Reviewer's report

Title: In-utero exposure to phenols and phthalates and the intelligence quotient of boys at 5 years

Version: 0 Date: 24 Sep 2017

Reviewer: Dave Saint-Amour

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This study investigates the associations between in-utero exposure to phenols and phthalates and IQ in children the EDEN cohort in France. The novelty here is the consideration of new phenolic compounds (parabens, triclosan, dichlorophenols and benzophenone-3), in addition to BPA. Structural Equation Modeling (SEM), taking into account several chemicals and control variables, revealed no statistically significant associations.

This is a nice paper. The data are coming from a well-documented prospective cohort and the statistical analyses are well conducted using state-of-the-art factorial analysis (SEM), a 'new' and 'trendy' approach in epidemiology. However, the study suffers from a major flaw: Only boys were included while the question whether those chemicals impair child IQ.

The EDEN cohort has been designed to primary evaluate male genital malformation in relation to phenols and phthalates. To this end, recruitment was focused on boys and this is fine (very nice studies has been published on that). The problem here is that the outcome is IQ. The authors argue that "focusing on one sex is not a source of bias, especially in the context where sex specific effects are plausible". I disagree (even though we are not dealing with the classical selection bias). I think that question research asked in the present study cannot be answered (adequately) from the EDEN cohort. Here some reasons why:

1. I don't quite understand why being sex specific would be better to avoid bias but even if it would be, evidence is lacking. We all know that sex is major variable in environmental epidemiology; sex-dependent effects have been reported by numerous studies (human and animal) for many chemicals (for endocrine disrupting chemical but also other contaminant). However, such effects go in all directions; sometimes adverse effects are seen in males, sometimes in females (within and across chemicals) and sometimes in both (or none). The lack of consistency is particularly important with cognitive functions. We don't know how and why these sex differences exist (probably through endocrine disruption but this is not an explanation) and are not able to truly predict them.

2. There are too few studies on child IQ and phenolic/ phthalates exposure to say whether or not they are sex specific. A very recent study by the present research team, in a different cohort, has shown that prenatal phthalate exposure decreased cognitive development (Bayley scale
score) in girls but not in boys (Environ Res. 2017 Jan;152:51-58), while others reported opposite sex result patterns.

3. One problem when accepting the null hypothesis and testing only one sex is the impossibility to distinguish whether the lack of significant association is due to being a boy (different susceptibility) or due to the "safety" of chemical exposure. The interpretation, and more importantly the generalization, of the data becomes thus limited. In line with this point, the first sentence of the conclusion (We did not observe clear association between any of the phenol and phthalate biomarkers assessed in maternal urine and child IQ at 5-6 years) Should be… in boy IQ at 5-6 years (idem for the conclusion in the abstract).

Here some minor points:

Methods, p7, line20: … log-transformed… Log10 or Ln? Please specify.

Discussion, line 399: In analyses stratified for center should be In stratified analyses…

Discussion, line 475: As pointed out by the authors, "most previous studies used multiple linear regression to study the associations between bisphenol A, phthalates and cognitive function". This is right. I am curious whether the authors have explored the data using multiple linear regression models. I am asking because 1) Although SEM has clear and advantages over common regression modeling, it does also have some limitations (e.g., see Annu. Rev. Clin. Psychol. 2005. 1:31-65) and 2) the authors used multiple linear regression in their very recent paper on the same topic (Environ Res. 2017 Jan;152: 51-5).

Conclusion: To be the first "to have considered possible effects of parabens, dichlorophenols, benzophenone-3 and triclosan" is certainly is a strength of the study, but certainly not a conclusion highlight.

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