Author’s response to reviews

Title: Association of urinary concentrations of early pregnancy phthalate metabolites and bisphenol A with length of gestation

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Author responses to Reviewer Comments:

Reviewer #2: I would like to thank the authors for quickly responding to my comments. Most of my questions have been clarified and the manuscript has been much improved. However, there are a few more changes I would still request.

I appreciate your response to comment 4 regarding the exposure assessment. But I feel the Supplemental Figures 1 & 2 do not align with the text in methods. For example, in manuscript it says "For the pre-implantation window pool, the first 3 Monday samples were selected from the interval starting the day after the end of the LMP (defined as the first two consecutive days of no bleeding after the onset of menses) and ending on the day before implantation was detected." There is nothing in the figure that indicates Monday samples, or days after LMP. The figure should also mention n of study subjects.

Author response: We have revised the referenced figures and figure legends in the supplemental material to better describe sample collection. The revised figure legends now include information
about the interval of sample collection (e.g., end of menses to implantation) and the sample size. See revised figure legends below.

“Supplemental Figure 1. Diagram of the urine samples pooled to measure phthalate metabolites and bisphenol A around the time of conception (pre-implantation measure). The sample period started the day after the end of menses and ended the day before implantation. Each sample was collected approximately 1 week apart and each woman (n=125) contributed 3 samples to her pooled sample.”

“Supplemental Figure 2. Diagram of the urine samples pooled to measure phthalate metabolites and bisphenol A after embryo implantation (post-implantation measure). The sample period started the day after implantation and ended approximately 3 weeks later. Each sample was collected approximately 1 week apart and each woman (n=121) contributed 3 samples to her pooled sample.”

We chose not to include information on the day of the week, but instead that samples were collected approximately one week apart, since not all samples were collected on Monday.

Regarding comment 9, thank you for adding the figure. In the figure's description, it is important to add the n for pre- and post-implantation measurements. Also, please add in the figure's description how the HR relates to days of gestation. The reader should be able to look at this figure independently from the text.

Author response: We have added the information requested by the reviewer to the Figure 1 legend. The legend now reads: “Associations between pre-implantation (n=125) and post-implantation (n=121) early pregnancy biomarker concentrations and implantation-based length of gestation. Pre-implantation (white dots) hazard ratios represent the risk of birth for women with pre-implantation measured biomarker concentrations above the median compared with those below the median (reference) and post-implantation (black dots) hazard ratios represent the risk of birth for women with post-implantation measured biomarker concentrations above the median compared with those below the median (reference). Hazard ratios <1.0, indicate a reduced risk of delivery (i.e., longer gestation) and hazard ratios >1.0 indicate increased risk of delivery (i.e, shorter gestation).”

Thank you for your response to comment 10. However, the discussion still does not address a suspected biological mechanism for their findings of interest.

Author response: Thank you for bringing to our attention that we did not address this part of your previous comment #10. We have added a sentence to the discussion addressing the proposed biological mechanism by which phthalates and BPA may affect length of gestation. The first
sentence of the second paragraph of the discussion now reads: “Phthalates and BPA have the potential to interfere with the hormonal changes that occur in early pregnancy (Ehrlich, Williams et al. 2012, Sathyanarayana, Butts et al. 2017) and induce oxidative stress and inflammation (Ferguson, Loch-Caruso et al. 2012), two pathways through which these compounds could affect overall pregnancy health and length of gestation.

References

