Author's response to reviews

Title: Evaluation of mortality among Marines and Navy personnel exposed to contaminated drinking water at USMC Base Camp Lejeune: A retrospective cohort study

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Author's response to reviews: see over
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Dear EH staff,

Thank you for your review of the manuscript “Evaluation of mortality among Marines and Navy personnel exposed to contaminated drinking water at USMC Base Camp Lejeune: A retrospective cohort study”.

We have carefully considered the reviewers’ excellent comments and revised the manuscript. Changes made to the manuscript include stating that long-term follow-up is necessary to provide a comprehensive assessment of the effects of the drinking water exposures at Camp Lejeune, adding text discussing the possible impact of confounding by smoking, adding text discussing the potential impact of non-differential exposure misclassification on the findings, clarifying how exposures to TCE in occupational settings relate to the drinking water exposures to TCE at Camp Lejeune, adding text about male breast cancer, and several other edits and clarifications recommended by the reviewers.

Responses to all the peer reviewer comments can be found below.

We feel that we have addressed all of the reviewers’ comments and hope that you will consider the manuscript acceptable for publication in your journal.

Sincerely

Frank J. Bove, Sc. D
Senior Epidemiologist, ATSDR

Reviewer: Aaron Blair

Reviewer’s report:
Comments for authors

General Comments:
This is an important study on environmental exposure to solvents. Environmental studies are challenging. The study design and analytic methods are well done. The findings make a very important contribution to the literature on hazards from solvent exposures.

Page 3 – The conclusion seems more tentative than I would expect based on the study findings and literature on these exposures. There are limitations of this study, but most would seem to lead to an under-estimate of risk. In addition, there is considerable literature linking these exposures with cancers observed here. The final sentence in the “Conclusion” in the Abstract might be made for an investigation of exposures that did not have such a relevant literature already available.
Response: We agree and have changed the last sentence of the abstract to read as follows:

“Because less than 6% of the Camp Lejeune cohort had died by the end of the study, long-term follow-up would be necessary for a comprehensive assessment of the effects of exposures to the contaminated drinking water at the base.”

We also have changed the first sentence of the conclusion in the abstract to be less tentative about the study findings: “The study found elevated HRs in the Camp Lejeune cohort for several causes of death including cancers of the kidney, liver, esophagus, cervix, multiple myeloma, Hodgkin lymphoma and ALS.”

Specific Comments:
Page 6, paragraph 2 – Cite the IARC review of TCE and PCE. I think the NAS had evaluated some of these solvents also. Might want to comment on their conclusions also.

Response: We have added the IARC review citation in this section. The NAS reviews are superseded by the EPA and IARC reviews.

Page 13, paragraph 1 – Subtracting the log HR for smoking related diseases, i.e., stomach cancer, from the HRs for diseases of interest is a useful procedure. I am a little concerned that this might be an over-correction because it is based on stomach cancer and not a disease more strongly associated with smoking. The authors might also make predictions of the maximum smoking effect likely based on the literature and the likely correlation between smoking and level of water contamination.

Should also analyze smoking-related causes that are known to be associated with solvents by exposure level. If smoking is confounding the relationship, ALL smoking-related causes should show an exposure response gradient. Show these analyses for these outcomes in Table 6. No real reason why stomach cancer should show this confounding relationship and it not be seen for lung cancer.

Response: On page 16, last paragraph, we discuss the possible confounding effects of smoking for the Camp Lejeune vs Camp Pendleton comparisons. We mention that the highest HR among the smoking-related, non-solvent-related diseases was 1.15 for stomach cancer indicating that the confounding effect of smoking would be no higher than 13% based on this finding. We have added to the text here that the HRs for the other smoking-related, non-solvent related diseases were 1.08 and 1.04 for COPD and cardiovascular disease, and that some of the smoking-related, solvent-related diseases such as laryngeal cancer and oral cancers have HRs less than 1.0 so that the confounding effects of smoking are likely less than 10% for the comparisons between Camp Lejeune and Camp Pendleton.

In the discussion section where confounding by smoking is discussed, we added the following text:

“For the comparisons of cumulative exposure within Camp Lejeune, there is mixed evidence of confounding by smoking. For example, the HRs for oral cancers and stomach cancer are between 1.4 and 1.8 which would indicate the potential for considerable confounding by smoking. On the
other hand, the HRs for COPD, esophageal cancer, and pancreatic cancer are all less than 1.00 indicating no confounding by smoking, and the results for lung cancer, bladder cancer and cardiovascular disease (i.e., HRs between 1.10 and 1.20) indicate that confounding by smoking would be no more than 15%. Given these results, the cumulative exposure comparisons within the Camp Lejeune cohort should be minimally affected by confounding due to smoking.”

Table 6 – Indicate that the referent group is the unexposed population from Camp Pendleton.

Response: Table 6 presents the results of cumulative exposure comparisons within the Camp Lejeune cohort. The referent group consists of those in the Camp Lejeune cohort with the reference levels given in Table 5 (e.g., ≤1 µg/L –months for the comparison of cumulative exposure to PCE). We have added text to Table 6 to make this clear.

Supplemental Material Table S3 provides results for cumulative exposures to the contaminants with the Camp Pendleton cohort as the referent group.

Page 15, paragraph 3 – The comparisons in Supplemental Material, Table S3 for low exposure and higher exposure is a useful way to evaluate exposure-response trends to assess the possibility of influences other than solvents on disease risks. It is easy, however, to over interpret the lack of a monotonic trend because the CIs of almost all of the comparisons of the HRs for the various outcomes overlap. Many of the ups and downs are probably just noise.

Response: We agree and, although we did emphasize those trends that were monotonic, we did not dismiss trends that were not monotonic, such as those observed for leukemias and ALS. We added a sentence in the methods section, subsection d “Interpretation of Findings” after the sentence defining monotonic trend: “Because exposure-response trends could be distorted by biases such as exposure misclassification, we also emphasized non-monotonic exposure-response trends when an elevated HR was observed in the high exposure group.”

Page 16, paragraph 4 – Although the adjustment for the HRs for diseases of primary and secondary interest by the excess HR for stomach cancer is a reasonable and useful approach to attempt to control for possible confounding by tobacco use, it should be noted that this is probably an over adjustment. If confounding by smoking, then all of the outcomes most strongly associated with tobacco use would show this, not just stomach cancer. Thus, it is likely that some of the stomach cancer excess, perhaps all, is an over-adjustment just based on a chance excess. This possibility should be mentioned in the discussion.

Response: Please see our response above regarding the issue of confounding by smoking.

Page 21, paragraph 1 – Not clear what the authors think is the best comparison of occupational air concentrations for the drinking water levels in this study. Is it the air levels in 1950s to 1980s, or the levels in Denmark in the 1980s? This would help orient the reader regarding the size of the HRs observed here in relation to those from occupational studies, giving the level of exposure. My
sense is that the HRs observed here are consistent, given the exposure levels, with what has been reported previously. Just would be nice to see this more clearly laid out.

**Response:** In this paragraph, we do state that TCE levels estimated to have occurred in the 1950s through 1980s, i.e. 38 ppm, would result in exposures “considerably higher than an exposure to a marine consuming Hadnot Point drinking water.” On the other hand, TCE levels estimated in Danish industries during the 1980s, which may also reflect levels in U.S. during this period, are more comparable to those occurring from drinking Hadnot Point drinking water at Camp Lejeune. We agree that additional clarification is needed and have added the following text:

“However, TCE concentrations in industry have decreased over time in the U.S. By the 1980s the geometric mean concentration of TCE in Danish industries was approximately 4.3 ppm [3,32], and this level of air concentration of TCE would result in exposure comparable to the drinking water exposure to TCE at Camp Lejeune. A meta-analysis of occupational studies conducted by EPA that evaluated “any TCE exposure” obtained RRs of 1.27, 1.23 and 1.29 for kidney cancer, NHL, and liver cancer, respectively [7]. Similar findings were observed in this study for kidney cancer and liver cancer, but not for NHL, when the Camp Lejeune cohort was compared to the Camp Pendleton cohort.”

Page 21, last paragraph – Not sure what is meant by the comment that Camp Lejeune rates were compared with the U.S. rates to “address concerns raised by some in the exposed population.” The paragraph goes on to discuss the “healthy veteran effect” which is a real concern. But this would seem to be an argument not to use the general population for comparison rather than use it.

**Response:** We have edited the paragraph to clarify why we compared the mortality rates at both bases with the U.S. mortality rates:

Although Camp Pendleton did not have contaminated drinking water, it was similar to Camp Lejeune with respect to NPL sites located on the base. A public health assessment conducted by ATSDR at Camp Pendleton found “no apparent public health hazard” from these toxic waste sites [14], however the potential for exposure could not be ruled out. Therefore, we decided to compare both the Camp Lejeune and Camp Pendleton cohorts to the U.S. mortality rates. We realized that it was unlikely that any of the mortality rates at Camp Lejeune or Camp Pendleton would be elevated compared to the U.S. mortality rates because of the healthy veteran effect bias [29]. The effect of this bias is sufficiently strong to produce SMRs of ≤0.80 for cancer mortality when military personnel are compared to the U.S. population [29]. Moreover, since the median age at the end of follow-up was only 49 years, we expected that it would be too soon to observe elevations in either cohort. Nevertheless, we observed SMRs > 1.0 for three diseases of primary interest in the Camp Lejeune cohort: kidney cancer, multiple myeloma, and cervical cancer.

Page 23, paragraph 2 – Would it be possible to provide an indication of the degree of exposure misclassification, which could then be used to estimate the relative magnitude of under-estimation of disease risk?

**Response:** It is likely that the sensitivity of the exposure classification for the comparison between Camp Lejeune and Camp Pendleton is very high, i.e., very few of those classified as unexposed
(the Camp Pendleton cohort) would have an exposure to these contaminants. (The sensitivity of the exposure classification is equal to the proportion of the truly exposed who are classified as exposed, which is also equal to 1 – the proportion of the truly exposed misclassified as unexposed.) In this case, a reasonable estimate of sensitivity would be 0.98. On the other hand, the specificity of the exposure classification would be much lower because it is likely that some of those in the Camp Lejeune cohort may not have been exposed to the contaminants. This would occur for example if a Camp Lejeune cohort member was training at another base (although his/her unit was classified as being at Camp Lejeune). It could also occur if the marine was residing off-base or in areas that did not receive contaminated drinking water during the marine’s period of residence, and the marine did not train in areas of the base supplied by contaminated drinking water. A reasonable estimate of the range of specificity would be between 0.70 and 0.85. (This range was estimated from a preliminary review of 1,000 survey responses from the Camp Lejeune cohort.) With a sensitivity of 0.98 and a specificity ranging from 0.70 to 0.85, the HR for kidney cancer in the comparison between Camp Lejeune and Camp Pendleton, corrected for non-differential exposure misclassification could increase between 6% and 18% (HR could increase from 1.35 to between 1.43 and 1.59).

It is much more difficult to evaluate the magnitude of exposure misclassification in the cumulative exposure comparisons within the Camp Lejeune cohort. It is likely that the overall sensitivity would be much lower, e.g., between 0.80 and 0.90 based on our preliminary review of 1,000 survey responses, and the overall specificity would be about the same as above. However, the sensitivity and specificity within each categorical level of cumulative exposure would be difficult to speculate.

We have added text to the exposure misclassification section that briefly discusses the possible magnitude of the bias for the Camp Lejeune vs Camp Pendleton comparisons.

I think it might be useful for the authors to discuss the confidence they have in the relationships between specific exposures and outcomes. Do the distributions for the various exposures look different across the population? It was mentioned that they were correlated, which raises the question whether or not effects from individual exposures can be separated?

Response: The correlations between the categorical cumulative exposure levels are between 0.85 and 0.98, i.e., highly correlated. The correlations between the continuous variables for cumulative exposure are highly correlated (> 0.94) between TCE, vinyl chloride, benzene and TVOC (because high levels of these contaminants occurred in the Hadnot Point system whereas only PCE was elevated in the Tarawa Terrace system), but the correlation between PCE and the other contaminants, although high, are considerably lower, ranging from 0.46 to 0.56. The results of the cumulative exposure analyses reflect these high correlations so it would be difficult to separate the effects of each of these exposures. We mention in the methods section that these exposures are highly correlated and therefore we analyzed each contaminant separately (page 11). We have added text to emphasize the difficulty of separating the effects of each of these contaminants.

Page 23, paragraph 3 – Although it is possible, smoking confounding is not likely to bias relative risks downward, as implies here. Would be useful to estimate how different the smoking rates at the two bases would have to be to account for the disease excesses observed. Should also note that smoking would also have to
be positively associated with estimated exposure levels to cause the exposure-response patterns. Is there any evidence that smoking is associated with the levels of solvent exposure from water at Camp Lejuene? Also if smoking is driving the excesses observed, there should be some discussion of why other smoking-related causes are NOT elevated. Smoking confounding should be discussed, but further comment on what would be required for it to account for the positive findings is needed.

**Response:** We added text in the “Confounder assessment” sub-section of the Methods section mentioning that for confounding to occur, the risk factor must be associated with exposure as well as with the disease.

**Level of interest:** An article of outstanding merit and interest in its field

**Reviewer:** Ann Aschengrau

**Reviewer's report:**

This important manuscript provides long-awaited information on the relationship between exposure to contaminated drinking water and mortality from cancer and other chronic diseases among military personnel stationed at Camp Lejeune. The research was well-conceived and soundly conducted and the data were appropriately analyzed. This manuscript should be published once the minor issues described below are addressed.

**Minor Essential Revisions:**

**Abstract:**

1. State that “Follow-up for mortality began in 1979 and ended in 2008.”

**Response:** We agree and have added this to the abstract.

2. State that “Cause-specific Standardized Mortality Ratio were calculated using U.S. rates as the reference.”

**Response:** We agree and have added this to the abstract.

**Methods:**

**Study Population:**

1. State the location of Camp Pendleton.

**Response:** We have added the location of Camp Pendleton:
2. Give available evidence documenting that there was no contaminated drinking water at Camp Pendleton. Also comment on the presence of other contaminants/exposures at Camp Pendleton that could affect the mortality rates in that cohort.

**Response:** We have added a citation for the Public Health Assessment at Camp Pendleton and briefly described its findings, i.e., that there was “no apparent public health hazard” from exposures to the NPL sites and that the drinking water was not contaminated during the period when the Pendleton cohort was stationed at the base.

**Confounder Assessment:**

1. Provide available information on the success of the method used to “adjust” the results for unmeasured confounding by smoking in other studies. Are there any validation studies to show how well this method actually works?

**Response:** The article referenced (Richardson et al, ref #23) provides information on the basis for the approach. The article compares the approach to an actual dataset where information was available on smoking to show that the approach adjusts for virtually all the bias from smoking.

**Results:**

1. Someone will inevitably ask why there were no elevations in male breast cancer mortality in the Camp Lejeune cohort. You might want to respond by stating the reported cluster is comprised of incident cases. A general statement about the distinction between incidence and mortality for other diseases might also be useful.

**Response:** We do not know if the reported cases of male breast cancer constitute a cluster or not. However, we have collected data from the Veterans Affairs cancer central registry (VACCR) and from the National Personnel Records Center in St. Louis, MO and are currently evaluating whether the data are sufficient for a case-control study that would assess whether exposures to the drinking water contamination at Camp Lejeune increased the risk of male breast cancer incidence. We have added text in the discussion that mentions that one death occurred in the Camp Lejeune cohort whose underlying cause was male breast cancer and that ATSDR is currently evaluating the data regarding conducting a case-control study of male breast cancer incidence.

**Discussion:**

1. Paragraph 7: The phrase “to address concerns raised by some in the exposed population” should be clarified.

**Response:** We have added text to clarify that the concern was that Camp Pendleton had NPL sites and that exposures to toxic chemicals could have occurred to the Camp Pendleton cohort. For this reason, we compared the Camp Lejeune and Camp Pendleton cohorts to the U.S. mortality rates.

2. Paragraph 1 of Limitations: Give the range of residence times at Camp Lejeune.
Response: We have added in the text the standard deviation and range for the average residence in months at Camp Lejeune.

3. Paragraph 4 of Limitations: It would be helpful to show available demographic characteristics of the Camp Lejeune cohort according to cumulative exposure levels. Showing no differences according to known risk factors will bolster the argument that unmeasured factors do not vary by cumulative exposure levels.

Response: We have decided not to show the demographics by cumulative exposure for each contaminant because of the number of tables this would entail. Instead, we have added text to the sub-section “Analyses internal to the Camp Lejeune cohort” in the Results section to describe the distribution of demographics among the cumulative exposure categories. The reference group and low cumulative exposure category for each contaminant had a higher percentage of officers, females, “white” race, and education than the medium and high cumulative exposure categories. The analyses of cumulative exposure did adjust for sex, race, occupation (blue collar/white collar) and rank (officer/enlisted).

4. Conclusion: Mention the need for continued follow-up of the Camp Lejeune cohort.

Response: We agree and have changed the last sentence of the abstract and the last sentence of the conclusion section of the manuscript. The abstract now reads as follows: “Because less than 6% of the Camp Lejeune cohort had died by the end of the study, long-term follow-up would be necessary for a comprehensive assessment of the effects of exposures to the contaminated drinking water at the base.

5. You also might want to mention that inevitable errors in cause of death information are likely to be non-differential.

Response: We agree and have added this to the manuscript in the discussion of limitations section.