Reviewer's report

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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Reviewer: Amy Branum

Reviewer's report:

General comment summary

This manuscript has good intentions and potential in examining the possible influence of PBBs on sex ratio; however, it fails to make a compelling case due to a lack of discussion on potential biologic mechanisms and potential analytic errors. The Authors never set the stage for the reader as to why PCBs are also being examined in this cohort given the differences in exposures between those compounds and PBBs. The Authors do a nice job of describing the PBB exposure incident but the same type of information is never given regarding PCB exposures. The Authors also chose odds ratios, presumably using logistic regression (although the Authors never specify which family of generalized linear models was used for analysis), which are most likely overestimating the “risk” of male proportion given the high prevalence rate of male births. The Authors also never mention two important factors that could potentially influence sex ratio: race/ethnicity and gestational age. Although they used gestational age to determine conception, they never characterize potential differences in birth outcomes (i.e., low birthweight, preterm birth) that may have been more prevalent in this cohort compared to the general public.

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

1. There is only one brief mention of possible biological effect (suspected endocrine disruptor). The authors do not paint a compelling picture of why it might be important to evaluate PBBs/PCBs' effect on sex ratio. In addition, the Authors do not seem to have a clear biologic hypothesis regarding PBB exposure and sex ratio. For example, on page 11 at the end of the section on Population Characteristics the Authors state that “the overall proportion male among these offspring with potential in utero PBB exposure was 0.542…” How would in utero PBB exposure affect sex ratio?

2. The Authors need to be more explicit about their statistical analytic methods. For example, there is no mention of what link function was used in the GEE analysis or what type of regression was performed. Logistic regression and odds ratio may not be appropriate due to the high proportion of male births (i.e., a high prevalence of the outcome).

3. The discussion regarding the time period of included study participants is
confusing. In the Methods, it sounded like the final sample for this analysis was restricted to births occurring between 1975 and 1988; however, the Authors give results for a final sample size of 1,392 offspring born between 1975-2005. Which is it? It seems like the sample should be restricted to the earlier births. Is the overall sex ratio given (0.542) for the 1,392 or the 865 born between 1975-1988? This section needs to be clarified.

4. The Authors never discuss the PCB exposure but mention at the bottom of page 11 that it was continuous rather than a one-time exposure like the PBB exposure. Why is that? The Authors should give more background regarding the PCB exposure if they are going to include it in the paper.

5. Why wasn't gestational age at birth characterized in Table 1? Male birth ratio is much higher among preterm births. Is it possible that the births in this cohort had a lower mean gestational age?

6. Why is there no mention of race/ethnicity of the study cohort in the entire paper?

7. From Table 2 the Authors conclude that there was a significant increase in the proportion of males in two combinations of parental exposures, including where one of the parents had moderate PBB levels and the other parent had high PBB levels, giving a range from 0.54 to 0.62. However, there is no indication of any statistical testing that has been performed to draw these conclusions other than a multivariate analysis, which is not explained well. The proportion male among mothers and fathers with the lowest PBB concentrations (0.53) is nearly the same as that from median mothers and highest fathers (0.54). How can the Authors conclude that these are really different from each other?

8. A good deal of the discussion centers around other results regarding PCBs. Considering that the impetus for doing this study was based on the PBB exposure in this cohort and that there were no significant results with PCBs in the current study, why do the Authors spend so much time on this in the Discussion?

9. There is also a lot of focus on paternal BMI as a potential covariate when those findings were barely significant, if at all. In addition, all of the examples the Authors give for an association between sex ratio and BMI deal with maternal BMI.

10. There is absolutely no discussion of potential biological mechanisms that might explain the effect of PBBs/PCBs on sex ratio. Given the discrepancy in the Results for maternal and paternal exposures the Discussion is missing some focus on the importance of why examine these relationships in the first place.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

11. Why wasn’t gestational age at birth characterized in Table 1? Male birth ratio is much higher among preterm births. Is it possible that the births in this cohort had a lower mean gestational age?

12. Why do the Authors characterize results differently in the text compared to the tables? Why is paternal BMI characterized as “significant” with a confidence interval of (1.0, 2.1) when the CI in the table is taken out to 2 decimal places and
contains one?

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

13. It might be helpful to put the information from the 3rd paragraph regarding the categorization of PBB/PCB concentrations in a table

14. It seems as if Table 1 should just be a frequency table of characteristics about the cohort. The univariate odds ratios are a bit ingenuous since it is likely that parents were a combination of these characteristics. In addition, see note about using odds ratios in a study with a highly prevalent outcome.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests