Author's response to reviews

Title: A cohort study of the association between secondary sex ratio and parental exposure to polybrominated biphenyl (PBB) and polychlorinated biphenyl (PCB)

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Author's response to reviews: see over
Dear Editors and Reviewers:

We would like to thank the Reviewers for their additional comments. Changes to the manuscript have been included in this final and complete version, where necessary. Our responses to the reviewers are as follows:

Editor’s Comments:

**Referee 2:**

1) *I do not see why the authors feel that it is inappropriate to combine people with PBB levels below the limit of detection with those that have somewhat higher levels. Surely this is a more continuously distributed contaminant and the 1microg/L is simply an analytic issue with no relevance to the biological significance of that cutoff. If for some reason, people with levels below this cutoff are in fact categorically different from those with levels above it, then the grouping may be necessary, but if so, I think this needs to be clearly explained. Otherwise the very small referent category is of concern to me. This is not just a power issue, but also with such a small category (n=19 or 11 in the PBB models with both parents) random fluctuation can much more dramatically affect the overall results. I would feel much more confident about more equally distributed groupings (as the authors did for levels above the LOD). If not split at the median (as the authors did do in response to my earlier comment for the individual parent analyses, but*
didn’t mention the results of the combined parent exposure approach using medians), then perhaps equal tertiles or even perhaps look at non-linear smoothing techniques.

PBB is a continuously distributed contaminant; however, evaluating PBB exposure as a categorical variable is important because it allows us to assess a dose-response relationship between varying levels of parents’ exposure and the outcome, offspring sex. We agree with the Reviewer, that small numbers are a limitation that may cause random fluctuation, but our results were quite consistent when exposure was categorized as two groups (split at the median levels) and three groups (at or below the limit of detection and split at the median above the LOD).

As suggested, we have changed our main analyses to include where PBB exposure was categorized as two groups (split at the median levels). These results (previously presented in the text only) have been moved to the tables (Tables 2 and 3). For consistency, we have also updated Table 4 for PCB exposure in the same manner (split at the median levels) and any additional analyses presented in the text.

Exposure categorized as three groups (at or below the limit of detection and split at the median above the LOD) is now described as additional analyses in the text for enrollment PBB exposure and estimated PBB exposure (results with enrollment PCB have been removed altogether). We have added that the referent group was based on small numbers and produced a wide confidence interval (Discussion section, 1st paragraph).
2) In the new version the crude secondary sex ratio is now not shown in any of the tables. A column should be added for these by category to tables 2-4. While I understand these would be crude (and the column could be so labeled), I think they are still important to see.

We have added the crude odds ratios to Tables 2-4 as suggested.

3) I still don’t understand why the authors don’t use all available children for the maternal only analyses (1,392 vs. 865 that were used). While it may be as the authors say that sex is primarily determined by the father, the issue is how are PBBs or PCBs acting. The very conclusions of this paper are suggesting that there is a maternal component, and the authors are doing and showing results of maternal only analyses that include children for which there isn’t data on the father.

We have added the odds ratio for the maternal enrollment PBB only model for all available data in the text of the Discussion section (n=1392 offspring, n=865 born 1975-1988, n=527 born 1989-2005). We found that the results were consistent to what we presented in Table 2, Model 1 (maternal PBB ≥ 3 µg/L: AOR=1.04, 95% CI: 0.85–1.28; referent group: maternal PBB < 3 µg/L). We now explain why we restricted our maternal only analyses to births from 1975-1988 in the Discussion section: considering births over the long time period (1975-2005), we could not effectively account for secular trends in sex ratios. Further, the estimated maternal PBB at conception for the later births would have been based on maternal PBB collected more than 13 years before their birth resulting in additional measurement error. Finally, our results did not suggest a maternal effect of PBB exposure on offspring sex, except in combination with paternal exposure.
Referee 3:

1) p. 7 Methods – first paragraph under Study Population. The information that is given in the last three sentences (starting with “Females who were adults…”) seems unnecessary and adds extraneous detail that is somewhat confusing. Would suggest deleting these last three sentences.

We have removed these sentences from the Methods section as suggested.

2) p. 7 Methods – first paragraph under Study Population. The sentence about excluding births before 1975 because offspring could have directly ingested contaminated food products is puzzling. Why would this have any bearing on offspring sex, assuming the Author meant that they may have eaten the contaminated food after they were born? It seems to make more sense to exclude them because their parental exposures of PBB may not have been as great since the contamination occurred in 1973-1974.

We agree with the reviewer that whether the offspring consumed contaminated foods has no bearing on their sex. In fact, Michigan birth records before 1975 were not available for use in this study. We have reworded the sentence accordingly in the text.

3) p. 7 – second paragraph. The Authors refer to “first-generation female cohort members”. This seems like a wordy way of saying “mothers”. May want to consider just referring to this group throughout the paper as “mothers” for sake of simplicity.
As this was the only reference to “first-generation female cohort members” in the text, we have changed it to “mothers”.

This work represents a collaborative effort of all authors. All authors contributed to the conduct of this research and have agreed to its submission. Please address all correspondence to:

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Sincerely,

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