessment by EPA (2012) (see p 64, paragraph on line 2), but could expand this to list the studies using higher quality exposure assessment methodologies, and the exposure settings in which they were conducted, as summarized in Guyton et al (2014; PMID: 24531164). Further, in describing the studies for each cancer type, the work setting (e.g., dry cleaners) could be listed. For instance, it could be noted that many of the studies relied upon by EPA (2012) were of dry cleaners, launderers and pressers and used additional information to distinguish workers exposed to PERC from other workers, while those in other work settings and in population-based case-control studies used an individual-level exposure assignment. It could thus be specified for which studies confounding “concomitant exposure to other chemicals” (e.g., p 65, line 34; p 66 line 18) is relevant. Additionally, particularly for the studies with very few cases and/or reporting wide confidence intervals (including of multiple myeloma, pancreatic cancer, esophageal cancer, brain cancer, etc), the number of cases could be specified. Finally, although acknowledging that the epidemiologic data on oral exposures is much more limited, studies cited are covered in much more detail than the inhalation studies that appear to form the basis of the conclusions. Accordingly, it may be appropriate to similarly present a concise, synthetic review of the oral studies.

RESPONSE: *This comment refers to Section 3.2.1.7 (Inhalation, Cancer). This section has been substantially revised. The additional information requested in the comment above has been added by including Table 3-2, a new summary table with exposure assessment methodologies, exposure settings, occupational setting, and lists of confounders considered (including exposure to other chemicals). Individual sections on cancer types have been deleted and study results for each cancer type are now displayed in forest plots (Figures 3-2 through 3-15). These plots also include the number of cases or cancer incidence and CIs for each study.*

Regarding the portion of the comments that refers to oral exposures (Section 3.2.2.7; Oral, Cancer), the Oral Cancer section was substantially revised and follows the revised format of the Inhalation Cancer section. Details of oral studies are summarized in Table 3-5 and results are displayed in forest plots (Figures 3-17 through 3-19) as described above.

COMMENT: Additional detail is also needed in introducing and describing the “recent studies”. For instance, how were these identified, and are the same quality considerations as applied by US EPA (2012) applicable for each? If it is not possible to provide such detailed information, the ATSDR could rely on the recent meta-analysis by Vlaanderen et al. (2014) (which fully details the methods for study identification, selection and analysis) as a basis for updating the EPA (2012) conclusions. Although

Vlaanderen et al. report on bladder but not other cancers, bladder is the cancer site with the stronger evidence, per EPA (2012) and IARC (2014) and is the only cancer noted to have “limited” evidence by IARC (2014). ATSDR only identifies one recent study, Silver et al (2014), that was not considered by Vlaanderen et al. (2014), but it isn’t clear if this would be appropriate to include in such a meta-analysis, as study strengths and limitations aren’t described (see below), nor is the number of cases given.

RESPONSE: *The comment above refers to Sections 3.2.1.7 (Inhalation, Cancer) and 3.2.2.7 (Oral, Cancer). The following text regarding criteria for higher quality exposure (e.g., reliable exposure) assessments for inhalation studies were added to Section 3.2.1.7 (Inhalation, Cancer):*

“Studies were selected based on the following considerations: studies that EPA (2012a) relied upon to support conclusions regarding associations between tetrachloroethylene exposure and specific cancer types; studies that EPA (2012a) considered to have higher quality exposure assessments; and studies published after EPA (2012a), with higher quality exposure assessments (as defined by EPA 2012a). EPA (2012a) considered higher quality exposure assessments to include the following: biological monitoring data; use job-exposure matrix (JEM) based on historical data or job title and/or tasks; and use of union records or other data for specific jobs/tasks (Guyton et al. 2014).”

The following text regarding criteria for higher quality exposure (e.g., reliable exposure) assessments for inhalation studies were added to Section 3.2.2.7 (Oral, Cancer):

“Studies were selected based on the following considerations: studies that EPA (2012a) relied upon to support conclusions regarding associations between tetrachloroethylene exposure and specific cancer types; studies that EPA (2012a) considered to have higher quality exposure assessments; and studies published after EPA (2012a), with higher quality exposure assessments (as defined by EPA 2012a). For oral exposure, EPA (2012a) considered higher quality exposure assessments to include the following: biological monitoring data; estimated exposure through use of statistical models of the water distribution system, and consideration of confounders.”

COMMENT: In the discussion of recent studies, ATSDR may also wish to clarify what is meant by “mixed results” (e.g., line 33 page 64), and whether this differs from the earlier conclusions that the studies as a whole provided “suggestive” evidence by US EPA (2012) (and in the case of bladder cancer, “limited” evidence by IARC (2014); note that page 12 could reference this recent IARC conclusion).

RESPONSE: *The comment above in is reference to Section 3.2.1.7 Inhalation, Cancer, Bladder Cancer. In the substantial revision of discussion of cancer, the term “mixed results” was deleted. In response to portion of the comment pertaining to page 12 (discussion of cancer in Section 2.2, Summary of Health Effects), discussion of the cancer summary has been revised and IARC (2014) conclusions have been added as follows:*

“Numerous epidemiological and experimental animal studies have assessed the potential carcinogenicity of tetrachloroethylene. The Health and Human Services Department (HHS) has classified tetrachloroethylene as “reasonably anticipated to cause cancer in humans based on sufficient evidence from studies in experimental animals” (NTP 2016). IARC (2014) has classified tetrachloroethylene as “probably carcinogenic to humans” based on limited evidence in humans and sufficient evidence in animals (Group 2A), and concluded that “positive associations have been observed for cancer of the bladder” in humans. The NRC (2010) concluded that there was suggestive evidence for an association between tetrachloroethylene exposure and lymphoma, despite weak and sometimes inconsistent data; 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. EPA (2012a) has characterized tetrachloroethylene as “likely to be carcinogenic in humans by all routes of exposure.” The EPA (2012a) Toxicological Review concluded that epidemiological data support a pattern of association between tetrachloroethylene exposure and bladder cancer, multiple myeloma, and non-Hodgkin’s lymphoma. EPA (2012a) also concluded that epidemiological studies suggest possible associations with other cancers (esophageal, kidney, lung, liver, cervical, and breast cancer), but the data on these cancers were more limited and/or inconsistent.”

COMMENT: Regarding the specific studies listed, for bladder cancer, it could be clarified that Vlaanderen et al. (2014) is a meta-analysis of studies considered in the IARC (2012) systematic review (see also comment above). Lipworth et al (2011) is included in this meta-analysis (and the reported SMR (1.81 (0.87, 3.33)) differs from that given on page 65, line 4), and it isn’t clear why a contrast is made of the results of this one study (with 17 cases) to an overall RR from a meta-analysis in which it is included. Christensen et al. (2013) is also considered in the Vlaanderen et al. (2014) meta-analysis; the number of cases could be specified (i.e., 2 for each group).

RESPONSE: *In reference to the comment above on Section 3.2.1.7 Inhalation, Cancer, Bladder Cancer. Section 3.2.1.7 (Inhalation, Cancer) has been substantially revised. Text noted above has been deleted. Results of all studies are now presented in forest plots (Figures 3-2 through 3-15) for each cancer type. Plots display studies in four categories: cohort, case-control, pooled case-control, and meta-analysis. Thus, for each study, the study type is clearly identified. The number of cases or cancer incidence data for all studies is included in the forest plot.*

COMMENT: Regarding Silver et al. (2014), it may be useful to indicate the number of cases and whether the study used an individual-level exposure assignment, as well as other sources of bias and confounding.

RESPONSE: *The comment above refers to Section 3.2.1.7 (Inhalation, Cancer, Bladder Cancer). In the substantial revision of Section 3.2.1.7 (Inhalation, Cancer), study results are now displayed in forest plots (Figures 3-2 through 3-15) that include risk estimates, CIs, and number of cases or cancer incidence. Table 3-2 was added to provide information for each study on occupational setting, methods for exposure assessments, confounders considered, and study strengths and limitations.*

COMMENT: Similarly, for NHL and multiple myeloma, some additional detail regarding the exposure setting, quality considerations (if any), and the number of cases could be included for the recent studies identified.

RESPONSE: *The comment above refers to cancer subsections of Section 3.2.1.7 (Inhalation, Cancer). In revision of Section 3.2.1.7 (Inhalation, Cancer), subsections on cancer types have been eliminated. Study results are now displayed in forest plots (Figures 3-2 through 3-15) that include risk estimates, CIs, and number of cases or cancer incidence. Table 3-2 has been added to provide information for each study on occupational setting, methods for exposure assessments, confounders considered, and study strengths and limitations.*

COMMENT: ATSDR may also wish to modify the statements concerning relevance of animal tumors to human risk to more accurately reflect the conclusions of NRC (2010). Specifically, it is not clear what is meant by “a different metabolic cascade” (e.g., p 71, line 31) in different species; species differences in metabolism are addressed by Chiu and Ginsberg (2011), and as they are quantitative in nature, are not

considered a reason to rule out relevance. On page 75, lines 19-20, the statement regarding the uncertain relevance of the animal tumors could be clarified, given the different conclusions of NRC on mouse liver tumors and rat MCL. Specifically, NRC makes reference to having “debated” the issues about human relevance regarding mouse liver tumors, noting that the majority concluded that there was insufficient evidence to rule out human relevance. The NRC included a minority opinion by one member, but also a rebuttal to this view by the committee as a whole. On the other hand, for rat MCL, some NRC (2010) committee members judged that similarities between a form of human leukemia (natural killer-cell large granular lymphocyte leukemia) and rat MCL and results of mechanistic studies were adequate to establish human relevance, while others believed more research was needed to establish the relevance. They noted statistical analysis and other factors (e.g., tumor latency) considered by Thomas et al (2007), in addition to mechanistic studies that add support to the biologic plausibility of the observed leukemic effects (NRC, 2010); these considerations were included by EPA (2012), see summary in Guyton et al. (2014).

RESPONSE: *The comment above refers to the discussion of cancer bioassays in Section 3.2.1.7 (Inhalation, Oral). This discussion was revised as follows:*

“Studies in laboratory animals demonstrate increased risks of mononuclear cell leukemias (MCL) and liver tumors after chronic exposure to tetrachloroethylene (JISA 1993; NTP 1986). NRC (2010) debated the relevance of MCL in experimental animals to humans, noting the following: results of the NTP (1986) study in rats were inconsistent regarding statistical significance between sexes, and there was uncertainty regarding the shape of the dose-response curve; lack of information on the mechanism of action for MCL; and unclear biological concordance between rat MCL and human lymphohematopoietic cancer. Despite these concerns, NCR (2010) concluded that MCL in rats is relevant to humans. NRC (2010) also discussed relevance of liver tumors in mice to humans. Although the strain of mice (B6C3F1) used in the NTP study (1986) have a high background incidence of hepatic cancer, findings have been reproduced in different laboratories and data demonstrate a dose-response relationship. The NRC (2010) committee considered hepatic tumors in mice to be relevant to humans, although the mechanism of action needs to be established. The NTP (1986) and JISA (1993) studies are reviewed below.”

COMMENT: Regarding kidney tumors, on page 72, line 16, it should be noted if there was statistical significance in trend tests, as positive results in either trend or pairwise tests is generally considered sufficient to rule out chance as an explanation for the findings. On page 72, line 33, it should be specified whether the ‘lack of statistical significance’ is in reference to trend or pairwise tests.

RESPONSE: *The comment above refers to the discussion of the cancer bioassay conducted by NTP (1986) in Section 3.2.1.7. Note that the page/line reference noted in the comment discusses gliomas, not kidney tumors, reported in the NTP (1986) study. This discussion was revised so that the types of comparisons for all statistical analyses noted are explicitly stated. The following provides an example of statistical comparisons as already discussed in the text:*

*“Gliomas were also observed in one female in the control group and two females in the 400 ppm group. Due to the lack of statistical significance in male rats exposed to 400 ppm compared to controls (**pairwise test**) and the occurrence of gliomas in the control group, NTP (1986) concluded that gliomas were not related to treatment with tetrachloroethylene.”*

The portion of the comment referring to page 72, line 33, pertains to tumors of the Harderian gland and hemangioendotheliomas of the liver and spleen in the study conducted by JISA (1993). This was revised as follows:

*“Dose-related trends were also noted for incidences of tumors of the Harderian gland and hemangioendotheliomas of the liver and spleen in males, but the incidences **in treatment groups** were not significantly different **compared to controls (pairwise test)** at any exposure level.”*

Comments provided by Peer Reviewer #3

General Comments

COMMENT: The document provides an excellent review of the extensive literature regarding possible cancer risks from exposure to tetrachloroethylene. My suggestions are largely to improve the clarity of the evaluation.

RESPONSE: *No response required.*

COMMENT: I suggest a slightly different characterization of epidemiologic findings that are not statistically significant. What is generally employed in the report is the use of comments such as “no association”, or “not elevated”. This is certainly appropriate if the RR is close to 1.0, but at other levels it may not fully convey the findings from such analyses. I think It would be more appropriate and clearer to the reader if the size and direction of the relative risk from the null is indicated and also whether or not the relative risk is statistically significant. The wording of “no association” and “not elevate” combines these two pieces of information and could indicate a relative risk of 1.0 or 1.5 (that is not statistically significant). In literature summaries, as performed in this document, these are quite different.

RESPONSE: *The cancer sections (3.2.1.7, Inhalation, Cancer and 3.2.2.7, Oral, Cancer) of the profile have been substantially revised. Individual study results are displayed in forest plots (Figures 3-2 through 3-15; Figures 3-17 through 3-19), including risk estimates and CIs. Discussion of results in terms of associations or elevated risk estimates have been deleted for individual studies. Conclusions regarding associations between tetrachloroethylene and specific cancer types are taken from EPA (2012a), NRC (2010), and IARC (2014). These conclusions are included in the introductory paragraph to the “Epidemiological Studies” section. The reader is also directed to these references for more extensive discussions of the literature databases for each cancer type.*

COMMENT: It might be useful to perform meta-analyses for cancer sites that have findings from several studies. These would be similar to the bladder cancer meta-analysis performed by Vlaanderen et al. (2014). This would provide a statistical evaluation for situations where there are excesses from several studies that are not statistically significant. Meta-analyses could be performed for all studies combined, as well as, for occupational and environmental exposures separately.

RESPONSE: *The general comment refers to Section 3.2.1.7 (Inhalation, Cancer). ATSDR does not typically independently conduct meta-analyses for toxicological profiles. There are extensive, comprehensive reviews of cancer epidemiological studies (EPA 2012a; IARC 2014; NRC 2010). The following text was added:*

“For additional details and reviews of these and other epidemiological studies assessing the potential carcinogenicity of tetrachloroethylene, the EPA Integrated Risk Information System (IRIS) Toxicological Review for Tetrachloroethylene (EPA 2012a), IARC (2014), and NRC (2010) may be consulted.”

Specific Comments

COMMENT: Page viii: Other Agencies and Organizations. Since cancer is one of the major outcomes discussed and several of studies reviewed in the cancer section were conducted at the National Cancer Institute (NCI), perhaps NCI should also be listed here.

RESPONSE: *This comment refers to the list of “Other Agencies and Organizations” in the Quick Reference for Health Care Providers. NCI was added to the “Other Agencies and Organization” section under “Quick Reference for Health Care Providers.”*

COMMENT: Page 1, lines 18-19: “You must also consider the other chemicals you are exposed to and your age, sex, diet, family history, lifestyle, and state of health”. This is probably true, but I did not see where information on these influences with TCE were presented elsewhere in the document. Perhaps this section could be expanded a bit to reference situations with other exposures that have demonstrated this principle.

RESPONSE: *The comment above refers to boilerplate text (paragraph 3) at the beginning of the Public Health Statement (Chapter 1). Information on potential influence of “other chemicals you are exposed to and your age, sex, diet, family history, lifestyle, and state of health” is discussed in Section 3.10 (Populations That Are Unusually Susceptible) of the profile. No change was made to the boilerplate text of the Public Health Statement for Tetrachloroethylene. However, the following paragraph was added to Section 3.9:*

“In many instances, individuals occupationally exposed to tetrachloroethylene in air or orally exposed through drinking water are actually exposed to several compounds (co-contaminants). For example, drinking water at the Camp Lejeune was contaminated with tetrachloroethylene benzene, vinyl chloride, and trans-1,2-dichloroethylene (Cohn et al. 1994; Ruckert et al. 2013) and drinking water in the Vartiainen et al. (1993) study of a Finish population was contaminated with both trichloroethylene and tetrachloroethylene. Co-contaminant exposure may result in effects that are different from those of tetrachloroethylene, or produce effects that are similar to tetrachloroethylene, potentially causing additive effects. For example, metabolic pathways for tetrachloroethylene and trichloroethylene are qualitatively similar, although quantitative metabolic differences exist between the two compounds (Cichocki et al. 2016). However, metabolism of both compounds produces a common active metabolite.”

COMMENT: Page 2, line 28: Exposures through “air, water, or soil” are indicated. Direct skin contact with the liquid itself should probably be mentioned here since this can certainly occur in the occupational setting.

RESPONSE: *In Chapter 1, under Subheading of “How can Tetrachloroethylene enter and leave my body?”, the text was revised to state: “Tetrachloroethylene can enter your body from the air, water, or soil. It can also absorb through the skin if there is direct skin contact with the liquid form of tetrachloroethylene.”*

COMMENT: Page 3, line 11: Might be helpful to provide some indication of the half-life of TCE in the blood.

RESPONSE: *This comment refers to Chapter 1, subsection “How can tetrachloroethylene enter and leave my body?” Since tetrachloroethylene is distributed into adipose tissue, blood, or plasma, the half-life does not reflect how long tetrachloroethylene stays in the body. The following sentence was added as follows: “It takes about 3 days for half of the tetrachloroethylene in your body to be eliminated.”*

COMMENT: Page 4, line 1: I wonder if the phrase “for a long time” might be not be clearer with some indication of what length of time would be a concern. Is it hours, days, or years.

RESPONSE: *This comment refers to Chapter 1, subsection “How can tetrachloroethylene affect my health?”. The sentence indicated was revised as follows (insertion noted in red): “Exposure to tetrachloroethylene for a long time (years) may lead to a higher risk of getting cancer....”*

COMMENT: Page 4, 12-13: Might want to add what IARC says about the comparability of mechanisms regarding TCE carcinogenic mechanisms in humans and experimental animals.

RESPONSE: *This comment refers to Chapter 1, subsection “How can tetrachloroethylene affect my health?”. No change was made to the profile in response to this comment. According to the previous (pre-2018) ATSDR Guidance for the Preparation of Toxicological Profiles, Chapter 1 of the profile “is intended to be a health effects summary written in layperson's [language], with the audience being the general public.” As such, discussion of tetrachloroethylene carcinogenic mechanisms in humans and experimental animals is beyond the scope of Chapter 1. The carcinogenic mechanisms are discussed in Section 3.5.2.*

COMMENT: Page 8, lines 25-26: Does ATSDR have information on vinyl chloride that could also be referenced, since it is a TCE metabolite and also an established carcinogen.

RESPONSE: *In response to comment on Section 2.1 (Background and Environmental Exposures to Tetrachloroethylene in the United States), the following revisions were made:*

“Members of the population can also be exposed to the degradation products, trichloroethylene and vinyl chloride, which are often found as a contaminant in products with tetrachloroethylene. More information on trichloroethylene can be found in ATSDR’s Toxicological Profile for Trichloroethylene (Agency for Toxic Substances and Disease Registry 1997). Information on vinyl chloride can be found in ATSDR’s Toxicological Profile for Vinyl Chloride (Agency for Toxic Substances and Disease Registry 2006b) and the Addendum to the Toxicological Profile for Vinyl Chloride (Agency for Toxic Substances and Disease Registry 2016).”

COMMENT: Page 12 and 63: Is there some reason why the IARC evaluations of tetrachloroethylene are not referenced and discussed here?

RESPONSE: *The comment above refers to Sections 2.2 and 3.2.1.7. The IARC (2014) cancer evaluation of tetrachloroethylene was added in these sections.*

COMMENT: Page 22, lines 30-31: Might be helpful to provide a few examples of what are the “less serious” effects?

RESPONSE: *In reference to the boilerplate text in the second paragraph of Section 3.2 (Health Effects, Discussion of the Health Effects by Route of Exposure), the following was added: “For example, respiratory tract irritation and changes in mood or behavior are considered “less serious effects.”*

COMMENT: Page 64, lines 1-2: Provide the actual numbers of cohort and case-control studies available.

RESPONSE: *This general comment pertains to presentation of inhalation and oral epidemiological cancer studies. The following sentence was added: “As summarized in Table 3-2, selected studies included 1 meta-analysis, 2 pooled case-control studies, 11 cohort studies, and 15 case-control studies.”*

COMMENT: Page 64, lines 21 to line 9 on page 65: Three cohort studies and 1 case-control study are considered in the evaluation of bladder cancer. Vlaanderen et al. (2014) included 15 papers in their meta-analysis. It is not obvious to me why most of the studies included in Vlaanderen et al (2014) were judged to be inadequate for review by EPA and apparently also by the CDC. A table listing all studies and the reasons for inclusion and exclusion would be helpful, or at least an indication of the specific information available in the studies included that was lacking in those excluded.

RESPONSE: *The comment above refers to the bladder cancer subsection of Section 3.2.1.7 (Inhalation, Cancer), but also applies to Section 3.2.2.6 (Oral, Cancer). It is not ATSDR’s intent to provide a comprehensive review of cancer studies in this profile. The intent is to provide a high-level overview of cancer studies and rely upon conclusions of other agencies that have conducted comprehensive reviews of epidemiological studies on potential associations between tetrachloroethylene and cancer. Conclusions regarding associations between tetrachloroethylene and specific cancer types are taken from EPA (2012a), NRC (2010), and IARC (2014). These conclusions are included in the introductory paragraph to the “Epidemiological Studies” section. The reader is also directed to these references for more extensive discussions of the literature databases for each cancer type.*

In addition, criteria for study inclusion was added as follows to Section 3.2.1.7 (Inhalation, Cancer) and Section 3.2.2.7 (Oral, Cancer):

Section 3.2.1.7: “Studies were selected based on the following considerations: studies that EPA (2012a) relied upon to support conclusions regarding associations between tetrachloroethylene exposure and specific cancer types; studies that EPA (2012a) considered to have higher quality exposure assessments; and studies published after EPA (2012a), with higher quality exposure assessments (as defined by EPA 2012a). EPA (2012a) considered higher quality exposure assessments to include the following: biological monitoring data; use job-exposure matrix (JEM) based on historical data or job title and/or tasks; and use of union records or other data for specific jobs/tasks (Guyton et al. 2014).”

Section 3.2.2.7: “Studies were selected based on the following considerations: studies that EPA (2012a) relied upon to support conclusions regarding associations between tetrachloroethylene exposure and specific cancer types; studies that EPA (2012a) considered to have higher quality exposure assessments; and studies published after EPA (2012a), with higher quality exposure assessments (as defined by EPA 2012a). For oral exposure, EPA (2012a) considered higher quality exposure assessments to include the following: biological monitoring data; estimated exposure through use of statistical models the water distribution system; and consideration of confounders.”

COMMENT: Page 65, lines 31-34: This sentence deals with the issue of excesses that are not statistically significant, but it is confusing because if there is no association or elevation in any of the individual studies (as excesses that are not statistically significant are usually characterized in the document) how can the data overall point to a consistent pattern of elevated risks? There needs to be some way of indicating that there excesses that are not statistically significant that should not be entirely ignored.

RESPONSE: *The comment above refers to the non-Hodgkin's Lymphoma subsection of Section 3.2.1.7 (Inhalation, Cancer), but also applies to Section 3.2.2.6 (Oral, Cancer). Sections 3.2.1.7 and 3.2.2.7 have been substantially revised. Subsections on cancer types have been eliminated from the profile. Discussions of cancer data from individual studies for each cancer type are now displayed in forest plots (Figures 3-2 through 3-15; Figures 3-17 through 3-19), including risk estimates and CIs. In addition Tables 3-2 and 3-5 have been added to provide more information on exposure assessment methods, considerations of confounders, and study strengths and limitations.*

COMMENT: Page 69, line 2: The following is the wording about TCE and pancreatic cancer in one study. "Among dry cleaners, no associations between tetrachloroethylene exposure and pancreatic cancer were reported by Andersen et al. (1999; SIR in males 1.41; 95% CI 0.98–1.96." I would describe this this as an excess that is not statistically significant.

RESPONSE: *The comment above refers to the Pancreatic Cancer subsection of Section 3.2.1.7 (Inhalation, Cancer), but also applies to Section 3.2.2.6 (Oral, Cancer). Sections 3.2.1.7 and 3.2.2.7 have been substantially revised. Subsections on cancer types have been eliminated from the profile. Discussions of cancer data from individual studies for each cancer type are now displayed in forest plots (Figures 3-2 through 3-15; Figures 3-17 through 3-19), including risk estimates and CIs. The text no longer states whether individual studies found associations or no associations. In addition, Tables 3-2 and 3-5 have been added to provide more information on exposure assessment methods, considerations of confounders, and study strengths and limitations.*

COMMENT: Page 69, lines 13-16: This is an example where an OR for prostate cancer of 4.3 (95% CI 1.4–13.0) is characterized as an association for substantial exposure, but an OR of 2.2 (95% CI 0.8–5.7) for "any" exposure is classified as not an association. Would be clearer to say that the 4.3 was statistically significant and the 2.2 was not.

RESPONSE: *The comment above refers to the Prostate Cancer subsection of Section 3.2.1.7 (Inhalation, Cancer), but also applies to Section 3.2.2.6 (Oral, Cancer). Sections 3.2.1.7 and 3.2.2.7 have been substantially revised. Subsections on cancer types have been eliminated from the profile. Discussions of cancer data from individual studies for each cancer type are now displayed in forest plots (Figures 3-2 through 3-15; Figures 3-17 through 3-19), including risk estimates and CIs. The text no longer states whether individual studies found associations or no associations. In addition, Tables 3-2 and 3-5 have been added to provide more information on exposure assessment methods, considerations of confounders, and study strengths and limitations.*

COMMENT: Page 71, lines 27-29: Additional comments would be helpful to explain why a high background incidence of mononuclear cell leukemia in mice would discount the excess that occurs in those exposed to TCE compared to controls lacking such exposure.

RESPONSE: *This comment refers to discussion of the cancer bioassays conducted by JISA (1993) and NTP (1986) in Section 3.2.1.7 (Inhalation, Cancer). The sentence noted in the comment above was revised as follows:*

“Regarding the relevance of mononuclear cell leukemia in mice to humans, NRC (2010) noted that there is uncertainty regarding dose-response data in mice and the mode of action for mononuclear cell leukemia is poorly understood.”

COMMENT: Page 75, lines 14-16: The overall summary of “suggestive evidence” for an association with bladder cancer, non-Hodgkin’s lymphoma, and multiple myeloma is reasonable, but it seems a bit contrary to how findings from individual studies that do not show statistically significant excesses are described.

RESPONSE: *This comment refers to Section 3.2.1.7 (Inhalation, Cancer). Section 3.2.1.7 has been substantially revised and this paragraph was deleted. ATSDR has relied upon NTP (2014), IARC (2014), NRC (2010), and EPA (2012a) for conclusions regarding evidence for cancer. These conclusions are now summarized in the first two paragraphs of Section 3.2.1.7 (Inhalation, Cancer).*

COMMENT: Page 95, lines 12-13: These comments imply that tetrachloroethylene exposure through the oral route may have a greater problem from confounding by other solvents than exposures through the inhalation route. Some documentation is needed to support this contention. I suspect that there is a greater potential for confounding from other solvents at the workplace, which would largely be through inhalation or skin contact than exposures than through water.

RESPONSE: *This comment refers to Section 3.2.2.7 (Oral, Cancer). Section 3.2.2.7 has been substantially revised. The sentence implying that confounding by exposure to co-contaminants by the oral route may be a greater problem than for the inhalation route was deleted.*

COMMENT: Page 95, lines 33-34 and Page 96, lines 1-8: I am not sure the technique of providing a range of ORs to indicate ORs from multiple comparisons works well. I think it would be better to clearly indicate the relative risks for the various comparisons.

RESPONSE: *This comment is in reference to Section 3.2.2.7 (Oral, Cancer). This section has been substantially revised. Results of all studies are now displayed in forest plots (Figures 3-17 through 3-19), including risk values, CIs, and population size.*

COMMENT: Page 97, lines 4-6: Should indicate how exposure misclassification from the lack of information on long-term residence and water consumption would impact the estimates of relative risk. Would this misclassification tend to bias the relative risks upward or downward?

RESPONSE: *The following statement was added to Section 3.2.2.7 (Oral, Cancer):*

“All studies relied on qualitative or semi-quantitative methods to assign exposure histories to subjects. Semi-quantitative methods included the use of leaching and transport models to estimate amounts of tetrachloroethylene delivered to residential supply lines along with self-reported information on residence addresses during the applicable exposure period (e.g., Aschengrau et al. 2015). Exposure misclassification is possible from use of these models because they do not estimate individual tetrachloroethylene intakes and the amounts of tetrachloroethylene delivered to each

residence may not reflect long-term drinking water exposure concentrations or tetrachloroethylene intakes. Non-differential exposure misclassification (misclassification rate is the same among exposure groups) will tend to bias the estimates of relative risk downward. However, differential exposure misclassification could bias the risk estimates in the up or down direction.”

COMMENT: Page 97, lines 16-21: Should indicate what are the results and interpretation from the integration of findings from the Camp Lejeune studies and the other occupational and environmental studies.

RESPONSE: *In reference to Section 3.2.2.7 (Oral, Cancer), this section has been substantially revised. Results of all studies are now displayed in forest plots (Figures 3-17 through 3-19). The ATSDR tetrachloroethylene toxicological profile relied on other agencies that have conducted comprehensive reviews of cancer (NTP, IARC, EPA) and provides no interpretation of the Camp Lejeune or other studies’ findings. The conclusions of these agencies are summarized in the beginning of Section 3.2.1.7 (Inhalation, Cancer), with reference to this discussion in Section 3.2.2.7 (Oral, Cancer).*

COMMENT: Page 98, lines 4-8: Should provide an indication of how the limitations listed here influenced the conclusions about the summary of study findings.

RESPONSE: *In reference to Section 3.2.2.7 (Oral, Cancer), Table 3-5 has been added to this section to include strengths and limitations of each study. The following statement was added:*

“Lack of consideration of confounding factors may add uncertainty to interpretation of study results.”