**Reviewer #1**

1. Are the individual disease tables sufficiently comprehensive to make our case or did we omit an important epidemiological study that should be included in the tables?

*Comment. The individual disease tables of the key epidemiology studies appear sufficient for most of the diseases, but, details that could be presented in the text are often lacking. For example, most often we don’t know how many people were in the studies, the number of cases, the length of follow-up, lots of the risk ratios are without confidence limits, and there is no indication of either the authors’ or reviewer’s conclusions. Also, in the write-up, there is very little discussion, not more than a sentence or two, on any of the individual studies. For most studies listed in the tables, there is no discussion. This leaves the reader to wonder which studies are important and which are not. It is, therefore, often difficult to understand how ATSDR made their classification decisions based on epidemiology. (see additional comments below).*

**Response: We agree. The text and tables have been rewritten for each disease addressing this comment.**

2. Are we interpreting the epidemiological evidence and available toxicological information for each exposure-disease relationship appropriately? Particular emphasis on the mechanistic information provided for PCE and bladder cancer.

*First, I found the ATSDR analysis, write-up, epidemiology table, and support for their classification conclusion on PCE and bladder cancer to be well done. Note details in the bladder cancer table, and accompanying discussion of the studies, not seen in some of the other disease write-ups. Presentations and analyses for the other diseases varied. If ATSDR uses the bladder cancer analysis as a template, and if they analyze the pancreatic, esophageal, and lung cancer data better, their conclusions might change.*

*I found the ATSDR discussion of the mechanism for PCE associated increase in bladder cancer among specific genotypes very good. For most other diseases, where there was mechanistic evidence, it was presented adequately, although there are no accompanying tables of mechanistic study findings, as there are for the epidemiology studies.*

*With particular attention to bladder cancer, I view both the IARC and the EPA analyses as supporting a limited positive finding for PCE and bladder cancer in humans, mainly from increased bladder cancer in studies of dry cleaning workers, (EPA 2012 pgs 4-83 to 4-100). I thought that the ATSDR mechanism write-up added much support for their final classification of “sufficient evidence for causation.”*

*The prostate cancer section needs additional discussion, clarification and analysis.*

*There were no Tables on animal bioassay cancer findings for any of the 4 contaminants examined. Since bioassay findings contribute to the weight of evidence, a separate section, with table(s) could list the important rodent bioassay results for the 4 major contaminant carcinogens. Thus, one to four table(s), placed in a separate section, could summarize the animal bioassay findings and could be referenced easily in the discussion of every disease. Most carcinogen risk assessment guidelines that I have seen specify that multiple tumors in multiple animal rodent species, dosed either by inhalation or orally, add to the weight of the evidence for presumptive human carcinogenicity, so tables of these bioassay results could add needed toxicological support for analysis.*

*An example of using toxicological (bioassay) evidence as additional supporting evidence for presumptive evidence for human carcinogenicity is for* ***esophageal cancer****. Here (pg. 57) the authors point out, “for both PCE and TCE, there is evidence of a positive association with esophageal cancer based on the epidemiological studies,” but they then cite “‘lack of supporting evidence from toxicological studies.” What does ATSDR mean by “lack of supporting evidence?” Why are the cancer findings from animal bioassays NOT “supporting evidence?” … I note that there was also in increase in esophageal cancer in the Linet (2015) study with benzene. To me, that’s at least some limited human evidence for this disease from three of the four contaminants. I strongly suggest that ASTDR provide a better analysis and reasoning for their classification and consider changing their conclusion of “below equipoise evidence.” I point out that the classification of interest is for the contaminated drinking water at Camp Lejeune. When there is positive (limited) epidemiologic evidence for three of these known water contaminants, doesn’t that count for something?*

**Response: The review is focused on the epidemiological evidence and the tables provide this information. The animal data and mechanistic information were considered in our evaluation of each disease when such data and information existed. Instead of a table for this information, a separate subsection is provided for each disease when this information is available. As far as we know (and according to the reviews by IARC, EPA and NTP), there are no animal data for esophageal cancer and TCE or PCE.**

3. For each exposure-disease relationship covered in our assessment, is the summary of the evidence and concluding classification sufficiently supported by the information provided in the disease table and the discussion that follows the table, or do we need to include additional information (e.g., findings from animal studies), to support our conclusion?

*Comment 3.1. See my comment The 4 tiered IOM (2009) classification system proposed by ATSDR for the “presumptive disability decision-making process for Veterans,” is meant to include evidence from animal and mechanism studies. Findings from animal studies are also included in the EPA, NTP, and IARC classification systems. However this ATSDR draft seems to give animal bioassay and toxicity data disproportionately less weight in its strength of evidence categorizations. For example, vinyl chloride caused mammary gland tumors in rats, mice, and hamsters; and lung tumors in mice. While these results were discussed for lung cancer, they were not even mentioned for mammary cancer. (While none of the carcinogen classification systems stress animal-to-human site-concordance necessity for presumptive human carcinogen classification, the EPA Carcinogen Risk Assessment Guidelines state that same site concordance increases the likelihood of human carcinogenicity in that organ.)*

**Response: It is true that in most instances, the epidemiological evidence is given much stronger weight than the animal data. In the revised draft, we have included mechanistic information when available and gave it strong consideration in the assessments. This was already done for bladder cancer and cardiac birth defects in the draft that was peer reviewed. In the revised draft, we have included and considered mechanistic information for kidney cancer, the hematopoietic cancers, liver cancer, Parkinson disease, scleroderma, and kidney diseases.**

**There were no epidemiological studies that we are aware of that evaluated vinyl chloride exposures and breast cancer. Therefore we did not evaluate vinyl chloride for this cancer.**

4.   Do you have any suggestions on how to strengthen our assessment of the evidence for any of the diseases evaluated (e.g., is their toxicological information that could be added to strengthen the assessment?)

*Comment 4.1. See comment to (2) and comment 3.1, above. Also note that, according to the evidence classification schemes, site non-concordance is NOT the same as no animal carcinogenicity. Furthermore, multiple tumor sites in multiple animal species, even if not specific to the site of interest, should carry more weight for presumptive human carcinogenicity than one, or no tumor sites.*

*Comment 4.2. I think that ATSDR should look for certain key epidemiology studies of very high quality for each contaminant/disease. Often, these are large retrospective cohort studies with JEM’s, good follow-up and good exposure-response analysis, so that a few key studies can provide the high quality evidence to support classification conclusions for several cancers.*

**Response: The purpose of the review was not to establish the evidence for TCE or PCE as carcinogens. This is the role of IARC, NTP and EPA. Our goal was to evaluate each disease for which there was some indication in the epidemiological literature that an association exists (e.g., a positive finding in one study with adequate exposure information). For this exercise, it is important that the animal data be relevant to the particular disease under evaluation. For example, if a rodent study found an increased incidence of tumor at a site different than the cancer under evaluation in this review, then there must be evidence that the finding in the rodent study is relevant to the cancer under evaluation.**

**We agree with the 4.2 comment and have revised the draft to emphasize specific studies as well as the meta-analyses for each of the diseases that were assessed in this report. For some diseases, no meta-analyses were available, so the revised document provides a discussion of individual studies in more detail than the peer-reviewed version.**

Reviewer’s Comments on Specific Topics.

1. Lack of sufficient information on level of contaminants in the Camp Lejeune Drinking Water.

*I feel, strongly, that this document would be improved with the inclusion of contaminant identification and level tables very similar to Tables 1 and 2 from Bove et al. (2014a). It is important for the reader to know which contaminants and at what levels the residents were exposed. The number of months exposed above the EPA’s maximum contaminant levels (MCL) is also of high interest (see also my comment B below):*

**Response: These tables have been added to the appendix.**

1. ATSDR Comments on adequacy of the Camp Lejeune Families Act’s 30-day minimum residency requirement at Camp Lejeune as eligibility for compensation.

In this Draft, ATSDR comments on “Duration of Exposure,” (pages 7 and 8), ATSDR concluded that, “**It is ATSDR’s position that the minimum exposure duration of one month in the 2012 Honoring America’s Veterans and Caring for Camp Lejeune Families Act is an appropriate minimum exposure duration and should be considered by the VA in developing its program for presumption at Camp Lejeune.” (page 8**).

The supporting evidence presented for this conclusion includes a statement that evidence from the “Camp Lejeune mortality studies tends to support a 30 day minimum duration with elevated risks … an exposure duration of 1-3 months.” (pg. 8) Also, the evidence for cardiac birth defects presented provide additional support that short exposures could be hazardous, if only for cardiac birth or developmental defects.

I think that this ATSDR conclusion could, and should, be further supported with the arguments, e.g. that 1 month of exposure to TCE from the Hadnot Point system (average of 355.5 µg/L is equivalent to 71 months of exposure at the TCE MCL (5 µg/L). And that is ONLY for TCE. Monthly Equivalents for PCE can also be in the high teens. While these equivalents are lower for VC and benzene, exposures are still > than their corresponding MCL’s. Furthermore, all these concurrent exposures can be additive to risk. So, although 30 days exposure might seem low at first, further analysis should solidify ATSDR’s support for their conclusion. I add that these MCL’s are concentrations derived from cancer unit risk estimates for 70 year exposures and 1/100,000 *de minimus* risk levels (I think).

At least worth a mention is increased dermal and inhalation exposure to the contaminated water through bathing and showering.

**Response: Text has been added to describe exposures for marines in training at the base. There is some disagreement as to whether the drinking water exposures at Camp Lejeune are comparable to inhalation and dermal exposures in occupational settings. The Camp Lejeune mortality study made this case that the drinking water exposures at the base were comparable to occupational exposures using the concept of “liter-equivalent” to combine inhalation, dermal and ingestion of contaminated drinking water and computing a daily intake of TCE. However there is uncertainty about whether this approach is appropriate. For example, occupational exposure to TCE is mostly inhalation whereas a drinking water exposure is in general about half inhalation and dermal and half ingestion. This difference may have implications for the absorption, distribution, metabolism and excretion of TCE and its metabolites. Because of this uncertainty, the revised draft simply mentions the amount of drinking water consumed via ingestion, inhalation and dermal that might occur for a marine in training in a hot climate such as NC.**

1. Hazard Identification using Risks for Each Contaminant vs. Risks for a Complex Mixture

In general, I think that ATSDR’s approach of using each contaminant separately for supporting evidence of each of the 15 individual hazards requested is well founded (i.e. treating the water as contaminated vs. a complex mixture). I don’t know if ATSDR also adequately present the studies of risk to “similar” complex chemical mixtures. For example, dry cleaners are used as an occupational exposure group surrogate for PCE exposure. The Cape Cod drinking water study was also only contaminated with PCE. But other exposures were compound (see Andreotti and Silverman, 2012). For pancreatic cancer, for example, and other diseases analyzed here, if effects for compound exposures to chlorinated hydrocarbons similar to the Camp Lejeune complex of contaminants in drinking water, or air, had been examined, these diseases might be upgraded to “above equipoise.” I know this is not an easy task, but I think it merits discussion, at least.

**Response: The studies that evaluated chlorinated solvents or aromatic solvents are included in the tables for the diseases. These studies were considered in the assessments but many had serious limitations such as small numbers of exposed cases and a limited exposure assessment (which is why many of the studies did not attempt to analyze individual chlorinated or aromatic solvents), and the findings for some of these studies were mixed (elevated risk in one sex only) and did not add any clarity to the epidemiological evidence provided by studies that did evaluate the individual contaminants separately.**

1. Discussion of the Bove et al. Camp Lejeune studies.

ATSDR’s Frank Bove et al have written a fine series of papers on exposure, disease and mortality at Camp Lejeune relating to the drinking water contamination there. I suggest that ATSDR include either an Appendix or a section at the beginning with a summary, analysis and critique of their findings, focused on how they apply to identifying the cancer and disease hazards of interest here. Their studies and findings are directly applicable to the purpose of this report.

**Response: The revised draft mentions the results of the Camp Lejeune mortality studies and mentions that the findings in these studies was a driving force for this review.**

1. ATSDR’s Use of Meta-analysis to Support Hazard Identification

In at least several of their disease analyses, ATSDR often refers to meta-analyses as being a benchmark for support of hazard ID. However, meta-analyses are highly varied in the populations they study, often combine results from studies of highly varying quality, and often limit their breakdown categories to “exposed” vs. non-exposed in order to get a summary average OR or RR, solely to get an overall “strength of association” and a confidence interval. In my opinion, and I have done a few meta-analyses, use of meta-analysis publications for hazard ID should not be put on the same plane as should studies of high quality, especially those showing strong associations and significant dose-responses. Some meta-analyses are much better than are others, and their quality and usefulness to task must be evaluated. Several of ATSDR’s conclusions, e.g. PCE and kidney disease, esophageal, and lung use statements like, “this evidence might be strengthened by a future meta-analyses.” No! Evidence is strengthened by better studies and better analyses. In my opinion, the ATSDR for several of their conclusions wisely relied on the carefully analyzed and highly reviewed evaluations of IARC, EPA, and NTP.

**Response: We agree. The revised draft takes this comment into account by identifying and discussing key individual studies as well as the meta-analyses, by including information on publication bias and between-study heterogeneity that was reported by a meta-analysis, providing the number of studies and the number of exposed cases included in a meta-analysis if such information was provided by the meta-analysis, and by providing a critique of a meta-analysis that included studies of low quality.**

1. Formatting, Numbering and Titling Tables and Sections.

An editor could make this look a lot better. For example, most of the tables are now titled “ XXXXX Cancer: 5-year survival % (SEER): …..” This makes no sense to me for two reasons: First, titles should tell us what’s in the Tables; second the SEER survival rates have almost nothing to do with the ATSDR analysis or the tables. If I were to estimate the population impact of this contamination, or even the increased individual risks, I would use them, but that’s not done here.

**Response: The 5 year survival % has been removed from the tables, and is mentioned only when necessary in the text.**

1. A Final Summary Table.

There needs to be a final summary table on how ATSDR categorizes the weight (you really are categorizing “weight” NOT “strength”) of evidence for > 30 day exposures to the Camp Lejeune drinking water during the period 1957 – 1985 for the 15 diseases. Categorizing the evidence for each contaminant separately is not really being responsive to your client’s needs, and this table doesn’t have to include a whole lot of information. The table can be preceded by a paragraph or two of how you came to your final conclusions. The final table itself should prominently appear near the beginning of the report, and might even have a column directing the reader to the pages where the evidence is analyzed. One final note: this drinking water contains four known human carcinogens, these people were exposed unwittingly, and Congress has already approved compensation.

**Response: It was decided to frame the review as an effort to integrate the findings from the Camp Lejeune studies with the findings in the epidemiological literature and not focus on the VA’s decision for presumption. (In other words, the VA is no longer the “client” for this report.) Therefore we have a summary table for each contaminant and disease instead of the summary table proposed by the peer reviewer.**

**Reviewer 2**

1. **The reviewer provided a list of new articles that should be considered for inclusion in the review. We have included all of them (except for the zebrafish article since there is sufficient evidence from other animal data for TCE and cardiac birth defects).**

2.   Are we interpreting the epidemiological evidence and available toxicological information for each exposure-disease relationship appropriately? Particular emphasis on the mechanistic information provided for PCE and bladder cancer.

The peer reviewer agreed with our assessment of the mechanistic information for bladder cancer but had concerns about our assessment of Parkinson disease: *I have, however, some concerns about the conclusions for Parkinson’s disease (PD) which labeled TCE and PD as “Equipoise and above evidence for causation based on epidemiological, animal and mechanistic studies”. This seems a strong conclusion given the few and relatively inconclusive epidemiologic study results this is based on. There are only 2 positive TCE specific studies and a meta-analysis of solvents; one study that specifically refers to TCE and not just solvents and was emphasized in the report is Goldmann et al that reported strong associations but relied on very few exposed cases (N=10 and only 3 exposed controls) and the meta-analysis combined data on solvent exposures from 2 cohort studies that did not find associations and a larger number of case control studies with an overall positive summary estimate, but these case control studies relied mostly on self-reported solvent exposures with potential for recall bias and did not specifically investigate TCE. The newer studies by Bouwer and van der Mark published after the meta-analysis estimated RRs of less than 1 for PD and high exposures to chlorinated solvents. Thus, it seems that the epidemiologic information is at the least insufficient to make a clear determination. The strong conclusion of “Equipoise and above..” would have to be made mainly based on mechanistic information (and possibly animal data) suggesting that TCE interferes with PD relevant pathways and causes Parkinsonism in animal models, but has not been sufficiently described. Specifically, even though the conclusion in the overall summary of evidence states that the conclusions are based on animal data, the discussion of TCE and PD does not even refer to or present any animal data to support this.*

*Primarily it seems that the Parkinson’s disease evaluations are not using the same criteria as some of the cancer studies, e.g. the esophageal cancer conclusions are weaker than for Parkinsons even though there seems to be a lot more epidemiologic data suggesting positive associations for these cancers. Even more so for cervical cancers, where there are strong exposure response trends in several large incidence cohort studies with urinary biomarker data, especially the Hansen et al, Antilla et al. and Raaschou-Nielsen et al. incidence study. It seems that the conclusions for cervical cancers and possibly esophageal cancers are too weak and not ‘on par’ with the rest of the report; i.e. the evaluations of other cancers and PD.*

**Response: We respectfully disagree with the peer reviewer on our assessment of the evidence for TCE and Parkinson disease, but the revised draft provides more of the rationale for our conclusion concerning the evidence.**

**We agree with the reviewer concerning cervical cancer. ATSDR is in the process of updating our assessment and will publish the assessment at a later date.**

**Our assessment of esophageal cancer has not changed since the findings from the epidemiological studies have been mixed and there is no supporting animal or mechanistic data.**

3.   For each exposure-disease relationship covered in our assessment, is the summary of the evidence and concluding classification sufficiently supported by the information provided in the disease table and the discussion that follows the table, or do we need to include additional information (e.g., findings from animal studies), to support our conclusion?

*Answer:*

*See above my answer to question 2. As far as the epidemiologic studies are concerned the review seems generally well conducted and mechanistic information is mentioned in several places. However, I recommend that in all instances in which the conclusion in the overall summary is ‘equipoise or above’ and reads “based on mechanistic and/or animal data” these data are presented. This has been done for many but not all outcomes; e.g. reports from IARC, NTP, EPA etc. have been appropriately cited in terms of these data. But when there is no such review, the animal data should still be mentioned when a conclusion of ‘equipoise or more’ has been drawn in part based on them, one such example is liver cancer in addition to PD (see above).*

**Response: We agree and have added a section for animal and mechanistic information for each disease in the revised draft when that data or information are available.**

4.   Do you have any suggestions on how to strengthen our assessment of the evidence for any of the diseases evaluated (e.g., is their toxicological information that could be added to strengthen the assessment?)

*Since I am not a toxicologist, I cannot comment on the existence of additional supporting data. In terms of the epidemiologic data however, formal meta-analyses would go indeed a long way; i.e. without such analyses it is much harder to come to a conclusion about the evidence. But as the report states the time was too short to conduct such analyses and for some outcomes there wouldn’t even be enough data for such a meta-analytical approach to be justified. However, another improvement would be to add sample size and exposed case numbers to the tables’ information about new studies published after meta-analytical summaries were published and also in those instances in which no meta-analysis has been performed yet. It would also help to sort the study lists according to some criteria such as cohort or case control studies, industry based or population-based etc. otherwise it is very hard to understand why some may have been more influential for the conclusions than others. Alternatively the text needs to be more explicit about which of the studies are more important or considered more influential than others. I suppose this the intent in the kidney cancer table where the Hansen et al and the Vlaanderen 2013 studies are considered low intensity and duration? Although this is not further substantiated with data and seems more like a commentary by the authors of the report?*

**Response: The revised draft has added the information requested to the tables. The text also mentions key studies when applicable. The section of the report on kidney cancer has been revised to describe the Hansen and Vlaanderen studies and their limitations in detail.**

**Reviewer #3**

The reviewer made suggested edits and provided comments in the margins of the draft. We have revised the draft based on these edits and comments.

2. *I wonder if the things assigned to the category “below equipoise evidence for causation” is such a broad grouping that it loses its utility to convey information. It covers a situation where there is some evidence but it does not rise to the level of “Equipoise and Above” as well as where the evidence is not sufficient to make a decision. I do not think it is a good idea to combine these two situations. It was the prostate and breast cancer assignments that go me thinking about this. They just seem weaker than some other assignments to this category. I recognize, however, that it may just be that I lose perspective about the strength of the data for different cancers as I move from one site to another. For sites without a meta-analysis this is especially difficult. This may be a problem for others also.*

**Response: In the revised draft, we mention when we think the evidence is insufficient to determine whether an association exists. But then we classify the evidence as below equipoise.**

3. *There is a discussion of possible of effects of exposure misclassification on estimates of relative risk on page 6, but I did not see where, or how, the principles mentioned there were included in the ASTDR conclusions regarding the link between the various exposures and diseases.*

**Response: In the revised draft, we mention this bias (and other biases) in the text for a disease evaluation when it is a salient issue for that disease. As we state in our overview section, all of the studies are limited by exposure misclassification, but most of the occupational studies used either a JEM and/or expert reviews by industrial hygienists, and the drinking water studies used modeling methods. These approaches would provide adequate exposure assessments.**

4. *I liked the “Appendix” table on possible confounding in the various studies. I only saw it cited one time in the text. May have just missed other citations, but it is an excellent summation and could be mentioned at various places in the text.*

**Response: We do only mention it once, however the information in the table is used in the text discussion of specific diseases, in particular, those that are smoking-related, in the revised draft.**

5. *The “Overall Summary of Evidence” table on pages 9 – 10 indicates when other organizations support your assessment of “Sufficient evidence.” You do not provide any such supporting information for your other conclusion categories. I realize that IARC, EPC and NTP do not have any categories exactly described as your “equipoise” categories, but the lack of the conclusions by the other institutions gives the impression that they conclusions differed from yours. In many cases, this is not the case, it is just slightly different words are used to describe the categories of less than sufficient evidence. I think you need to include conclusions of these other institutions somehow to avoid the conclusion there is serious disagreement with your conclusions*.

**Response: In the revised draft, we have removed this information from the summary table. Instead, we mention the positions of IARC, EPA and NTP in the text discussion for each disease, where applicable.**

**Reviewer #4**

Are the individual disease tables sufficiently comprehensive to make our case or did we omit an important epidemiological study that should be included in the tables?

*Most of the tables are fine; however, the following additions/changes should be made:*

*1. Text should be added to introduce the overall summary table. The types of kidney disease should be added in a footnote. Text should also be added to introduce the individual tables.*

**Response: We have decided not to add text to introduce the summary table and individual tables since we are not sure what is needed to introduce these tables other than what is mentioned in the overview section. The specific kidney diseases that were evaluated (when provided by a study) are mentioned in the table for kidney disease.**

*2. Kidney Cancer Table: Add kidney cancer results from Aschengrau et al., 1993. Results for exposure duration and intensity seem to be missing for Hansen 2013 and Vlaanderen 2013.*

**Response: Done.**

*4 NHL Table: Vlaanderen results for PCE median intensity are unclear. Is the RR for exposure above the median?*

**Response: The table clarifies that it is the 90th percentile not the median.**

*5. Multiple Myeloma Table: Vlaanderen 2013 results for PCE median intensity X prevalence and median cumulative exposure are unclear. Are the RRs for above the median cumulative exposure?*

**Response: 90th percentile, not the median. This is clearly stated in the table.**

*6. Bladder Cancer Table: Give numerical data for exposure response gradients for the Vlaanderen 2014 meta-analysis. These data should strengthen your argument for sufficient evidence for causation.*

**Response: The exposure response gradients mentioned in the Vlaanderen 2014 meta-analysis are for the individual studies included in the meta-analysis. These gradients are presented (along with other information) for each of the individual studies in the bladder cancer table.**

*7. Kidney Disease Table: Define ESRD. Are the Radican 2006 results for incidence or mortality? What are the overall RRs observed in Silver 2014?*

**Response: The revised table provides all the information available for each of these studies. ESRD is now defined as per Radican et al 2006.**

*8. Rectal Cancer Table: Paulu et al. 1999 examine colorectal cancer combined and, I believe, that most of the cases were colon cancers. This should be noted in the table and text.*

**Response: This is noted in the revised draft.**

*9. Scleroderma: I would add a table for these findings. It will make the results easier to digest.*

**Response: Done.**

Are we interpreting the epidemiological evidence and available toxicological information for each exposure-disease relationship appropriately? Particular emphasis on the mechanistic information provided for PCE and bladder cancer.

*I believe that you are interpreting the available evidence (including the evidence for bladder cancer) appropriately, but I would revise the interpretation based on the following comments:*

*1. Throughout the text, you need to clarify when the animal and toxicological evidence is null vs. when it is just not available.*

**Response: the review is focused on the epidemiological evidence and considers animal and mechanistic data when available and when it provides support for a positive association between a contaminant and the disease under evaluation. For example, the assessment of TCE and multiple myeloma supplements weak epidemiological evidence with strong animal and mechanistic evidence to conclude that the evidence is above equipoise. If only the epidemiological evidence were considered, the evidence would not be sufficient to achieve equipoise for TCE and multiple myeloma. Null animal evidence was not considered because of our emphasis on the epidemiological evidence and because of our view that positive epidemiological evidence trumps null animal evidence. Therefore, the review did not attempt to determine whether animal studies were null or just lacking, since in either case, the information would not provide support for positive epidemiological evidence.**

*2. You need to better justify your conclusion for NHL. Why isn’t the epidemiological evidence for PCE as strong as for TCE? What exactly do you mean by lack of supporting animal and mechanistic evidence?*

**Response: Done. The revised draft goes into more detail on the rationale for our conclusions concerning NHL.**

*3. You need to better justify your conclusion for TCE as leukemia. Give references for the animal data on autoimmune disorders. Elaborate more about the supportive animal and human data for immune disorders.*

**Response: Done. The revised draft provides this additional material. In particular, the leukemia section discusses the recent study by Bassig et al 2016 that found that TCE affects lymphoid cells and benzene affects both lymphoid and myeloid cells among workers in a Shanghai plant. We reference the EPA toxicological review of TCE for the animal studies.**

*4.* *You need to better justify your conclusion for TCE and pancreatic cancer. It seems to rely quite heavily on the gender differences. A closer look at the studies included in the meta-analysis might reveal positive associations for TCE among men. The elevated risks among women also may be relatively unstable due to small numbers.*

**Response: More detail is provided in the revised draft. We disagree with the reviewer. The Hansen et al study had 21 exposed cases among women workers and clearly had an elevated risk (SIR=2.18, 95% CI: 1.35, 3.34) whereas male workers did not have an increased risk based on 17 exposed cases (SIR=0.88, 955 CI: 0.51, 1.41). The other study, Radican et al, had small numbers of exposed cases among women workers (n=7) so the risk estimate was elevated (RR=1.71) but unstable. Nevertheless, the RR for male workers indicated no excess risk (RR=0.91) based on 39 exposed cases. In other cohort studies, male and female workers had RRs at or near the null value.**

*5. The justifications for prostate, cervical, and brain cancer are quite brief and should be more detailed. The cervical cancer section should also mention HPV infection, a well- established cause for this cancer.*

**Response**: **More detail is provided in the revised draft. The assessment for cervical cancer and lung cancer has been removed from the report because ATSDR is updating its assessment of these two cancers and will publish the assessment at a later date.**

*I think that it would be useful to provide information on the inclusion criteria for the meta-analyses. You want to be sure that all of the major studies were included in your assessment.*

**Response: We did not conduct a meta-analysis. We mention in the overview section that studies are included in the tables: (1) if they are not included in a meta-analysis or (2) if they were included in a meta-analysis but provide additional information on exposure-response gradients.**