

Dear Editor, Dr. Jin-Lei Wang,

Thank you very much for your e-mail from February 20th, 2023 concerning the Manuscript No. 82756, Review entitled "Food contaminants and potential risk of diabetes development " which was submitted to *World Journal of Diabetes*.

Authors appreciate all the comments and suggestion made by Reviewers since they have considerably improved the original paper. We have thoroughly revised the manuscript to address concerns. A revised version of the manuscript prepared in accordance with Reviewers` suggestions is attached. All changes made based on the suggestions of Reviewer can be found in track changes in the revised version. The enclosed amendments to Reviewers` comments could be found below.

We deeply hope that the revised manuscript will meet the requirements of your eminent journal and will be considered for publication in *World Journal of Diabetes*.

On the behalf of all authors,

Sincerely yours,

Jelena Marković Filipović, PhD, AssociateProfessor

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Replies to Reviewer#1 comments

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: *Milanović et al. described the environmental agents that affect glucose metabolism and their potential role in the development of diabetes mellitus. Since environmental agents get less attention based on glucose metabolism, this review is very important to educate physicians. The authors focused on three major agents: phthalates, bisphenol A, and acrylamide.*

Authors' response: The authors thank Reviewer for the compliments and appreciate the opportunity to submit a revised version of the manuscript. Below please find point-by-point responses to all remarks and suggestion since they have finally improved the paper.

1. *Adding figure(s) that shows potential mechanisms for these agents on diabetes development will help understand readers more clearly.*

Authors' response: The authors appreciate this remark. As suggested, the schematic mechanisms of phthalates, bisphenol A and acrylamide role in diabetes have been inserted in the revised manuscript as Figure 2.

2. *If the authors can find the manuscript which describes decreasing phthalates, bisphenol A, and acrylamide concentrations in the blood (e.g. avoiding packaging materials, or chemical reactions during food processing) resulting in improvement in glucose metabolism, please describe them.*

Authors' response: Thank you for this comment. To the best of authors knowledge, there is still no published data about the relationships between phthalates, bisphenol A, and acrylamide concentrations in the blood (after avoiding packaging materials, or chemical reactions during food processing) and glucose metabolism. Regarding the BPA and phthalates short half-life, most of the biomonitoring studies are focused on measuring their concentrations in urine. However, there is still limited number of studies exploring the association between phthalates, bisphenol A, and acrylamide urinary levels and dietary factors. Due to the significant obstacles in establishment of a limit as a safe dose, avoiding exposure via packaging materials is tricky. Most of the articles that investigate the possible association between phthalates, bisphenol A, and acrylamide levels and diabetes are performed on an animal model instead of humans due to the ethical issues of carrying out this type of study. Another obstacle is that the disruptions in the glucose homeostasis caused by bisphenol, phthalates or acrylamide are difficult to study by excluding possible interactions with other factors. Considering the ubiquitous exposure to these contaminants, biomonitoring studies with the aim to investigate the association between phthalates, bisphenol A, and acrylamide levels in the blood and parameters of glucose homeostasis after the reduction of exposure (via packaging materials or food processing) is difficult to perform. Up to now only Hutter and coauthors performed the "real life" intervention and evaluated the differences in urinary BPA and phthalate metabolites levels after the modification in diet and removal of plastics (**Hutter HP**, Kundi M, Hohenblum P, Scharf S, Shelton JF, Piegler K, Wallner P. Life without plastic: A family experiment and biomonitoring study. *Environ Res.* 2016;**150**:639-644. [PMID: 27235111 DOI:

10.1016/j.envres.2016.05.028.]). Although, no biochemical measurements were done, avoiding plastic materials resulted in reduced urinary concentrations. A recent study has confirmed that different dietary habits can affect phthalates exposure, concluding that dietary patterns high in fruits, vegetables, as well as, low-fat foods and low in processed foods may be useful in avoiding exposure to phthalates (Vieyra G, Hankinson SE, Oulhote Y, Vandenberg L, Tinker L, Mason J, Shadyab AH, Wallace R, Arcan C, Chen JC, Reeves KW. Dietary patterns and urinary phthalate exposure among postmenopausal women of the Women's Health Initiative. *Environ Res.* 2023;**216**(Pt 3):114727. [PMID: 36356671 DOI: 10.1016/j.envres.2022.114727.]).

Based on all above mentioned, the new sentence is inserted in conclusion:” Risk assessment of these contaminants in mixtures of EDCs and the exact level of exposure associated with diabetes development over time remained unanswered. The effects of decreased exposure to phthalates, bisphenol A, and acrylamide through avoidance of specific packaging materials, or chemical reactions during food processing on glucose metabolism should also be addressed. Therefore, further prospective well-designed studies with multiple measurements and longer follow-up, together with experimental studies, are required to completely understand the underlying mechanisms and confirm the causal association between PAEs, BPA, AA and diabetes outcomes.”

Replies to Reviewer#2 comments

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: *Milanović M et al. provide a more comprehensive review of the progressive research on food contamination and diabetes mellitus, using three specific substances (PHTHALIC ACID ESTERS, BISPHENOL A, and ACRYLAMIDE) as examples. This is a narrative review with novel arguments and recent references. However, there are some shortcomings and suggested changes.*

Authors’ response: The authors thank Reviewer for the compliments and appreciate the opportunity to submit a revised version of the manuscript. Below please find point-by-point responses to all remarks and suggestion since they have finally improved the paper.

1. *It is suggested that the title of the manuscript should be changed to "Food contaminants and potential risk of diabetes development: A Narrative review".*

Authors’ response: Following your suggestion, the title is modified as "Food contaminants and potential risk of diabetes development: a narrative review".

2. *Page 6, the relationship between factors other than food contamination and diabetes mellitus should be streamlined as much as possible; page 8, the content related to "reproductive toxicants" can be streamlined.*

Authors’ response: As recommended, the part related to T2D is streamlined “T2D is known as „adult-onset diabetes”, and develops as a result of increased insulin resistance to a level where overproduction

of insulin can no longer cope with insulin insensitivity, leading to β -cell dysfunction^[28]. In addition ~~to T2D~~, several other non-communicable disorders are associated with insulin resistance, such as obesity, metabolic syndrome, non-alcoholic fatty liver disease, polycystic ovary syndrome, cardiovascular disease and cancer^[20]. ~~Permanent hyperglycemia triggers both oxidative stress and inflammation and can interfere with lipid metabolism[29]. Moreover, obesity during pregnancy is a risk factor for the development of gestational diabetes[23]. Family history, a sedentary lifestyle, an unhealthy diet that includes excessive intake of saturated fats and cholesterol, obesity, and ageing are major risk factors for development of insulin resistance and T2D[30].~~ However, there is a growing amount of data that also supports a role for food contaminants such as PAEs, BPA and AA in the onset of diabetes and the development of related conditions."

The sentence "Hence, DEHP, DBP, DiBP and BBP are classified as reproductive toxicants and substances of very high concern for human health^[56]" is deleted.

3. The common PAEs on page 7 can be streamlined, and the same effect can be achieved by using general language and making the correct references. Similarly, the first paragraph on page 14; the first paragraph on page 19; and the second paragraph on page 19 should be streamlined.

Authors' response: Following your suggestion, mentioned parts are shortened.

4. Page 9 "Also, alterations in gene expression specific for pancreas and β -cell development and function in offspring were measured^[68]." is not properly connected. The same deficiency is also manifested in "Also, DiBP reduced fetal plasma insulin levels in offspring and decreased PPAR α mRNA levels in liver were observed^[72]."

Authors' response: We appreciate the above-noted remark and made necessary changes in the text: "~~Also, in DEHP treated offspring, alterations in pancreas specific gene expression were observed and impairment in β -cell development and function were reported^[65]. In addition, DiBP reduced fetal plasma insulin levels in offspring and decreased PPAR α mRNA levels in the liver ^[69].~~"

5. Page 10 "Gender and weight differences related to DEHP and diabetes development" can be simplified, in addition, it seems that "homeostatic model assessment of insulin resistance (HOMA-IR)" has a language defect in the manuscript.

Authors' response: The authors appreciate this remark. As recommended, this part is rewritten: "~~Additionally, gender and weight differences related to DEHP and diabetes development were seen in adulthood. Namely, DEHP exposed female offspring had lower birth weights, disturbed glucose tolerance, impaired insulin secretion and high blood glucose levels. DEHP exposed male offspring had increased serum insulin levels and lower birth weights at a significant level^[65]. ... Namely, in DEHP exposed female T2D mice during puberty, higher levels of several parameters were detected such as insulin, C-peptide, fasting blood glucose levels, homeostatic model assessment of insulin resistance (HOMA-IR), low density lipoprotein (LDL), C-reactive protein and aspartate amino transferase (AST).~~"

6. On page 10, "A reduction in insulin levels was found in DEHP-treated adolescent T2D mice.", it is suggested to add a reference here.

Authors' response: Thank you for this comment. We have added the reference in the revised version of the manuscript: "A reduction in insulin levels was found in DEHP-treated adolescent T2D mice^[72]."

7. The title of the manuscript is "Food contaminants and potential risks of diabetes development". The author wants to highlight the relationship between food pollution and diabetes. Many content unrelated to diabetes seems useful, but in fact it makes the manuscript seem lengthy, which is no good for highlighting the theme. Therefore, it is recommended to delete the following content:
 - 1) It is suggested to delete the contents related to triglyceride in the first paragraph of page 13.
 - 2) The second paragraph on page 15 related to "sex hormone" is suggested to be deleted.
 - 3) The first paragraph on page 20 suggested deletion of other toxicity related contents except diabetes.
 - 4) It is suggested to delete the relevant contents of "gender differences" on pages 21 and 22.

Authors' response: Authors appreciate this comment and following Reviewer suggestion, the mentioned sentences are deleted. Since we deleted suggested content of manuscript corresponding references are expelled. Therefore, numbers of subsequent references have changed.

8. The authors have talked about three substances in this narrative review. When describing each substance, it is better to use a subtitle to indicate the content to be described (for example, research status, physiological mechanism with diabetes, and future research direction). In this way, the manuscript will be more organized and the reader's thinking will be clearer.

Authors' response: Authors appreciate this comment very much. In order to better organize the manuscript following subtitles are inserted: **Research status, Potential mechanisms associated with diabetes, Epidemiologic evidence.**