Author's response to reviews

Title: The influence of the water distribution system on the assessment of population exposure to chlorination by-products

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Editors
Environmental Health

Dear Editors,

We are pleased to submit the second revision of the manuscript entitled after the first revision *THE INFLUENCE OF WATER DISTRIBUTION SYSTEM OF THE POPULATION EXPOSURE TO CHLORINATION BY-PRODUCTS*, MS: 1068883755366253. Following the editor’s comments, the title of this paper was modified in order to follow the Instructions for Environmental Health authors on the title format: *THE ASSESSMENT OF POPULATION EXPOSURE TO CHLORINATION BY-PRODUCTS: A STUDY ON THE INFLUENCE OF THE WATER DISTRIBUTION SYSTEM*. This manuscript version includes the comments and the suggested revisions made by the reviewers and editors on the second version. The marked copy of the manuscript (added in additional material files) illustrates the changes that have been made. The responses to the comments and the suggested revisions are included in this file.

With thanks in advance, please feel free to contact us if you have further questions or comments.

Yours sincerely,

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RESPONSES TO REVIEWER’S COMMENTS AND SUGGESTIONS
MS: 1068883755366253

THE INFLUENCE OF THE WATER DISTRIBUTION SYSTEM ON THE ASSESSMENT OF POPULATION EXPOSURE TO CHLORINATION BY-PRODUCTS

by Legay, Rodriguez, Sérodes and Levallois

We thank the three reviewers and the editor for their highly relevant comments and suggestions. The following is a detailed description of how we addressed the suggestions/corrections made by the reviewers, as well as an explanation of the modifications made. Changes were made in the new version of the paper in accordance with comments from the reviewers. These changes are indicated in red in the marked copy of the paper. Text that was removed is also indicated in this copy. Section numbers, paragraphs (Pages and Lines) mentioned in the author’s responses are those of the marked copy. Comments by reviewers on the original paper are shown in blue.

REVIEWER 2
The authors have addressed my comments.

REVIEWER 3
The authors have satisfactorily responded to all of my original comments.

REVIEWER 1
General Comments
The revision of the manuscript addresses most of my concerns. In addition there were some changes in terminology introduced that I find confusing. Both of these are identified in the specific comments below.

At a general level, my major remaining concern is that most epidemiological studies have not focused on a single water system and/or single water sources. The continued use of combined groups of chemicals as indicators of CBP stands in the way of getting at relationships based on routinely gathered information or information that is readily calculated. My main concern is that the toxicology among members of the haloacetic acid class are very different and the relative amounts of the trihalo, dihalo and monohalo members of this class can vary significantly by the nature of organic carbon in the source water (and maybe whether chlorine or chloramine disinfection is used). The differences the toxicology of the THMs on the other hand are trivial. I recognize that this kind of detail is not critical to this manuscript, but I would like to for epidemiologists to
recognize that there is information in routinely gathered data that they are not even pursuing. These differences may make have a larger impact on the associations with outcomes than spatial differences in occurrence within the distribution system.

Again, this criticism does not detract from the results of the present paper as it is making a more general point that I think is important and is made clear by the new title. However, I suspect even within this system there would be some differences in the character of the subclasses of HAAs when the source water is a flowing stream vs. a lake or reservoir during certain parts of the year that would end up adding to the spatial diversity of exposure assessments even within this system. It appears that most of the sources are lakes or reservoirs in this case, but there has to be an explanation for the very high variability of some of those systems, while two within each system appear pretty stable. Such variability may well show up in the relative amounts of the HAA subclasses that are being produced and this would imply a different character of the organic carbon in each of those sources.

Response: We agree with the reviewer’s comments. In fact, the use of data on combined groups of CBPs does not differentiate the presence (which is different according to the water source supply and treatment) and thus the impact of individual compounds or subclasses. Future studies should focus on this latter point which could be carried out using available data (e.g., individual THMs and HAAs from regulatory data).

Specific Comments

1. Page 7. Lines 15-17. This is sentence is confusing on several levels. THMs and HAAs are not compounds they are a group of compounds, which can be loosely called classes (depending upon what you think is more important, the degree of halogen substitution or the acid functional group). More important, I do not understand “In order to minimize the temporal impact of the occurrence”. It would seem that this approach actually enhances (limited of course by the frequency of sampling) the ability to identify temporal variations in a subject's exposure assessment.

Response: Following the reviewer’s comment, we replaced “these compounds” by “THMs and HAAs” (Page 9 Lines 16 and 17) to describe that this sentence was focused on compounds included in THMs and HAAs (i.e., individual THMs and HAAs).

About “In order to minimize the temporal impact of the occurrence”: In fact, in the assessment of the CBP exposure during each trimester of the subject’s pregnancy under study, we used monthly data. However, important seasonal variations are observed in the area under study. This seasonal variability differs according to systems (Figures 2 and 3). As shown in Figures 4 and 5, the intensity of the spatial variability of CBP levels in systems differs according to seasons thus the difference between CBP levels measured at two different locations in a system could vary according to seasons. As a result, the impact of using one method to assign CBP data vs. another method could be also different according to seasons. Moreover, the difference between the spatial variability of CBP levels within a system observed for each season varies according to the system (Figures 4 and 5). In order to avoid misclassifications in the study of the impact of the applied method on the CBP exposure assessment (including the study of the influence of
the system) due to this temporal variability, we studied different trimesters of pregnancy for each subject (which represented different periods and thus different seasons of the year).

2. In regard to the first part of the above comment, the use of "CBP species" in other places within the ms. (e.g. p. 20 line 21, p. 21 line 15) is very confusing. That term appears to have been eliminated in the marked up copy, where its use was clear, and technically correct. In the latter pages "species" seems to be referring to the class of DBP, which is clearly incorrect.

**Response:** Yes we agree, the use of “CBP species” in the manuscript may be confusing. Therefore, “species” was replaced by “class” or “classes” in Page 3 Line 8, Page 23 Line 9, Page 24 line 3. Also, the term “species” in Page 10 Line 3 from the previous marked copy version of the manuscript was replaced by “compound” (Page 10 Line 21 from the new marked copy version) because we were referring to each individual THM and each individual HAA measured.

3. Page 21, lines 14 & 15. There are differences the mechanisms among individual DBPs that should be of concern. However, the major differences are among monohalo-, dihalo-HAAs and the trichloroacetic acids (the brominated trihaloacetic acids may act through the dihalo HAA intermediate, but TCAA is very poorly metabolized). Just breaking these up into those groupings would provide more specificity to the exposure assessment. The odd thing is that the measurements of individual compounds have been made, but no use is made of this data.

**Response:** In fact, the study of the relationship between human health defects and individual compounds or subclasses (particularly for HAAs) could easily be achieved in future work with existing data.

4. Figures 4 and 5. It seems peculiar to refer to quarterly averages as trimesters. That term is technically correct, but sort of implies that it corresponds to how subject's exposures may have been assigned and as a result is confusing. Consider changing the designations to quarters both in the figure legends and in the text (e.g. page 14). Alternatively, explain why you are designating them as trimesters.

**Response:** Modifications were carried out according to the suggestions made by the reviewer (Page 17 Lines 2, 4, 5 and 7; Figures 4 and 5)

**EDITOR’S COMMENTS**

In reviewing your manuscript, we have noted the following requires editing:

- On the cover page the title should be in the format of A versus B in the treatment of C: a randomized controlled trial.
**Response:** Following the Instructions for Environmental Health editors on the title format, the original title of this paper was modified as “The assessment of population exposure to chlorination by-products: A study on the influence of the water distribution system”.

- Below the title, the authors should be listed as first and last name with a superscript number after the last name indicating the author’s institution(s) of affiliation. Then, list the institutional addresses with an assigned superscript number before them. A line with a symbol and then the phrase "Corresponding author" should be inserted. The symbol should be placed after the superscript number of the corresponding author. Lastly, the heading Email addresses should be inserted and the initials of the authors and their corresponding email separated by a colon and listed in sentence format with the pairs separated by a semi-colon e.g. JD: johndoe@university.edu.

**Response:** Done

- The line numbering and page numbers should be removed.

**Response:** Done

- The headings in the abstract should appear above the text and the colon removed.

**Response:** Done

- The numbering of the headings in the body of the manuscript's text should be removed.

**Response:** Done

- The italicized text (other than in the references) should be changed to normal.

**Response:** Done

- Numbers greater than 999 should have a comma after the thousands marker e.g. 480,000.

**Response:** Done

- The conclusions should state clearly and succinctly the main conclusions of the research and give a clear explanation of their importance and relevance. Please tighten up and shorten this section.

**Response:** Following the editor’s comments, the conclusions were modified and shortened (Page 22 Lines 7 to 13, Page 22 Lines 15 to 17, Page 23 Lines 1 to 5, Page 23 Lines 14 to 18).

- Before the Acknowledgments, please insert the headings Abbreviations, Competing interests and Authors’ Contributions section.

**Response:** Done

- For further guidance and proper wording, see the Instructions for Authors. The references should be formatted as number, period, space and reference and without the issue numbers. Only references cited may be included in the text or must be removed from the references section e.g. #34 and #35.
**Response:** Modifications in the references section were carried out according to *Instructions for Authors*. Regarding the references 34 and 35, they are cited in the text (Page 24 Line 4). As a result, these references are included in the references section.

- Tables on a landscape page must be reformatted onto a portrait page or submitted as additional files.

**Response:** Tables (Table 1 to 6) on a landscape page were reformatted onto a portrait page.