Reviewer’s report

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

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Reviewer: Roberta White

Reviewer's report:

This interesting paper describes a study that explored whether changes in white matter microstructure, as evaluated by diffusion tensor imaging (DTI) in children aged 2-5, is associated with PBA exposure and whether DTI-detected white matter changes mediate children's scores on the Child Behavior Checklist (CBCL). Apparently, 98 children underwent DTI and of these there were CBCL scores for 56 children. The authors conclude that mean diffusivity (MD) in the splenium and right longitudinal fasciculus was associated with prenatal BPA and that splenium diffusivity scores mediated the relationship between BPA exposure and internalizing behaviors on the CBCL.

The paper could benefit from more clarity on methods, results and conclusions.

In the introduction, the authors mention brain structure changes in animal studies of BPA exposure but do not state that what these were and how they guided study hypotheses. Further, the rationale states that white matter microstructure was chosen as a possible indicator of CNS effects of BPA because "early childhood is a critical developmental period where considerable white matter development takes place." This is true, though white matter development extends into early adulthood and starts rather late in fetal development. Both prenatal and childhood BPA were explored in the study, with positive findings only for prenatal. Is the hypothesis that BPA exposure changes the trajectory of white matter development (in which case effects of prenatal exposure might be seen at any point through early adulthood) or that BPA has a direct effect at the time of exposure? What do the authors think the CBCL outcomes can reveal about BPA-mediated behavior changes and how they relate to brain structure specifically?

Were the children ages 2-5 or 2-6? Perhaps the confusion results from the oldest child or children being 5.99 (?) but the paper gives different age ranges in different places.

The section on participants does not give adequate detail to understand the study. The text states that the original cohort had 2169 mothers and 2189 children. The number of children who underwent DTI should be stated (98?) and the number children for whom there are CBCL data (56) should be stated. A table that summarizes important characteristics of the overall cohort, the DTI sample and the CBCL subsample on important variables like age, gender, BPA levels, CBCL scores etc. should be included. Was the DTI sample in any way different from the overall cohort? Was the CBCL subsample representative of the full DTI sample? Are 56 children enough to produce adequately powered mediation analyses?
The results section should have a participant characteristics data table, as mentioned above. It looks like the CBCL data indicate that some scores were at clinically impaired levels? Would these children be considered outliers and how were their scores evaluated relative to the rest of the group?

The authors state that there were 16 outcomes for the factional anisotrophy (FA) and MD outcomes on DTI for both hemispheres. Did this produce 16 outcomes or 32? Of these, only two outcomes were significant, and the authors state that "results did not withstand FDR [false discovery rate] correction for multiple comparisons." Perhaps this reviewer is misunderstanding, but this last statement seems to indicate that it is possible that the significant results are spurious?

The Discussion and Conclusions appear to rely heavily on the outcomes that may be tentative but are stated quite definitively. The MD findings, if replicated, are interesting. What are the implications for development? Could they be corrected over time or they likely to become more exaggerated (just wondering)? Also, there were no findings for FA, though this outcome is often associated with prenatal, childhood and other brain insults and neurological disorders. Does this mean anything?

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