Author's response to reviews

Title: Public health concern behind the exposure to persistent organic pollutants and the risk of metabolic diseases

Authors:

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Author's response to reviews: see over
Dear Editor and reviewers,

Many thanks for your critical and fruitful comments on my manuscript. Please find below a point-by-point response to each critique.

Best regards

J. Ruzzin

Reviewer: David Carpenter
Reviewer's report:
*You imply that present regulation of POPs is protective against certain diseases, by which I suspect you mean cancer. What is the basis for this statement? There is some evidence that there is more carcinogenicity in the non-dioxin-like PCB fraction than in the dioxin-like fraction, so it is likely that using TEQ methodology does protect against cancer in addition to metabolic diseases.  
Answer:  
Thanks for this pertinent remark. I have now changed some sentences of the Abstract to avoid any confusion for the readers.

*While I agree that the setting of standards based on TEQs is totally inadequate, this review would benefit from elaboration on the relative role of chlorinated pesticides as compared to dioxins/furans/PCBs. Many studies now indicate that some pesticides are more strongly associated with diabetes in humans than other POPs, and as well documented in the review, these are often not regulated at all. Furthermore they are often found at high concentrations in meats, dairy products and eggs as well as seafood.  
Answer:  
The role of chlorinated pesticides in diabetes has now been more highlighted (Lines 89-90; 207-212; 248-249; 597-598; the effect of organochlorine pesticides on insulin-stimulated glucose uptake has also been included in Figure 1)

Reviewer: Andreas Gies
Reviewer’s report:  
This manuscript of Ruzzin is a review on the assessment of POPs and Dioxins in particular. It is well written except many orthographical and grammar errors. In an edited and improved form it is worth publishing as it addresses some main points of discussion in this field.  
However there is some room for further improvement.  
Major revisions to be made:  
In the Stockholm Convention 12 different POPs have been agreed to be phased out. This paper only deals with two of them substantially: Dioxins and PCBs. There are three lines (120-123) discussing the use of DDT. The author should decide either to discuss the use of DDT in malaria vector control thoroughly or to omit this paragraph. There is a WHO position paper on this from 2007 that is worth discussing together with numerous papers carefully trying to weight burden of disease and environmental effects of DDT. Whatever the position of the author might be: this issue is one of the most challenging in modern toxicology with
many ethical implications. So if this will be included in this review it deserves a thorough discussion. If the author decides to omit the DDT paragraph, the title of the paper should reflect that only PCBs and dioxins are discussed.

Answer:
This is an important issue, and I thank the reviewer for this comment. I have now discussed in more details the use of organochlorine pesticides, especially DDT and its use in malaria vector control (Lines 116-133).

Line 182-198
The authors argue that AhR receptor binding derived TEFs do not reflect metabolic effects in humans. Here alternative modes of action (not through the AhR system) should be discussed. There are pros (Wang 2011 in EHP) and cons (Alonso-Magdalena 2011 in Nature Rev. Endocr.) that AhR-Receptors are involved. Are conventional TEF-based assessments suitable to protect humans from metabolic outcomes of dioxins also? Or is metabolic disruption the most sensitive endpoint.

Answer:
The discussion about modes of action of POPs should be carefully addressed. From our own experience in this field, metabolic disorders can be observed without the AhR activation. However, the modes of action of POP mixtures, relative to single POP, remain still poorly identified and difficult to discuss in this review. We are currently performing different studies to determine the molecular pathways by which POPs may induce insulin resistance, and I have highlighted some potential mechanisms in the manuscript (line 216-219).

Time trends of metabolic disease and POPs:
There have been numerous papers on time trends of dioxin and PCB concentration in human blood (Humblet 2011, Furuya 2010, Rylander 2009, LaKind 2009, Wiesmüller, 2007). It would be worth discussing these time trends and the time trends of metabolic disease to strengthen the hypothesis that both might be related.

Answer:
The time trends of dioxin and PCB concentration in human blood are now described in the manuscript (lines 154-162). The suggested references have been included in the manuscript (ref 62-66).

Minor revisions:
Line 48 to 59: The author claims that the prevalence of metabolic diseases increases worldwide. It would be appropriate to discuss time trends given in lit. 1 and 2 and not only rates of obese people.

Answer:
I have now presented data regarding the time trends of diabetes and obesity (lines 48-55).

Line 163 ff:
Limitations of risk assessment: It should be mentioned that the derivation of TEFs by SCF has only be based on non-carcinogenetic endpoints (Gies, 2007)

Answer:
This is now mentioned (line 170)

Table 1: No source given, not novel, in my view not necessary

Answer:
Table 1 has been removed.

Careful revision by a native speaker is advised. There are numerous orthographical and grammar errors throughout the manuscript. Some of them are listed below:

- Line 72: areas not area
- Line 73: physical not chemical
- Line 77: contains not containing
- Line 80: Cross-sectional studies with a link to diabetes are epidemiological studies, too
- Line 83: omit “people with”
- Line 88: shown not showed
- Line 105: disruptor not disruptor
- Line 129: believed not believe
- Line 190: my collaborators and I: avoid personal style
- Line 192: were not was

I have carefully checked the manuscript for orthographical and grammar errors. In addition, a native speaker reviewed the manuscript.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests