Author’s response to reviews

Title: Drug use disorder following early life exposure to tetrachloroethylene (PCE)-contaminated drinking water: a retrospective cohort study

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“Drug use disorder following early life exposure to tetrachloroethylene-contaminated drinking water” by Ann Aschengrau, Alexandra Grippo, Michael R. Winter, Margaret G. Shea, Roberta F. White and Richard Saitz

Reviewer 1: Thanks you for your positive comments.
Reviewer 2:
Major comments:
1. The formal DSM 5 diagnosis of drug use disorder requires that two or more of the 11 established criteria be present in a one-year period. Because this was a retrospective study, our survey ascertained the lifetime presence of each of the criteria. As such, we did not investigate the formal diagnosis of drug use disorder and tried to be careful about the language we used to describe our outcome variable. That being said, we conducted additional analyses that examined the lifetime presence of two or more criteria and have added them to the manuscript. The results were similar to those for any criteria of drug use disorder (adjusted RR: 1.3, 95% CI: 0.9, 2.0).
2. We did not obtain physician confirmation of the drug use disorder criteria. This fact has been added to the text.
3. Information on the criteria for drug use disorder was obtained only during Phase 2. Phase 1 obtained information only on ever use of certain illicit drugs. This had been clarified in the text.
4. Thank you for providing the Alofe et al. reference. The discussion now includes a sentence about the possibility of a non-linear dose-response relationship.
5. At the reviewer’s suggestion, we conducted the main analyses stratified on sex at birth. We found that the modest association remained among females (adjusted RR: 1.5, 95% CI: 1.0, 2.3) but that no association was present among males (adjusted RR: 1.0, 95% CI: 0.6, 1.5). While the interpretation of possible effect modification by sex is hampered by the smaller proportion of male respondents (34% males vs. 66% females), these results have been added to the text.

6. A footnote has been provided in Table 2 with the types of mental disorders included in these percentages. These include (in descending order of prevalence): anxiety, depression, post-traumatic stress disorder, eating disorder, bipolar disorder and schizophrenia. Two mental health disorders (anxiety and eating disorders) were added to the Phase 2 questionnaire; hence the increase in the prevalence of mental disorders from Phase 1 to Phase 2.

Minor Comments:
1. The final analysis excluded 76 subjects who only had childhood exposure to PCE. This was because the numbers were too small to provide stable results. The different numbers between Tables 1 and 2 is noted at the beginning of the statistical analysis section.