

## **Author's response to reviews**

**Title:** Impact of Tetrachloroethylene-Contaminated Drinking Water on the Risk of Breast Cancer: Using a Dose Model to Assess Exposure in a Case-Control Study

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**Author's response to reviews:** see over

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Authors: Veronica Vieira, Ann Aschengrau and David Ozonoff

### **Editorial Comments**

*Your revised manuscript should be in strict accordance with our instructions for authors, cf. the pre-acceptance checklist at <http://www.biomedcentral.com/info/edgr-preacceptcheck.asp>.*

*Please upload a Word copy or .rtf format. The type of study should be included in the title (i.e. - "Comparing x and y to reveal z: a case-control study"). Make sure author names listed are identical to those in the online submission system. Department addresses should be separated. Please change periods after subheadings in abstract to colons. Please make sure entire paper is unjustified with no hyphens at line breaks (you may use 'soft' returns – shift+enter). The appendix should be uploaded as an additional file, not as part of the main text. If no competing interests, please just state "none declared". The tables need to be formatted in close accordance with the instructions at <http://www.ehjournal.net/info/instructions/>. You may want to look at one of the previously published papers for guidance.*

- We have made the appropriate changes to the tables and removed the Appendix from the manuscript.

**Anna Axmon:**

#### *Major concerns*

1. *The definition of exposure is rather unclear. Although the authors make an effort to explain the different exposure levels, the concept of non-exposed are not introduced until in the results-section.*
  - The Data Analysis section has been revised to include a more thorough explanation of the exposure categories (pages 8-9).
2. *To find out the number of subjects in each category (cases / controls, proxy / non-proxy, and exposed / unexposed) I had to collect information from the text, table legends and tables, and perform calculations on my own. It would be helpful if this information was given in a table or figure, or at least in the text.*
  - A table has been added that contains the number of subjects in each category to make it easier for readers (Table 1).
3. *The authors state that the distribution of core confounders were similar among non-proxy subjects and all subjects. Furthermore, they found the odds ratios similar in the non-proxy analyses and in the analyses with all subjects. Nevertheless, they decide to use only non-proxy subjects in their final analyses, thereby losing 30% of their observations. Why? (See also minor concerns)*

- The authors had no choice but to use only non-proxy subjects because questions pertaining to bathing habits and drinking water consumption (which are necessary for calculating the personal delivered dose) were not asked in proxy interviews. We clarify this point in the Data Analysis section (page 8).
4. *In several places in both Results and Discussion do the authors mention specific odds ratios to show that exposure has an effect on the outcome. However, none of the odds ratios presented in the paper is statistically significant, and several of the confidence intervals provided are very large. However, in almost all cases (different latency periods, and different measure of exposure) the odds ratio for breast cancer increases with a more strict definition of exposure. This should be emphasized rather than individual odds ratios with wide confidence intervals.*
- Additional text was included in the Results section to emphasize the point that odds ratios increased with latency and exposure level (page 11).

#### *Minor concerns*

1. *The authors present odds ratios adjusted for a large number of factors. What approach was used to determine which factors should be included in the model? Did they correlate with exposure and outcome? Did they result in a change-in-estimate? Or was there any other reason for including them?*
- A group of core confounders was controlled in all regression analyses: age at diagnosis or index year, family history of breast cancer, personal history of breast cancer (before current diagnosis or index year), age at first live birth or stillbirth, and occupational exposure to PCE. These factors were chosen as confounders *a priori* based on the current scientific literature. Additional potential confounders were added to the logistic regression models along with the core confounders, including history of benign breast disease; past use of diethylstilbestrol, oral contraceptives, and menopausal hormones; cigarette smoking history; alcohol drinking history; history of ionizing radiation treatment; quetlet index (measure of obesity); race; marital status; religion; education level; and physical activity level. None of these additional variables changed the adjusted estimates by more than 10%, and so the final models included only the core confounders. We have clarified this point in the text (page9).
2. *The authors state that there is no difference between non-proxy subjects and all subjects with respect to the core confounders. This is most likely due to the fact that the non-proxy subjects constitute a major part of all subjects. It would be interesting to know if the non-proxy subjects are similar to the proxy-subjects with respect to the same core confounders.*
- We do not believe that the distribution of core confounders among proxy subjects is relevant to this analysis. Readers interested in the distribution of core confounders among proxy subjects can calculate the percentages using the numbers provided in the table for non-proxy and all subjects.

3. *It is stated that a goodness-of-fit analysis was performed on each model (PDD and RDD), and that there was a close agreement between the measures. The results of these analyses should be provided numerically.*
  - The authors thought that presenting pages of deviance values for every analysis would be tedious for the reader, when the results could be summarized in the text. If the editors feel the manuscript is not suitable for publication without the results of these analyses, the authors will insert the table upon request. However, we have included the table as an additional file in addition to the Appendix.
4. *Several abbreviations are introduced in the paper. However, some abbreviations are actually used before they are defined, and some abbreviations are not used even though they have previously been defined.*
  - Appropriate changes were made to the text with regards to abbreviations.
5. *Rather than presenting the 25 subjects with the highest RDD and PDD rank (table 1), the authors should give the number of subjects who had different exposure levels of RDD and PDD.*
  - The table presenting the 25 subjects with the highest RDD and PDD rank was removed. A sentence was added to the Results section (page 10) stating that 39 of the 189 exposed subjects had different exposure categories for RDD and PDD.
6. *It would be helpful if the number of observations in each cell was included in table 2.*
  - The authors added the number of observations to Table 2.
7. *Page 23 is the same as page 30, and should be removed.*
  - The page was removed.
8. *Most of the table legends do not provide enough information for the tables to be read without reading the text. More specifically, in the legends to tables 1 and 4, abbreviations are used without having been previously defined. In the legend to table 3, it is not stated whether the analyses are performed on RDD or PDD.*
  - We have clarified the legends. The analyses in Table 3 were ever PCE-exposed versus never exposed, and were therefore not specific to RDD or PDD.

Judith Klotz:

*Of the 19 comments below, those I consider major are numbers 1-3, 5, 6, 8, 9, 14, 16.*

*1. This manuscript has the potential to make contributions toward two important questions: (1) whether exposure to PCE might be a risk factor for breast cancer and (2) to what extent, and under what circumstances, are personal exposure data drawn from interviews useful in assessing potential associations of contaminants and health outcomes. The manuscript as it stands as of November 2004 has data gaps that I believe*

*need to be rectified before the paper is useful toward these ends and ready for publication. The writing is overall clear and well organized.*

*2. In particular, some questions in this reader's mind were addressed only when reading the earlier paper (References # 4 and #5, Aschengrau et al. 1998 and 2003). The current paper should be able to stand alone, even though it is based upon and further develops the earlier work.*

- In addressing the specific comments below, the authors feel we have revised the current manuscript so that it can now stand alone.

*Exposure characterization and distributions:*

*3. The paper should specify (tables recommended) the actual distributions of responses to the queries on showering, drinking habits, including the distributions of subtotals for inhalation, ingestion and dermal exposures, so that it can be determined which of these were the most important sources for calculated doses. Subsequently, there should be a table of the modeled exposure distributions in the non-proxy data using only RDD and also using PDD models.*

- As stated in the Discussion section, the distribution in bathing habits were similar with regards to interview data, making the percent contributions from inhalation, ingestion, and dermal absorption similar among the subjects. Data on model parameters and exposure routes is beyond the scope of this paper and will be written up in a technical paper.

*4. It would be helpful to specify earlier than page 13 that both RDD and PDD are cumulative rather than average annual quantities.*

- Additional details concerning the models were added to the manuscript (pages 4, 8-9).

*5. Comment on the possible role of faulty recall, particularly comparing recent to distant past. There is ample literature indicating that very recent recall (several days or weeks) is less apt to be biased compared to recall for many years ago.*

- Women were interviewed in 1997 about residential histories up to 40 years before diagnosis/index year (1987-1993) so there was no recent recall in this study. In the Discussion section, we include faulty recall as a possible bias in the study.

*6. The original units and distributions from which the RDD and PDD percentile categories were derived are not specified. This reader had to go back to the 1998 paper to determine that the RDD was intended to be based on milligrams of PCE.*

*In particular, this paper should include more description of what constitutes "unexposed", the lowest exposed group, and the higher exposed groups.*

- The units are now clearly stated in the paper. In addition, the exposure categories are described in more detail in the Methods section (pages 8-9).

7. *Regarding the RDD modeling: was there any actual measurement data that were used to verify the model results?*

- A validation study was performed but the results are not yet published.

8. *What evidence if any leads you to expect that the distributions of showering, bottled water use, drinking habits, etc. are either typical or atypical of this locale and typical or atypical of the U.S.? These are important considerations if you intend the results to refer to the larger populations.*

- We have no knowledge that the bathing habits in this population are representative of other populations. As stated in the Discussion section, a limitation of the PDD model is that bathing habits in the population do not vary enough to make a large difference in the PDD model. This may or may not be true for other populations.

9. *Were swimming pool activities included in the PDD modeling? If not, why not?*

- No. The study area of Cape Cod is close to beaches and we decided that swimming pools were not a major source of exposure.

*Statistical analysis and presentation of results:*

10. *I found the nested percentile approach interesting but novel: Acknowledging that it was also used in the 1998 and 2003 papers (references 4 and 5) can you cite other case control studies for which it's been used? It would be helpful to compare (or at least cite a comparison for) the odds ratios yielded by the nested percentile approach vs the more traditional quantile approach.*

- The authors know of no other PCE–exposure study that uses nested exposure categories. The numbers were too small when using mutually exclusive categories.

11. *Goodness of fit data are mentioned on page 12 but no data are presented.*

- See Reviewer 1, Comment 3 above.

12. *like the presentation of the non-parametric comparison of RDD and PDD.*

- The comment is unclear so we are unable to respond.

*Interpretation:*

13. *I would suggest beginning the discussion section with material from the top of page 13, i.e. “we would expect moderate elevation in risk observed in RDD to increase further in the current PDD analysis etc”. Although on the whole the writing in this paper is clear, the text presentation of results often gets confusing and the general picture is lost in the details.*

- The Results section has been revised with more of a focus on the comparison between the model results and less on the odds ratios themselves.

14. *As above, the Discussion section of the manuscript text relies too much on the results of references #4 and #5 without providing the reader with enough information from those earlier papers to evaluate the comparison of the previous analyses according to modeled comparative drinking water concentrations vs an exposure model that includes the personal exposure variables that were queried via interview and that form the focus of this paper. In particular, the odds ratios and their confidence intervals from the earlier papers should be specifically cited in this paper in order for the reader to evaluate and compare the two sets of findings.*

- Because the original RDD study used all the subjects, results from the PDD analysis can not be compared to results of the original RDD analysis. This is why the RDD analysis was recalculated using only non-proxy subjects. The odds ratios and confidence intervals for the restricted RDD analysis are provided in Table 4. While the manuscript makes reference to the methods used in the previous papers, the data necessary for comparing the different model results are all provided within this manuscript.

15. *State what you mean by ‘low’ and ‘moderate’ odds ratios. 1.0 to 1.5 and 1.5 to 1.9, respectively?*

- The manuscript has been revised so that the terms ‘low’ and ‘moderate’ are no longer used to refer to odds ratios. In the original papers, ‘low’ described odds ratios ranging from 1.0 to 1.4, ‘moderate’ described odd ratios ranging from 1.4 to 1.9, and ‘high’ described odds ratios above 1.9.

16. *Whereas I agree with avoiding over-reliance on p values, the degree of precision of the OR estimates, as indicated by confidence intervals, are important considerations in evaluating the likelihood those OR estimates. The discussion does not seem to put any weight on the relative width of the C.I.s (or to note those that do or don’t exclude 1.0)*

- The focus of the paper was to compare the results using two different exposure models. Because the widths of the CIs were generally the same for the two models, we do not devote much space to discussing it, but we do mention it on page 11.

17. *The fact that PCE is carcinogenic under some circumstances does not necessarily indicate that it must be carcinogenic to breast tissue under typical community exposure scenarios.*

- The biologic rationale stems from a hypothesis described by Labreche and Goldberg (1997) that organic solvents such as PCE may act either directly as genotoxic agents or indirectly through their metabolites to increase the risk of breast cancer.

18. *Latency: other than the findings of the previous paper, do you have any a priori data that would suggest that 15 years or other specific latencies for breast cancer are most pertinent?*

- We do not. We considered latency as far back as the data would allow. At 19 years latency, the numbers were too small to perform adjusted analyses.

19. Did you consider analyzing only the more recent interview data to explore the possibility that faulty recall might be less operative for more recent time periods?

- That was not possible in our study because the earliest possible exposure began in 1968-1969 with the installation of PCE vinyl-lined pipes and ended in 1980 with the flushing and bleeding of pipes these pipes. Considering subjects were not interviewed until 1997, there was no recent interview data. Also, reducing the number of exposed would limit the latency analyses we could perform.

**Neil Pearce:**

*The topic that the paper addresses is of interest. In principle, the fact that the results from the PDD analysis did not differ greatly from those of the RDD analysis, should not count against publication, because it is potentially an important methodological finding that there was little difference*

*The major problem is that the data set that is used doesn't show much of an association between PCE exposure and breast cancer. If you want to see which dose model shows a stronger dose-response then you need to have a reasonably strong dose-response to start with. Unfortunately, the data set used just doesn't have the power to do this, both because the numbers are small and because the dose-response association is too weak.*

- We acknowledge that the number of exposed subjects is small and limits the analyses we can perform, but the modest association consistently observed in earlier studies warranted a follow-up.

*A second issue is that, despite the general problems of continuous dose-response analyses, and the general advantages of using categories, this is one example where a continuous dose-response analysis is required, because the categorical analysis has very low power. Even if the dose-response curve is not quite the right shape, it should be monotonically increasing and one would therefore expect the better dose measure to show a stronger continuous dose-response.*

- The distribution of exposures was heavily skewed to the left with a small percentage of extremely high exposed. The RDD model was a relative estimate designed with exposure categories in mind. Using a continuous exposure measure would require remodelling the RDD to include constants and variables that were not included in the original model, which is beyond the scope of this manuscript.

*Table 1 could just be summarised in the text.*

- The content of the old Table 1 was summarized in the text and was replaced by a new Table 1 that describes the number of cases/controls, exposed/unexposed, and proxy/non-proxy subjects.

*It's not really necessary to show both the crude and adjusted ORs in table 3, since assessment of confounding is not the main issue here. The adjusted ORs are sufficient. There is also no need to have such a large number of latency categories.*

*The same comments apply to table 4.*

- We have revised the tables to only include adjusted odds ratios. We kept the latency categories to show how odds ratios tended to increase with higher latency.