Author's response to reviews

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

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Author's response to reviews: see over
Comments of the authors to the reviewer:

We would like to thank the reviewers for their constructive comments. They made us realise how much work we were trying to do. As a result we have worked on the scope of the paper. Furthermore, we have addressed the comments they had. Specific comments are given below.

Reviewer's report

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

Version: 1 Date: 20 September 2012

Reviewer: Gayle Windham

Reviewer's report:

This paper takes on the large task of reviewing meta-analyses on a number of chemical risk factors in relation to several adverse pregnancy outcomes. While this is an important topic, the paper suffers from a lack of focus and presentation of new insight or recommendations.

Major Compulsory Revisions:

It is not clear whether the authors wish to present a review of exogenous risk factors for adverse pregnancy outcomes that might be useful as a synthesis of current data for potential policy (or etiological) purposes, or a methodological evaluation of the conduct of meta-analyses in this topic area. Perhaps both, but unfortunately it does not succeed, so further focus would be most helpful.

1. As it is organized by chemical group it would appear to be a review article, but it only summarizes what has already been presented in published meta-analyses (M-A) There is no further synthesis of data into conclusions about
risk, by for example, combining the meta-analyses’ results, even qualitatively, or comparing meta-analytic results and how those vary by the methodological aspects of the analysis chosen or studies included, or attempting to fill the gaps of meta-analyses examined to draw conclusions or calculate some final summary risk estimate for each of the various chemical groups. When determining risks, it is important that all appropriate data is included—did these meta-analyses do this or are there other papers available, or pooled data not as formal as a meta-analysis? Are M-A from only the last ten years enough to make conclusions? Be clear, in revising, on how this review adds to the understanding about risks of these chemicals.

2) If it is to serve as a methodological piece evaluating meta-analytic practices, much more information about the methods should be provided and explained. For example, “meta-analysis guidelines” mentioned in 2nd para of methods should be spelled out for the reader, as well as the various tests considered. In this case it would not seem necessary to split out the meta-analyses so finely (e.g. only 2-3/chemical), but rather evaluate them as a whole. I found little actual evaluation of the techniques used, but rather just a listing, with no summary. How did the methods affect results of the M-A? Is that M-A of high enough quality to consider in assessing risk? Or going further, can the M-A be replicated from information provided? An evaluation would usually lead to recommendations—what is still needed in this area, e.g. improvements in M-A in order to make conclusions about risks? The area that becomes the focus of the paper will determine further revisions needed, so specific suggestions are difficult to make.

Response: we realised by reading the comments that we set out to do an impossible task and therefore have reduced the scope of the paper. It is impossible to conduct a critical evaluation of the methodology of all the meta-analyses, including whether they have included all the appropriate papers or not, whether they have applied the methodologies correctly and whether they results are
different or not depending on what they have applied or did not apply. Even synthesizing the results is difficult because of the variety in quality, size and exposure-outcome associations included and also because of the possible overlap in the included studies in different meta-analyses. Therefore, we have changed the aims of the paper to more worldly aims. We still believe that these are very informative and helpful for the reader by bringing together for the first time a number of meta-analyses on the topic of environmental exposure and birth outcomes with a brief discussion of their quality. A further analytical approach requires much more and as Dr Windham suggests may need to focus on a smaller number of studies.

The new scope is as follows: “We aimed to describe the methodologies used in recent meta-analyses of environmental exposures and pregnancy outcomes. Furthermore, we aimed to report their main findings.”

3) For example, the abstract and introduction will need to reflect the specific aim.

Response: we have updated the aims in the abstract.

4) Methods section should be expanded as noted. I have some concern that the term “adverse pregnancy outcomes” (or others similar) were not used in the initial search so summary papers may have been missed. This appears to be the case by the 2 additional papers (of only 16 total) picked up by “other sources.”

Response: we have provided some update of the methods section but we have not included all the guidelines because these are longer than the paper. We have given appropriate references if the reader wants to read them. We tried a search with “adverse pregnancy outcomes” and it did not give a different results than
without (currently at least-but we have not updated it in the paper because of the end of the search date given in the paper). The 2 papers missed were not in the database we searched.

5) If this becomes more of a review paper, other studies that contribute to risk, not included in M-A’s, should be added.

**Response:** we do not want to beyond meta-analyses because that opens up a whole new field and is outside the scope of the paper. We were particularly interested in quantified risk estimates by meta-analyses rather than qualitative evaluation of available literature, partly because this quantification can be of prime importance in translating research into policy. Certainly there are many more studies contributing to risk.

**Results:** 6) Might only need 1 of the tables, depending on focus. Table 2 might also be split if there is any way to group more similar exposures.

**Response:** we have split up table 2 to make it more manageable (air pollution vs. rest).

7) If this is an evaluation, the second paragraph should provide some quantification of the studies that followed guidelines, etc., and then actual assessment of the impact.

**Response:** we think this now outside the scope of the study, and wondered even if this actually could be done. A number of studies have reported following the guidelines, but even those not following the guidelines may have done to some extent. We cannot take away the guidelines and see what difference it would make, and therefore think it is not feasible and have excluded it from the scope of the paper.
8) There may the most studies on ETS, but not the most meta-analyses, what is the evaluation of this result?

Response: specific interest of researchers

9) See comments above if this is to be a review piece.

10) Heterogeneity tests are mentioned, but not with respect to how many studies are included in the M-A, wouldn’t this affect possibility of heterogeneity?

Response: we have clarified now in the discussion the issue of the number of included studies and power to detect heterogeneity. Certainly the power to detect heterogeneity depends, amongst others, on the number of studies involved.

Minor Essential Revisions (not necessarily for publication if fixed):

There were numerous problems with grammar, punctuation, formatting and errors, so these should be reviewed before publication as here I only note some examples. In addition, I note some areas needing clarification.

1. Abstract: Describe direction of associations with birthweight.

Response: we have ´´negative´´

2. Introduction: punctuation to indicate associations greatly needed in 2nd sentence.

Response: we have rewritten the sentence
Methodology:

3. formatting of references with their test in last paragraph, first sentence is very confusing, but improved by end.

Response: we have reformatted the references

4. Last phrase of last sentence is very awkward; I would say “conducting” analyses by sub-groups “defined by....”

Response: we have re-written the sentences

5. Define acronyms like MOOSE and ENRIECO.

Response: we have defined MOOSE and ENRIECO:

MOOSE: Meta-analysis Of Observational Studies in Epidemiology.
ENRIECO: Environmental Risks in European Birth cohorts.

Results:

6. Spell out all acronyms when first used (or in methods), and define endpoints once (e.g. LBW).

Response: we have spelled out acronyms.

7. Shouldn’t flow diagram be referred to as “figure”?

Response: we have referred to it as a figure
8. Formatting of studies to list year and ref # is awkward.

Response: we do not know what is meant by this.

9. $I^2$ became I2 in many places, which was confusing.

Response: we have changed all to $I^2$

10. Leonardi-Bee et al. 2008 and 2011 (or 2010 in ref list!) are not cited consistently or correctly in text and tables.

Response: we have corrected this now. References were moved around (18, 20 and 31)

11. Results of ref 17 must be wrong as upper CI is same as OR (in water DBPs).

Response: we have correct this.

12. Ref 24 in text has slightly different OR than in table.

Response: we have corrected this

13. Throughout, one study is stated as: “conducted meta-analyses”, why plural for one study? Prefer single as for first sentence under occupation—at least make consistent.

Response: general studies do not conduct one meta-analysis but a series of meta-analyses for different exposures, outcomes and subgroups.
14. “Pesticides” sub-head should be inserted before Ngo studies. Ngo 2010 paragraph: said no heterogeneity, but then try to describe non-Vietnamese studies as having different RR than Vietnamese, so would delete. Results split out by study design—it appears there is only 1 cross-sectional, so add that N or say “study” not studies. The sentence really isn’t very useful, so would delete—e.g. risks all rather similar.

Response: we have added the sub-head. Even though there was no heterogeneity, they did analyses with subgroups. We just reported what they did.

15. Punctuation really needed in third and sixth paras to aide understanding.

Response: we have done this.

Table 2:

16. Hard to read, might consider splitting.

Response: we have split the table into 2.

17. List studies in order presented in text.

Response: studies are listed in order as far as we can tell.

18. There are several places where the specific outcome is unclear, e.g. Sapkota 2010, no assoc with what? If all congenital anomalies are lumped, so state.

Response: no association with the outcome that is in the title. When all congenital anomalies are included we mention all, otherwise specific ones.
10. In several places “only” appears but is not at all clear what it refers to—
col 4 for ETS, or 5 for PM10, etc.

Response: see above.

20. Watch the negative sign for bwt CI’s (Pope et al), may need CL’s with
comma vs. hyphen.

Response: we do.

21. Different fonts in different columns.

Response: we have changed this now.

22. Under occupation, “Paternal” should be inserted before solvents for
Logman.

Response: we have added this now.

Discretionary Revisions:

1. Comment about the 2 M-A’s on DBPs and VSDs producing nearly identical
results—is this true or a typo?

Response: these are the same M_A based on the same 3 studies.

2. Metals and other water contaminants were mentioned in methods, but not
results, were none found? Or PFCs? (If so, lead to a possible
recommendation?).

Response: we did not find any meta-analyses.
3. Mention results for DDE under POPs.

Response: we did.

4. Discussion: another reason for small number of M-A may be only examining 10 years. More studied chemicals may have prior M-A’s.

Response: we are not sure this is the case. We also do not think that meta-analyses older than 10 years, if any, is not updated enough to be included in our manuscript.

5. In paragraph 5, say more how approaches followed guidelines even though not explicitly reported.

Response: this is difficult to establish since there are many guidelines.

6. Several statements are rather vague—end of 4th, 6th and last paragraphs.

Response: we have tried to clarify these now.

7. Paragraph 7 has interesting points that could be developed further, possibly into a recommendation.

Response: we do not have a recommendation section, but good to keep in mind.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published
Reviewer's report

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

Version: 1 Date: 1 October 2012
Reviewer: Rémy Slama

Reviewer's report:

'Environmental risk factors of pregnancy outcomes; a summary of recent meta-analyses of epidemiological studies'
Mark J Nieuwenhuijsen et al.
Environmental Health

Comments from the reviewer
Sept. 30th, 2012

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).

**Response:** Certainly meta-analysis is not only one form of summarising information, and there are many other forms such systematic reviews. In this paper we would like to focus on meta-analysis though, and see whether the meta-analyses have been conducted and reported properly according to the available guidelines and which their main findings were. We have tried to clarify the aim and also make it less ambitious:

"We aimed to describe the methodologies used in these recent meta-analyses of environmental exposures and pregnancy outcomes. Furthermore, we aimed to report their main findings."

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.

**Response:** there is some overlap between the meta-analyses in that they are using the same epidemiological studies in their analyses. However, giving the limited number of studies it is not a great problem. We have tried to keep the meta-analyses with the same topic together. We have reordered them where was necessary.

**Minor essential revisions:**

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

**Response:** we have broken up the sentence

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.

**Response:** we have added POPs to chemicals, and also realise that the division is still not ideal, with some exposures that could be in different groups.

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

**Response:** we have added this

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.

Response: we have changed this to ‘‘some of it can be dealt with by meta-analysis...’’

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.

Response: we have included in the methods the aspects that have been reviewed.

“We reviewed each meta-analysis according to; the databases they used, whether meta-analysis guidelines were used (MOOSE (Meta-analysis Of Observational Studies in Epidemiology) , [4], Quorom statement (Quality of Reporting of Meta-analyses), 2009 [5,6]), whether included studies were rated on quality (e.g. Newcastle-Ottawa scale [7], Cochrane Handbook guidelines, [8]), the statistics used to test for heterogeneity in the data (Cochran’s Q [9], I2 [10], whether fixed or random effects models were used in the pooling of individual studies (fixed [11] or random effects, [12]), and which tests of publication bias were used i.e. funnel plots [13], Egger’s test [14] or Begg’s test [15]. Furthermore we checked whether sensitivity analyses had been carried out e.g. for influential studies by leaving one study out at the time, or analyses defined by subgroups.”

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

Response: we have rephrased this as follows:
“We aimed to describe the methodologies used in recent meta-analyses of environmental exposures and pregnancy outcomes. Furthermore, we aimed to report their main findings.”

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.

Response: we ran another search and it did not make a difference (at this date—we cannot go back in the past)

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.

Response: we have removed this.

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?

Response: we agree, and it seems unrealistic, given the diversity in study results and numbers involved. We have added a little comment as follows. It is however what they reported.

“They estimated a 15% increase in the risk of PTB for each 10-µg/m3 increase in PM2.5 (OR 1.15; 95% CI, 1.14–1.16), although with unlikely tight confidence intervals.”
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?

**Response:** we have added results on DDE.

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 presented in the book chapter by Slama and Cordier (2010) that they quote.

**Response:** we have decided not include this.

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.

**Response:** we agree.

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.

Response: we have added a reference and added that stratifying studies according to quality of exposure assessment is another option.

Now it reads as: “In general, with various exceptions, non-differential measurement error/exposure misclassification may lead to attenuation in risk estimates and/or loss in power but could be compensated in the increased numbers of subjects in the combined studies (34). A further option is to stratify analyses by the quality of the exposure assessment.”

16. Discussion, p.16, 2nd paragraph before end: "…found less heterogeneity in studies of PM$_{2.5}$ than PM$_{10}$, 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.

Response: we have clarified the statement and added a few sentences

Now it reads as:
“Sapkota et al. 2010(16) found less heterogeneity in studies of PM$_{2.5}$ than PM$_{10}$, suggesting that the former may be a better exposure index, since in PM$_{10}$ may be acting as an imperfect surrogate for PM$_{2.5}$ with differences between areas in how good to the surrogate is. Of course, other explanations are also possible, including for example large variability in toxicity.”

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.

Response: we have clarified the statement and added a few sentences

Now it reads as:
“This may have resulted at times in more conservative effect estimates (i.e. larger confidence intervals), but may better reflect the reality, where heterogeneity exist but may not be detected because of a small numbers of studies.”

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

Response: it has been revised as follows:

“However I^2 is not a measure of the magnitude of the between-study heterogeneity, nor a point estimate of between-study heterogeneity.”

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?

Response: we have added a sentence stating that enough studies are needed to have sufficient power.

Now it reads:

“Funnel plots and the Egger test were mostly used to detect publication bias. There was little publication bias observed. One of the reasons may be that many of the studies were time consuming and difficult to conduct and that therefore authors made great efforts to get the data published. Furthermore, a sufficient
number of studies are needed to be able to detect publication bias, and where few studies are available, it may not be possible. Sensitivity analyses generally consisted of some subgroup analyses or leaving one study out at the time to determine if there were some influential studies. Generally the results did not change appreciably, suggesting that the results presented were robust.”

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 statistical association"

Response: we have divided the table into 2.

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.