Reviewer’s report

Title: Fetal growth in environmental epidemiology: mechanisms, limitations, and a review of associations with biomarkers of non-persistent chemical exposures during pregnancy

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Reviewer: Megan Romano

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The authors present a well-researched and very nicely written summary of a large body of interesting research investigating the influence of non-persistent EDCs on size at birth or fetal growth parameters. Some opportunities to highlight common themes across studies were not fully explored, and the manuscript would benefit from additional work to synthesize the reviewed literature and recommendations for future research directions.

1. There are a few opportunities in this review that I'd like to see the authors explore.
   a. Overall, the topic of possible effect measure modification of the associations by infant sex is a bit diffuse in the manuscript, though the discussion in section 5.3 is robust.
   i. Setting up the need to look at sex-specific associations earlier in the manuscript would improve the flow of the manuscript.
   ii. Additional detail related to observations of sex-specific effects would be beneficial. For example at lines 428-435, clarify whether the associations described among boys versus girls were due to formal assessment of effect measure modification by child sex or due to the study only including male or female infants (like reference 145 was restricted to boys). Studies restricted to one sex could be more clearly designated in the tables.

2. Section 5.1 would be improved by addressing a few additional points related to challenges of exposure assessment of non-persistent chemicals. If you feel strongly that any of these points are outside of your intended scope, then kindly add language to the section that clarifies your intended scope.
b. Address the importance of considering season of measurement for non-persistent chemicals. My research and that of others has shown evidence suggesting that chemicals like benzophenone-3 and triclosan (and to some degree organophosphate flame retardants) have seasonal exposure patterns. As birth weight also tends to follow a seasonal pattern (admittedly, exactly what this trend is and how strong it is varies given the population under study), it would be worth mentioning that consideration of season of measurement may be important to address in future research. Time of day may likewise be an important consideration (there is some indication of this in Dr. Kate Hoffman's work on organophosphate pesticides). These factors may obscure or inflate true associations if not considered.


c. Consider specifically commenting on the appropriateness of measuring chemicals in urine collected at delivery (or at least the need to carefully consider incorporating these into exposure averages). My general concern is that the hospital environment may increase exposure to chemicals such as phthalates that may be present in medical tubing used to administer fluids or triclosan/triclocarban which may be present in soaps or other products used frequently in hospital settings. I have not seen much discussion of this in the literature, but I worry that something like high phthalate concentrations measured at delivery may be a marker for a difficult labor and delivery (or proxy for increased medical intervention) which may unduly influence associations observed with birth weight as opposed to measurements taken earlier in pregnancy. It is another important point relevant to temporality issues surrounding exposure assessment raised by the authors.
Minor revisions and clarifications

1. Section 2 on potential etiologic mechanisms should be streamlined.

2. Delete "whatever you measured" at line 231.

3. Was there variability across the studies in terms of the investigators definition of IUGR? This is sometimes defined just a little bit differently by different researchers. Please comment on any discrepancies in definitions across studies or clarify that you excluded studies that did not define IUGR as "estimated fetal weight in the lowest 10th percentile for gestational age" (lines 245-246).

4. Line 279 - although you deal with this in more detail later in the manuscripts, covariates used in multivariable models were also fairly variable across studies, and this would be worth noting/briefly acknowledging both here and in the sections on other EDCs.

5. Although they may be familiar terms to most readers, it would be prudent to provide a brief definition of "high molecular weight phthalates" at line 364 and "low molecular weight phthalates" later.

6. At Line 441, specify the specific organophosphate flame retardant that was associated with reduced birth weight in girls.

7. At lines 452-455, similar concerns about at least some non-urinary measures of phthalates are also raised by reference 84. This should be stated in the section on phthalates (or this information should all be saved for section 5.1, but I think the point bears repeating throughout the manuscript as it is an important one).

8. Though I agree with the statements made, you should add some references to lines 622-628. Additionally, it may be of use to cite some studies that have examined intraclass correlation coefficients (ICCs) of the chemicals of interest, particularly where this information is available during pregnancy (I believe reference 91 contains this info for at least some of the compounds of interest).

9. In section 5.2, it would be worthwhile to mention efforts to create international fetal growth standards (such as Intergrowth-21st) and to comment on the challenges of interpreting studies that might rely on different growth curves for these purposes.
Discretionary revisions, formatting, and typos

10. I would prefer to see the authors spell out expectations as opposed to speculating about typical expectations of the readers at lines 112-114 "These associations may interact with fetal growth in the opposite direction that is typically expected but need to be carefully considered in the study of these contaminants and fetal growth."

11. At lines 210-218 the authors mention effects on fetal hormones, but don't explicitly mention the possible influence of EDCs on fetal/newborn thyroid hormones. This literature is decidedly mixed, but several of the EDCs of interest have been suggested to influence neonatal thyroid hormones. Dr. Tom Zoeller has published a few nice review articles on the topic.

12. The description of how studies were selected for the review in the methods is clear and very helpful. Though not absolutely necessary, a flowchart might be useful to help readers follow the process for selection of papers to be discussed.

13. The in text references are sometimes inside of and sometimes outside of the punctuation. I believe that inside of the punctuation is correct, but please consult journal guidelines to confirm.

14. Line 633 "number of benefits" - typo?

15. Line 762 – parental- paternal - typo?

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