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

Version: 0 Date: 10 Feb 2019

Reviewer: Jessie Buckley

Reviewer's report:

This manuscript presents a detailed review of the literature examining associations of non-persistent chemicals and fetal growth as measured at birth and in utero. This is a welcome review of the literature given the increasing velocity of research on effects of these chemicals on perinatal outcomes. The authors synthesized a large literature base, and the review will be a valuable resource for those interested in the topic. The authors find that there is little consistency of findings and suggest several potential sources of study-to-study variation that may contribute to this heterogeneity. While this review is comprehensive, it could be improved by addressing several additional points.

Major comments:

1) This review paper compelling demonstrates that variability in the exposure and outcome assessment and statistical approaches likely leads to inconsistency of published results. However, the value and impact of this review could be greater if the authors made concrete recommendations to aid investigators planning new studies or evaluating the existing literature. Are there best practices for exposure assessment, outcome assessment, or statistical approaches that can be recommended? Are there specific areas in need of methods development? Specific examples of instances when recommendations would be useful are noted in the comments below.

2) Please include the reference numbers next to the study names in the Tables. Currently, it is extremely cumbersome to link information in the text to the data presented in the tables.

Abstract

3) Here and throughout, consider replacing the term "phenols" with "environmental phenols, parabens, and organophosphate ester flame retardants" or "environmental phenols and other non-persistent chemicals": the scope of the review is on phenols arising from
environmental sources and it does not include other phenolic compounds. Parabens and organophosphate ester flame retardants are not phenolic compounds.

4) Line 9: Is instability the right word here? Perhaps high temporal variability? Instability made me think of sample degradation or other laboratory factors.

Introduction

5) Lines 94-105: Would sex hormones also be relevant in this discussion? It seems they would be particularly important for phthalates, which are anti-androgens.

Methods

6) Line 231: What outcomes are meant by "whatever you measured"?

7) Lines 238-253: It appears that child's sex and, for the OP pesticides, PON are additional criteria that could be added to this section. Perhaps also assessment of non-monotonicity if this was done systematically?

Results

8) Overall, I found this section difficult to evaluate since the references are by number in the text but by author in the Table.

9) The discussion of phthalate metabolites could be improved by considering individual metabolites or molecular weight groupings since biological activity varies among members of this large class. For example, in lines 284-290, which phthalates were associated with increased birth size and which with decreased? Was there a pattern by metabolite or molecular weight group?

10) Lines 301-307: It is unclear why tests of non-monotonicity are discussed only for these two studies. Did no other studies assess non-linear dose response relationships, or did you choose to only report on studies for which there was evidence of non-monotonicity?

11) Lines 328-355: These paragraphs state the information found in the table. This text could be condensed or replaced by a synthesis of whether the five papers in Table 1B are consistent (as was done for Table 1A). In particular, the conclusions noted in the
Summary section (4.1.3) are highly relevant but not fully discussed/supported in the preceding sections.

12) Line 372: This statement warrants a citation.

Discussion

13) Lines 593-601: How would conflicting results lead one to believe that human pregnancy is impervious to the exposures? This argument would hold if all studies were well-powered and null, but many of the studies in the table reported associations.

14) Lines 593-601: Beyond study design, it seems that there are a number of additional considerations when evaluating "conflicting conclusions" - such as differences in exposure level and population susceptibility that could result in differences in true effects between studies - these are not discussed. In particular, exposure level could be an important factor explaining differences between studies. While reporting these levels for each chemical and study is probably beyond the scope of this paper, perhaps some discussion of exposure levels could be incorporated in the text? For example, I wondered whether dichlorophenol levels were lower in the one study that did not find an association compared to the four that did (Line 424-426).

15) Line 603: Reading through the results, there is an implicit suggestion that the authors prefer studies that use repeated exposure measures (Line 314, Line 408, Line 413, Line 492), though the authors' stance is less clear when this issue is discussed in Section 5.1. While I don't disagree that repeated measures are useful, there is an open question of whether averaging exposure over all of pregnancy is always better for analyses of health outcomes: if the critical window of susceptibility were in the first trimester, averaging levels across the first, second, and third trimester may actually introduce exposure misclassification compared to the single first trimester measure. Is it known whether there is a susceptible period for the fetal growth outcomes discussed in this paper? I did not see a discussion of susceptible periods in the background section. Related, it would also be important to note if there is no evidence of susceptible periods - if cumulative exposure is indeed most important, this supports averaging exposures over pregnancy.

16) Line 603: Do you have a recommendation about the number and timing of repeated measures? Perhaps repeated measures within each trimester would allow for improved exposure assessment without compromising ability to assess susceptible periods? It may also be worthwhile to discuss potentials solutions to this issue, such as leveraging pooled samples or statistical methods for exposure measurement error correction (see Perrier et al. Epidemiology 2016; PMID: 27035688).
17) Line 603: I wondered if the authors' have a recommendation regarding type of urine sample? Were there differences in associations based on whether spot urines, first morning voids, or 24-hour urines were analyzed? There are major differences in how well each of these types of samples perform for different chemicals based on exposure sources.

18) Lines 619-621: Considering this suggestion that timing of exposure may be important, did you evaluate whether associations were more consistent among studies that assessed biomarkers in early versus late pregnancy?

19) Lines 622-628: This argument about reproducibility of low versus high molecular weight phthalate concentrations due to differences in exposure sources would be strengthened by reporting quantitative information from the literature, such as correlation coefficients or ICCs.

20) Lines 603-628: Considering these points, what are your recommendations about measurement of urinary biomarkers of non-persistent chemicals during pregnancy? There is a solid recommendation regarding temporality, but are there other "best practices" you would suggest?

21) Lines 681-686: If the lack of similarity in timing of ultrasound measurements is a limitation of the current literature base, do you have a recommendation for when these measurements should be conducted?

22) Line 708-710: Consider recommending splines or other flexible approaches for assessing non-monotonic dose-response relationships given that using categorized exposure variables (i.e., quantiles) is itself subject to limitations (see Greenland Epidemiology 1995; PMID: 7548341).

23) Lines 740-741: If there are differences in interpretation between methods, do you have a recommendation as to what statistical approach(es) should be used to assess modification by sex?

24) Line 697: I expected to see some discussion of diet as a confounder in this section. Maternal diet during pregnancy is a primary source of exposure to many non-persistent chemicals and is also strongly related to fetal growth, but often not well-characterized in environmental epidemiology studies. Do the authors have an opinion on whether confounding by diet may explain differences in results among studies, or whether information on maternal diet is a key confounder that should be addressed?
Level of interest
Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests

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

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal