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Dear Editor-in-Chief
World Journal of Diabetes

Respected Sir,

Please find enclosed the revised version of our manuscript entitled "Organophosphate pesticides and new-onset diabetes mellitus: from molecular mechanisms to a possible therapeutic perspective" written by Ya-Ling Chung, Yi-Chou Hou, I-Kwan Wang, Kuo-Cheng Lu and Tzung-Hai Yen.

First, we would like to thank the Reviewers' for critically reviewing this manuscript and providing us many invaluable comments and suggestions. We feel that all the comments are very helpful in improving the legibility, objectivity and scientific evaluation of the manuscript.

We have responded to each of the reviewer' comments and clarified/amended every necessary part raised by the reviewer. The detailed statements, reviewer-by-reviewer, and point-by-point are enclosed as following.

We highly appreciate all your help and further arrangement. We hope that the revised version of the manuscript could meet the academic standard of *World Journal of Diabetes*. Thank you.

Yours truly,
Tzung-Hai Yen

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Reviewer 1

Comment: This review's logic is reasonable, the thinking is clear, the arguments are sufficient, and there are many references, which can better summarize the latest literature in this field; However, there are still some problems that can be further improved: the review does not discuss the difference and connection between acute organophosphate poisoning and organophosphate exposure; The literature discusses the possible mechanism of organophosphorus exposure to diabetes, but it does not directly prove that organophosphorus can cause diabetes, and further evidence is needed. This document can quote some clinical cases to further supplement the explanation.

Response: Thank you for the critical comments. The concerns have been addressed in the following paragraphs.

Clinical studies of new-onset diabetes mellitus after organophosphate exposure
Previous studies revealed that organophosphate exposure could increase the risk of new-onset diabetes mellitus (Table 1 and 2). Moore et al [9] first noticed that acute organophosphate ingestion was associated with hyperglycemia, and hyperglycemia required insulin intervention for blood sugar control (Table 1). Serial studies also demonstrated that organophosphate-mediated acute pancreatic injury might induce hyperglycemia. [10, 11] In 2008, Montgomery et al [12] provided epidemiologic data to link chronic exposure to organophosphate with diabetes mellitus (Table 2). Within the 5-year follow-up, the incidence of diabetes mellitus increased in organophosphate users. The study conducted by Liu et al [13] demonstrated that acute exposure to organophosphate led to hyperglycemia, but the effect on the development of diabetes mellitus was only marginal. In a meta-analysis study conducted by Lakshmi et al [14], hyperglycemia was common. A recent study by Velmurugan et al [15] demonstrated that organophosphate exposure was associated with higher insulin resistance and higher plasma glycated hemoglobin levels. From the clinical study, acute organophosphate exposure was associated with hyperglycemia and then regressed after atrophine treatment. From the study published by Javeres et al [16], red blood cell acetylcholinesterase activity decreased within the organophosphate exposure group, and the plasma concentrations of lipase/amylase and insulin increased in the organophosphate-exposed group. Such evidence demonstrated the effect of organophosphate on insulin resistance and direct damage to pancreatic cells in clinical investigations.

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Clinical studies shows that acute hyperglycemia developed in the acute organophosphate intoxicated subjects, and such hyperglycemia was associated with poor clinical patient outcomes. However, the hyperglycemic status was mostly observed in in animals with chronic or subchronic exposure. [17, 18] Several in vivo studies demonstrated the acute effect of organophosphate on the variation of blood sugar. Rodrigues et al [19] reported variation of blood sugar after acute organophosphate exposure. For rats receiving a single intraperitoneal injection of malathion, the blood glucose increase within 2 hours, followed by hypoglycemia after 8 hours of injection. [19] In the brain tissue, organophosphate could decrease the storage of glycogen within brain by activating the glycogenolytic enzymes such as glycogen phosphorylase and phosphoglucomutase. [20] The glycolytic enzyme such as phosphofructokinase and hexokinase might decrease in the acute exposure of organophosphate. [21] Collectively these mechanisms could explain the occurrence of acute hyperglycemia following organophosphate exposure.

The original Table 1 has been subdivided into Table 1 (acute organophosphate exposure), and Table 2 (chronic organophosphate exposure) so as to highlight the human studies on the association between organophosphate exposure and the development of new-onset diabetes mellitus.