Reviewer’s report

Title: Environmental risk factors of pregnancy outcomes; a summary of recent meta-analyses of epidemiological studies

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Reviewer: Rémy Slama

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'Environmental risk factors of pregnancy outcomes; a summary of recent meta-analyses of epidemiological studies'

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Environmental Health

Comments from the reviewer
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Many epidemiological studies have been published over the last years on the impact of specific exposures on birth outcomes. Instead of considering a single exposure-outcome pair, this article rightly attempts to give a broader picture of this research field. Meta-analyses dealing with the impact of environmental and occupational factors on birth outcomes are reviewed, in particular in terms of appropriateness of the approach.

Main comments:

1. There is some ambiguity in the stated aim. Focusing on meta-analyses only is probably not the best way to summarize current knowledge from epidemiological studies, which is not the main aim of the paper; instead, the methodology of the published meta-analyses is being discussed. However the formulation of the abstract may let the reader think that the aim is indeed to summarize the existing evidence. This could be clarified. Summarizing the existing evidence regarding the impact of environmental factors on birth outcomes would imply to focus on "good quality" meta-analyses and also to consider individual papers on pollutants for which the literature is scarce (which is not what authors do).

2. Meta-analyses on a given topic are presented as independent one from another (i.e. each is presented as if it brought new evidence) whereas I suspect there is a large overlap in the individual studies considered in meta-analyses over a given topic. This should be at least mentioned; moreover the results section could be rewritten so that all meta-analyses dealing with a given topic are presented successively; currently, all results from each meta-analysis are presented before presenting another meta-analysis; for example, in the part of the results discussing with water contaminants, the meta-analysis by Hwang et al (2002) on birth defects is presented, followed by a meta-analysis on THM and
foetal growth and prematurity, by another one on still birth, after which a meta-analysis by Nieuwenhuijsen et al (2009) dealing again with chlorination by-products and congenital anomalies is discussed.

Minor essential revisions:

3. Introduction: The 3rd sentence ("Various epidemiological…and pregnancy outcomes (1,2,3).") is too long.

4. Introduction, 3rd sentence: it is a bit strange to see "persistent organic pollutants (POPs)… and chemicals such as bisphenol A…" POPs are chemicals too.

5. Introduction, 1st paragraph, l.13 "supporting associations between environmental exposures and adverse…" Consider adding "specific" after "supporting".

6. Introduction, 2nd paragraph, 1st sentence "One way to address some of these issues is by combining information from various epidemiological studies…" The limitations quoted in the previous sentence include the limited number of studies available, bias and confounding and limitations in exposure assessment. To my knowledge, these are unlikely to be dealt with by a meta-analysis of the existing studies.

7. Introduction, aim (last paragraph): "Here we have conducted an evaluation of recent meta-analyses…" Authors could indicate under which aspect meta-analyses have been evaluated.

8. Introduction, l.4 before end of last paragraph "Where in addition to the main aim…." Consider rephrasing.

9. Methods, bibliographic search: I am not sure that this would change results, but I do not see why the only compound of the phenol families explicitly considered was apparently bisphenol A.

10. Methods, focus of review: it is stated in the last sentence of the first paragraph of page 6 that neonatal deaths were not considered; however in the abstract, results regarding the impact of ETS on still birth are provided.

11. Results: The confidence interval of the meta-analytical OR of preterm delivery associated with an increase by 10 µg/m3 in PM2.5 levels is very narrow (1.44-1.16); this may be worth discussing. Also, a comparison is done with the estimated effect of PM10, but was the number of studies (of subjects) the same for both pollutants?

12. Results, POPs: only the results by Govarts et al (2012) dealing with PCB 153 are quoted, whereas it is stated that pp'-DDE was also considered: could results for pp'-DDE be also mentioned?

13. Drugs may not be in the focus of the paper, but authors could consider mentioning a meta-analysis on DES and hypospadias in the second generation

14. Discussion, p.15, l.10 "resolution of measurements or the distance to the measurements stations, which could lead to some doubt to how representative these were for the population". It is clear that these measures are not representative of personal exposures. What could be discussed is the possible impact of measurement error due to measurement stations being used. However, this would be a further step in discussing the plausibility of the associations, which is not done systematically for all outcomes and does not seem to be the main aim of the paper.

15. Discussion, p.15, last sentence of 1st paragraph "The measurement error… may lead to attenuation in risk estimates… but could be compensated in the increased numbers of subjects..." First, that measurement error leads to bias towards the null should be justified by references (this is only generally true for binary exposures); second I do not see how biased ORs can be corrected by increasing sample size. Stratifying studies according to quality of exposure assessment might be a better option.

16. Discussion, p.16, 2nd paragraph before end: "...found less heterogeneity in studies of PM2.5 than PM10, suggesting that the former may be a better exposure index..." This should be justified/clarified; see also my comment above on the number of studies: the comparison is only relevant if the comparison is done for the same studies or subjects.

17. Discussion, p.16, 2nd paragraph before end: "This may have resulted at times in more conservative effects but may better reflect the reality." I do not follow; moreover a reference on the impact of using random effects models should be given.

18. Discussion, p.16, last paragraph, 2nd line: "However I² is that it is not a measure": a word may be missing.

19. Discussion, p.17, last paragraph (publication bias): authors mention that meta-analyses include a limited number of studies; is it clear that the tests of publication bias mentioned here have a good power in this context?

20. Table 2 does not read very well and is very long. I would suggest reporting measures of association with 95% CI rather than indicating "no stat sign association"

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

My only potential conflict of interest is that I do have collaborations with some of the authors.