Reviewer’s report

Title: Prenatal Maternal and Childhood Bisphenol A Exposure and Brain Structure and Behavior of Young Children

Version: 0 Date: 10 Apr 2019

Reviewer: Joseph Braun

Reviewer's report:

This study examines the potential mediating effect of white matter integrity in the association between early life BPA exposure and childhood behavior problems in 98 children from the APRON Study. This is an interesting study and the first to investigate BPA and brain structure/organization in children. The authors report that prenatal, but not childhood, urinary BPA concentrations are associated with some white matter integrity measures and that mean diffusivity of the right-inferior-longitudinal fasciculus may mediate associations between prenatal BPA and internalizing behaviors. The strengths of this study include the use of DTI and the prospective design to investigate prenatal BPA and subsequent neurodevelopment and brain structure. Weaknesses include overreliance on p-values and lack of reporting betas/CIs, some unclear methods, potential issues related to the wide age range of children, and lack of investigation into modification by child sex.

Major Comments:

1. Exposure assessment: Page 6: Please describe what urine was collected in and how child urine was collected, particularly for younger children. Were field blanks collected and analyzed? Or were other precautions taken to minimize exogenous contamination? Page 14: Most no longer believe that rank ordering is preserved with this much misclassification. See Perrier et al., Epidemiology 2016.

2. MRI and neurobehavioral measures: Page 8: Was the CBCL administered at the same time as the MRI? Page 7: Please specify what these mean measures (MD and FA) in terms of white matter integrity.

3. Study Participants: Page 6: Need to describe how this n was arrived at and why it was only a subset.

4. Statistical Methods, Page 9: Why not use linear regression and show beta's and 95% CIs? This is more appropriate. Also, there is a movement away from using p-values and null hypothesis testing; see the latest statement from the American Statistical Association. Also, why use Spearman in the CBCL analysis? Please specify the causal model basis of this mediation method? Is it Baron-Kenny? Why not use Vanderweele’s method?

5. Age Range: Did the authors consider stratifying by child age since the wide age range in the participants and known variability in DTI measures over this age range? I would be important to know if the association is consistent in younger vs. older children.

6. Context/Discussion: I strongly recommend highlighting the heterogeneous nature of this literature and the lack of consistency in sex specific associations.

7. Sex modification: Given that previous studies observe that child sex modifies the association between BPA and neurobehavior, I strongly recommend that the authors investigate this as well. It
would be important to consider these findings in light of potential sexual-dimorphisms in brain structure/organization.

Minor Comments:
1. Abstract and Discussion: How is the study cross-sectional? You have exposure measured prospectively relative to the MRI.
3. Page 4, line 37: But levels of free BPA are very low and most of the BPA reaching the fetus is glucuronidated. Doerge's work in primates and rodents demonstrates this.
4. Page 4, line 47: I would not even mention these studies as serum BPA is a potentially flawed measure of exposure.
5. Page 6: How did 2 year olds provide verbal assent?
6. Page 8, line 51: What does "comparison-wise rate" mean?
7. Page 10, line 15-17: This does not mean that your sample is representative, just the exposure distribution is similar. Also, samples of participants are drawn from populations.
8. Page 14, lines 1-14: Citations for this statement?
9. Page 14, line 12: Consider rewording "biologically relevant." I think that you mean human exposure is lower than the exposures used in animal studies.

Level of interest
Please indicate how interesting you found the manuscript:

An article of importance in its field

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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