Reviewer's report

Title: Association between bisphenol A exposure and body mass index in Chinese school children

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Reviewer: Justin Teeguarden

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- Major Compulsory Revisions

1. The authors must point out that given the rapid pharmacokinetics of BPA, first morning void is at best a measure of exposure at the prior (dinner) meal, not daily or average exposure expected to be related to biological effects (Calafat et al, several publications, Doerge et al, several publications, Teeguarden et al. (2011). The choice to use first morning void would likely limit variability, but would also bias collection towards lower exposure estimates.

2. The authors must justify the use of urine outputs of 600 and 1200 mls per day for the two age groups. Urine output is related to body weight, which in this study, if not corrected for, could be a major confounder. Daily intakes, calculated here from urine volume estimated by age, might be expected to be larger in the high BW individuals. Explain how this was addressed.

3. One contributor to the findings in this study may be a reduced urine output per BW in the obese population, which would increase urine BPA concentration, and without the BW adjusted urine volume estimate, increase exposure estimates in proportion with BMI, leading incorrectly to the associations reported in the paper. Several papers to examine of this topic follow. The authors must establish that this was not a confounder to their analysis by calculating BW specific urine outputs and re-analyzing the data:
   b. Siener, obesity research, volume 12, #1, 2004
   c. Gundersen, American Journal of Clinical Nutrition

4. The authors reporting that there were no associations between obesity and urinary BPA when adjusted for specific gravity AND no associations between obesity and daily exposure to BPA are the critical findings of the paper. In fact, the authors state that the specific gravity adjustment of urine BPA concentrations is appropriate, and this reviewer agrees that it is important to do so for individuals. Use of the preferred data leads to a finding of no associations. Moreover, we would expect that if BPA causes obesity, it would do so through interactions with systemic organs, not the bladder epithelium. For this reason, total daily exposure is the best metric of exposure for associations with obesity in this study if blood concentrations are not available. The authors also found no associations between exposure and obesity, which, in the pharmaceutical
literature, would be clear evidence that a drug had no effect at the delivered doses. Why is this insufficient evidence then for these authors to conclude that there is no association between BPA and obesity?

a. It would seem that despite careful work, the authors have left scientific objectivity behind in an attempt to publish positive findings, forgetting that the finding of no associations is not only plausible, but just as important. This kind of reporting is damaging to any field. The TITLE must be changed, because is falsely represents the findings of the paper. “BPA urine concentrations and exposure are unrelated to BMI” would seem to be more reflective of the work.

5. Association studies like this one should always be placed in the context of the available biological data. The authors should state whether or not the 2 multigenerational rodent bioassays resulted in obesity in a rodent model. The author should also state whether ANY animal study has shown any effects at doses equal to their measured human exposures of 0.005-0.015 µg/kg per day. They will find none. Which reveals the duplicity in the introduction, which uses the words “low dose” in citing the Rubin et al study as evidence of a BPA effects on BW in mice. Rubin et al. employed doses of 100 µg/kg, 5000 to 20000 times higher than the exposures in your study. Their follow on work used lower doses, but osmotic pumps to bypass oral exposure. The concentrations used in the cell culture study by Sargis et al were much higher than one would find in humans exposed to the doses of BPA in this study. To summarize, if the authors are to cite the Rubin et al study, they must also cite the dose, 100 µg/kg, replacing the words “low dose.” They must also cite the exposure concentrations in the Sargis study. In the discussion, the authors must place their human exposures in the context of these to studies, for example: in our study, exposures were 5000 to 20000 times lower than exposures shown to cause weight gain in mice. If the literature is to be used, it should be used objectively.

6. The discussion has a paragraph that says “ in the present study, we found that high urine BPA was associated with increased BMI.” If the authors intent on emphasizing the one positive association which is based on the approach (uncorrected urine concentrations) they felt was the least appropriate, and is clearly the least biologically valid, they must also add a corresponding paragraph discussing the two more credible, methodologically valid findings: no association with total exposure and no association when using their preferred method (specific gravity corrected urine concentrations). As a reviewer, I am disappointed that the authors seem to have abandoned objectivity and balance in favor of promoting what appear to be selected or favored conclusions.

7. The discussion section should have a full paragraph devoted to comparing the exposures in this study to those in cell culture studies and animal studies causing BW changes. The paper by Völkel et al (2002) on the human pharmacokinetics can be used to calculate nM blood concentrations from the doses in the authors work. For example, in the Völkel study, 71 µg/kg doses led to no observable aglycone BPA, but the value can be estimated to be no more than 9 nM. So, since the kinetics are linear, in the study reported here, the daily exposure would lead to peak blood concentrations of 0.002 nM, or 2 pM at most. This can be easily compared to the 1 uM exposure used by Sargis. Its 1 million times lower,
which begs the question of plausibility or even whether the Sargis citation has any bearing on the results of the present study.

Level of interest: An article of importance in its field

Declaration of competing interests:

No competing interests.