Author’s response to reviews

Title: A Repeated Measures Study of Phenol, Paraben and Triclocarban Urinary Biomarkers and Circulating Maternal Hormones during Gestation in the Puerto Rico PROTECT Cohort

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Author’s response to reviews:

Reviewer #1: Thank you for the opportunity to re-review this manuscript. While the authors have made some important changes and aimed to address the comments made in the first round of review, I still have some concerns which stems from an unclear prespecified direction/hypothesis/purpose of this body of research, which becomes evident as the manuscript progresses to the results and discussion. The results are still not streamlined and remain difficult to follow - the results section reads like a laundry list of exposure-outcome associations. Perhaps consider grouping the results by biologically relevant endpoints of interest (again this should be grounded by a clear pre-specified direction) and then by windows of exposure, rather than listing each chemical one by one down a list. The discussion also suffers from the same concern - at more than 2700 words, it is difficult to know what is important and why. I urge the authors to read this editorial by the previous Editor in Chief of Human Reproduction, Hans Evers, entitled "The Texas Sharpshooter Fallacy" (https://doi.org/10.1093/humrep/dex103). I think most of the concerns I have raised in my first review and now in this second round stem from a the need for a clear a priori direction that guides the study and its communication. Please consider re-packaging your results and discussion so that a primed reader can discern the results and their relevancy.
Response: We would like to thank you for the thoughtful review and comments. We understand and acknowledge your concerns with regards to 1) the lack of clearly defined a priori hypotheses, and 2) the detailed nature of our manuscript.

Therefore, we included specific hypotheses in the Background for the chemicals BPA, triclosan, methylparaben and propylparaben, and their expected direction of associations with thyroid hormones. We also included language to the Results section that states whether these associations were in line with our hypotheses or not. We did not have any a priori hypotheses for any of the other associations because it is difficult to make justified a priori hypotheses on associations that have little to no research. The purpose of our manuscript was to introduce these findings, and begin filling this gap in the literature. As described in the Background section, there is strong biologic plausibility that led us to explore these associations. First, some of the newer less studied chemicals are in the same class of more studied chemicals, such as the case of BPS and BPF. Thus, it is likely that these chemicals could also influence circulating hormone levels, although not necessarily in the same way. Second, even though many of the reproductive hormones we included in our analysis are yet to be studied in association with the exposure biomarkers, they are important hormones that play vital roles in pregnancy. Furthermore, some have similar chemical structures to hormones that have been shown to be affected, such as the case of estriol, which is structurally similar to estradiol. The effect of endocrine disruptors on estradiol has been studied in great detail, and it is plausible some chemicals could also influence estriol levels. As such, we decided to explore these associations even though we did not have any specific hypotheses with regards to the direction of the associations. We hope the reviewer sees the value of our exploratory research, and its attempt to help untangle the effects these chemicals seem to have on our bodies via hormone disruption.

As per your suggestion, we also attempted to re-write the Results and Discussion sections around the endpoints of interest, rather than the chemicals; however, we felt this made the document more difficult to follow. Given that the purpose of our study was to explore the potential effects of these chemicals on hormones, discussing the associations observed from the perspective of the hormones did not allow the reader to effectively understand the potential effects of chemical exposure. As a small example, when we tried to discuss the associations observed with total triiodothyronine (T3) as you suggested, we reported that BPA and triclocarban may increase T3. However, BPA and triclocarban are unrelated and have different chemical formulations. Thus, the fact that BPA and triclocarban both increase T3 explains very little. However, when we look at the associations by chemical, we notice that alongside the increase in T3, BPA also increases FT4. Because of the workings of the negative feedback loop, these two findings together make sense, and provide more evidence that this association is real. Likewise, alongside the increase in T3 in relation to TCC, we also observe a decrease in TSH with TCC. Again, providing more
evidence that this observation may be real, and not just a mathematical random occurrence. Therefore, we opted to leave the Results and Discussion sections as is, reporting the findings by chemical and chemical classes. We did, however, try to streamline the Discussion section even further to help draw attention to the most interesting results. Because we are looking at multiple chemical classes and many hormones, the manuscript by its very nature will be lengthier. As indicated in the "The Texas Sharpshooter Fallacy" article cited, a lot of research is wasted due to a lack of publishing. To this, and in an effort to reduce publication bias, we wanted to include all of our findings, and not only the interesting significant ones.

We hope the changes made to the manuscript make it easier for the reader to understand and interpret our results.

Reviewer #2: has no further comments.

Response: We are glad we were able to address all your comments.