

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The manuscript of “New environmental factors related to diabetes risk in humans: systematic review and meta-analysis of emerging bisphenols used in the synthesis of plastics” by R. Moreno-Gómez-Toledano and co-authors aims to analyze the potential new dangers that society faces with the replacement of bisphenol A (BPA) by new bisphenols. For this purpose, the meta-analysis of the relationship between new bisphenols and diabetes in humans was carried out for each bisphenol, using the RevMan software. In addition, funnel plots were developed to study publication bias. The primary outcome measures were serum/plasma or urinary bisphenols (except BPA) in diabetic context. The analysis was limited to humans and English language, but no restriction was applied in the academic search engines. The results showed that new bisphenols could represent a health risk equivalent to Bisphenol A. The manuscript is quite interesting and well written; all the conclusions are supported by the data obtained. The topic of the manuscript is highly relevant and timely in view of recent the statistics on the incidence of diabetes mellitus (DM) in the world. The manuscript contributes to the development and systematization of knowledge about a relationship between DM and environmental pollutants.

Authors' response:

We thank the reviewer for the positive comments. We consider that the study of new substitute molecules for BPA is a recent problem that should be urgently addressed by governmental institutions. Consequently, we are glad to know that the manuscript is interesting and contributes to the development and systematization of knowledge about a relationship between DM and environmental pollutants.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: In this manuscript, the authors aimed to investigate the association between environmental pollutants such as Bisphenol A (BPA) and Diabetes Mellitus (DM). The study conducted a systematic review and a meta-analysis of the academic literature to evaluate the state of the art. The systematic analysis of the literature revealed 13 recent academic articles (2017-2023) related to the study paradigm. The qualitative analysis showed interesting data linking diabetes to the three most widely used substitute bisphenols in the industry: BPS, BPF, and BPAF. Finally, the meta-analysis determined a positive relationship with BPS, BPF, and BPAF, which has only been statistically significant with BPS. The study highlights the critical public health issue of DM and the potential adverse health impact of environmental pollutants such as BPS, BPF, and BPAF. The results of the study could be used to alert regulatory

authorities and policy-makers to take necessary measures to regulate the use of BPA substitutes and reduce the environmental exposure to these chemicals. As the authors mentioned the present study underscores the need for further research to strengthen the evidence base on the associations between DM and environmental pollutants. The study provides valuable insights into the potential health risks of BPA substitutes, which could help guide future research and public health interventions. However, one of my most concerns is how can the new environmental factors obtained by data analysis be verified by experiments.

Authors' response:

We appreciate the reviewer's positive comments. Our work aims to demonstrate the need to influence government policies to regulate environmental exposure to endocrine disruptors.

It is important to highlight the difficulty of developing methods that identifies causal relationships in population-based studies. Some authors explored the possible relationship between new bisphenols and diabetes in *in vitro* and *in vivo* experimental models, but the evidence is still scarce. To further explore the issue, it would be of vital importance to improve pharmacokinetic studies and to continue working on basic research models. However, there is controversy in basic research models due to the lack of consensus in human translational approaches. Institutions such as the European Food Safety Authority (EFSA) have been working for years on the tolerable daily intake (TDI) of BPA in humans and have recently proposed a 20,000-fold reduction from the previous TDI. Consequently, the precautionary principle should be applied to molecules that are structurally analogous to BPA.

In human cohort study models, the most consistent and useful approach to study causal relationships are longitudinal studies. By following study subjects for years, it is possible to identify whether BPA or its derivatives are implicated in the development risk of the pathology of interest. In addition, statistical analysis models being implemented in academic publications, such as Bayesian Kernel Machine Regression, analyze the combined effect of different xenobiotic compounds, which provides a more realistic perspective.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: I have only 1 minor concern: Does the authors performed meta-analysis about "(Bisphenol) AND (Diabetes OR Hyperglycemia)" with any positive or negative control?

Authors' response:

We thank the reviewer for reviewing the text. We consider that the introduction of positive or negative controls is not possible in our study. In the academic literature, articles have been published that perform meta-analyses on observational database studies. In that case, the

combination of patients allows the use of controls. However, in the present manuscript we performed the inverse analysis of variance of odds ratios, to obtain a new pooled data. In our analysis model, we do not work with the data of the individuals in each study, but combine the odds ratios obtained in each study.