Author’s response to reviews

Title: Bisphenol A Increases Risk for Presumed Non-Alcoholic Fatty Liver Disease in Hispanic Adolescents in NHANES 2003-2010

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Author’s response to reviews:

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Dear Editors,

Thanks for reviewing our manuscript entitled, “Biphenol A Increases Risk for Presumed Non-Alcoholic Fatty Liver Disease in Hispanic Adolescents in NHANES 2003-2010”. Revised is a point-by-point description of our responses and changes made.

Reviewer reports:

Editor’s comments:

• The text needs to be rewritten for clarity in several places. The last sentence before Statistical analysis is an example, but ambiguities occur throughout the text.

The text was revised and edited

• The reference style is not in accordance with the instructions, please correct and follow strictly the instructions.

References were modified according to the journal guidelines.

• Please do not repeat results in the Discussion, but paraphrase them.

The text has been edited accordingly
• Once an abbreviation has been explained, you do not need to repeat that. Toward the end, there is a list of abbreviations, but without explanations.

The abbreviations used throughout the manuscript have been explained in the list of abbreviations at the end.

• Grant support is listed on the cover page, and there is no Acknowledgments - please follow the required style.

Grant support was moved to Acknowledgments

• As Hispanics are mentioned in the title and clearly a focus of this study, you need to justify this focus in the Introduction - what is the support for the a priori hypothesis, or is there none?

The analysis was stratified by race/ethnicity given the high prevalence of NAFLD in Hispanic patients and the hypothesis that a relationship between high BPA concentrations and NAFLD may not be as evident in a population with a low disease prevalence (such as non-Hispanic black populations). However, BPA levels have been described (Calafat 2008) as lower in Hispanic populations.

• In regard to the selection of the study population, please explain if the "random" selection was done by the NHANES study or by you.

NHANES selected a random third of patients to obtain BPA levels in and a random half to obtain fasting laboratory results. This has been included in the text and cited.

• Please do not use the word "level" when the specific term is concentration. The text has been edited accordingly.

• Please clarify if metabolites were measured.

Metabolites were not measured

• On p.8, line 25, please insert references when referring to "the current literature".

Citations were added

• As the identification of eligible subjects is hard to follow, we suggest that you include a graph that shows how you reached the number of participants for your analyses. If that is not helpful, you need to revise the text so that it is easier to follow how you identified the eligible subjects.
Figure 1 was included per your recommendations

- All studies on the rapidly metabolized BPA need to consider the imprecision due to single urine analyses that may not reflect long-term exposures. Please insert this in the Discussion and, if appropriate, consider sensitivity analyses to take this into account.

The discussion was edited to reflect these comments.

- The term "labs" used on p. 11 is not explained and should be substituted by a commonly known term.

Labs was changed to “bloodwork”

- We prefer using ethnicity rather than "race".

“Race” was changed to “race/ethnicity” to reflect the nomenclature used by NHANES.

- While we would expect that a revised manuscript to be in accordance with the required style, this submission is far from expectation. We would normally reject at this stage, but we will consider a final revision if thoroughly revised in regard to style and linguistics.

We appreciate the opportunity provided and hope the corrections are sufficient.

Reviewer #1: These revisions satisfy my original comments but now there are new grammatical errors and typos in the added sections. I would suggest giving it to someone else to proofread before submitting proofs to the journal. I would also suggest the conclusion to be changed slightly to reflect that BPA is certainly not the only cause of NAFLD if at all since this is a cross-sectional study, but definitely may play a role and is associated with NAFLD.

We appreciate the feedback, and have reviewed and revised the text accordingly.

Reviewer #2:

- In the methods, please add more detail regarding the method used to quantify urinary BPA. Is the this total BPA or free BPA?

Total BPA is considered a valid biomarker of exposure to BPA. We have edited the text accordingly and added citations.

- The citation #30 is not complete.

The citation has been completed
Discussion should also address if the liver is compromised metabolically from NAFLD, this could influence the BPA metabolism and disposition, and ultimately what is detected in urine. Livers with NAFLD tend to have lower glucuronidation and sulfonation.

This is a very interesting point, and an extremely difficult one to answer. We agree that BPA both undergoes hepatic metabolism and has a direct effect on hepatic metabolism, and thus patients with fatty liver disease could have elevated levels due to impaired metabolism—which would be consistent with our findings but not with our conclusions. We have included this important point in the discussion as a limitation. We could not find any literature exploring BPA in other liver pathologies or animal studies that could clarify this “chicken or egg” question.

Sincerely,

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