Author’s response to reviews

Title: Application of the Food Quality Protection Act Children’s Health Safety Factor in the U.S. EPA Pesticide Risk Assessments

Authors:

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Author’s response to reviews:

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Dear Dr. Etzel and Dr. Grandjean,

I am writing to re-submit for the Editorial Board’s consideration a revised manuscript on the application of the Food Quality Protection Act children’s health safety factor in EPA pesticide risk assessments. The manuscript was updated following the suggestions provided by the peer reviewer and all revised files submitted today are identified with a "Jan2020" in the file name. Additionally, as indicated by the Editorial Office, I included a version of the revised manuscript with all changes in 'track change' mode as a Supplementary file.

Manuscript revisions in response to peer reviewer comments are explained below. Section 1 of the Results includes a new analysis of acute dietary exposures as emphasized by the reviewer, and a new table in Section 3 summarizes the information on non-dietary exposures (Table 4). Throughout the manuscript, FQPA assessments for acute dietary exposures, chronic dietary exposures, and other exposure pathways are now presented separately. Additional File 1 submitted with the revised manuscript now includes quotes for the EPA rationales for the assignment of all FQPA factors greater than 1X.

I appreciate the thoughtful feedback provided by the peer reviewer and I hope that this study will be of interest for the readers of the Environmental Health journal.

With best regards,

Olga Naidenko
Reviewer comment: p. 5, lines 14-16. Please be clear that "other sources of uncertainties" existed prior to FQPA and these were folded into the definition of the FQPA SF. Therefore, the general understanding that the FQPA SF always represents a protection for children's health is a misnomer.

Author response: To reflect reviewer’s feedback, the sentence was modified to read, “The FQPA introduced an additional 10-fold margin of safety, and the FQPA-mandated safety assessment applies both to the children’s health safety factor and to other sources of uncertainty.” Similarly, text in the bottom box in Figure 1 was modified to read “FQPA-mandated additional 10-fold margin of safety.” This language follows exactly the text of the Food Quality Protection Act, which states, “In the case of threshold effects, for purposes of clause [FFDCA sec. 408(b)(2)(C)] (ii)(I) an additional 10-fold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of the data with respect to exposure and toxicity to infants and children.” Additionally, this point raised by the reviewer is addressed in the Discussion, where a new sentence was added that reads, “Importantly, even if an additional FQPA factor is assigned, it does not necessarily represent children’s health protection; for non-organophosphate pesticides, the EPA’s primary rationale for applying an additional FQPA factor is due to data uncertainties.”

Reviewer comment: p. 8-9, Table 3 for OPs. Although presumably the FQPA SF is not included as is for Tables 1 and 2 because the FQPA will likely be equivalent for all of them, it would be helpful to include this column.

Author’s response: Column included as requested.

Reviewer comment: p. 9, line 1,2 - Please rephrase "The FQPA regulations require the EPA to review each registered pesticide at least every 15 years" by deleting "at least".

Author’s response: “at least” was deleted.

Reviewer comment: p. 10, lines 3-5. There are updated human health risk assessments for 5 pyrethroids from November 2019 that could be cited:


Author’s response: As EPA writes in the above document, “Cyphenothrin is a non-food use chemical and has no outdoor uses that could result in potential residues in drinking water; therefore, dietary and drinking water assessments are not needed.” The above document does not have an FQPA determination for cyphenothrin, and therefore the pesticide was not included in my revised analysis.

Author’s response: For the same reason as described for cyphenothrin insecticide, it is not included in my revised analysis. As EPA writes in the above document, “A dietary (food + drinking water) exposure and risk assessment is not required for flumethrin since there are no registered food uses and the registered pet collar use is not anticipated to result in drinking water exposures.”


Author’s response: same as above. According to the EPA, “Imiprothrin is considered a non-food use chemical because it is not applied to crops grown for food, nor is it applied in ways where food and water contamination would likely occur.”


Author’s response: Same as above. According to the EPA, “There are currently no registered food uses for momfluorothrin and drinking water exposure is not expected.”


Author’s response: Same as above. According to the EPA, “A dietary exposure assessment was not conducted. Exposures through food and drinking water are not expected since tetramethrin is not used on agricultural sites and other applications do not result in tetramethrin reaching surface and ground water sources of drinking water.”

Reviewer comment: p. 10, lines 5-6: For metalaxyl, it is not quite right to say that "EPA did not publish an FQPA determination for the chronic dietary exposures". Rather, "No chronic dietary endpoint was identified for mfenoxam or metalaxyl; therefore, no chronic dietary assessment was conducted in this assessment." [51]

Author’s response, Sentence has been re-written to read, “For the fungicide metalaxyl, the EPA did not assess chronic dietary exposure scenario, and this pesticide is not included in the FQPA summary statistics for chronic dietary exposures in this study”. Author would like to also highlight that the EPA’s rationale for not assessing chronic dietary exposure for this pesticide is that, “No systemic toxicity was observed in the reproduction and fertility effects study or in any of the chronic toxicity studies.” In contrast, the European Union assessment of metalaxyl did establish a health-based value for chronic dietary exposure (called the acceptable daily intake, or ADI, based on a 2-year study in dogs. (see https://ec.europa.eu/food/plant/pesticides/eu-
Reviewer comment: p. 10, line 8: when referring to acute exposure, please clarify this is acute dietary exposure.

Author’s response: Edits made as requested.

Reviewer comment: p. 10, lines 17-19. Please provide a justification for not including the consideration of the FQPA SF for the acute dietary exposures in your assessment; there may be children's health concerns based on adverse effects observed after an acute dietary exposure. Also, provide a citation for stating that chronic dietary exposure "is most relevant for daily exposure to pesticide residues for the general public."

Author response: Manuscript has been revised with the inclusion of a new analysis of the FQPA SF use for acute dietary exposures, as emphasized by the reviewer. This information is now listed in Tables 1 and 2 and manuscript text was updated accordingly.

Reviewer comment: p. 12, lines 14-15. For tebuconazole, please clarify that while EPA first used an FQPA SF of 3X in 2008, it was retained in 2018 [56]. Please also include a discussion as to why the 10X was reduced to 3X in 2008.

Author’s response: That sentence was edited, and the new text reads, “In 2008, the EPA substituted a 3X FQPA factor for tebuconazole by referring to an unpublished benchmark dose analysis of toxicological studies for this pesticide [84], and that decision was maintained in a 2018 assessment [56].”

Reviewer comment: p. 12, lines 21-22. For thiophanate methyl, please include a discussion as to why a 3X was selected over a 10X for lack of a developmental thyroid study.

Author’s reply: The entire paragraph discussing thiophanate-methyl assessment was updated.


Author’s response: Study suggested by the reviewer is now cited as reference 85.
Reviewer comment: p. 14, line 17. The citation [90] does not seem to match with the text. This reference is the 2011 chlorpyrifos human health risk assessment, and the text refers to a non-published study.

Author’s response: Citation list updated.

Reviewer comment: p. 14-16. When referring to the FQPA SF for exposures other than chronic dietary, it would be helpful to discuss briefly that the selection of an endpoint may be from a different study most relevant to that exposure route, necessitating the use of a different FQPA SF.

Author’s response: Entire section 3 has been updated in response to the reviewer’s feedback from the second round of review. In response to this specific comment, first paragraph of section 3 now includes a sentence that reads, “Risk assessment for exposure pathways other than diet may draw on toxicological studies specific to those exposure routes and the FQPA factor determinations may differ between different exposure scenarios.” New Table 4 has been added to Section 3, summarizing FQPA determinations for exposure routes other than diet.

Reviewer comment: p. 15, line 2. Note that residential exposures include both indoor and outdoor settings; see the Standard Operating Procedures for Residential Pesticide Exposure Assessment (Residential SOPs. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Author’s response: Opening paragraph of this section was updated as indicated by the reviewer, and the above EPA report included as reference 93.


Author’s response: Cited as reference 95.

Reviewer comment: p. 15, line 15. Please consider revising "an additional 10X factor was applied" to "a 10X factor was also applied".

Author’s response: Revised as requested.

Reviewer comment: p. 16, lines 6-7. Please confirm that for all of the other pesticides reviewed in the document, only the two listed had FQPA SF above 1X for acute dietary exposures.
Author’s response: Revised manuscript has incorporated additional information in tables 1 and 2 on acute dietary exposures. Overall, of the group of 47 non-organophosphate pesticides, 31 chemicals had an acute dietary exposure assessment, and 4 of those 31 chemicals had an FQPA SF factor above 1X.

Reviewer comment: p. 17, lines 13-17. To explain the "baffling decision" to change the endpoint in the metalochlor assessment, please note that the metalochlor tolerance cited dated 3/21/18 used a 1-year chronic dog study with a LOAEL of 33 mg/kg/day based decreased body weight gain in female. EPA has, as required for Registration Review, reassessed all endpoint selections. In the 9/12/19 risk assessment EPA determined that decreased body weight gain in absence of a decrease in body weight ≥10% is not an adverse effect. The endpoint for chronic dietary exposure was replaced by the 2-generation reproduction study in rats with a LOAEL is 86 mg/kg/day based on decreased pup body weight.

Author’s response: In addition to metolachlor, the author is familiar with other instances where the EPA has deemed a change in physiologic markers of laboratory animals exposed to a test substance not “adverse”. Scientifically, the author disagrees with this approach. The author has also noted that a dismissal of an observed effect from an animal bioassay results in a higher pesticide exposure level for the public, for example for the herbicides metolachlor and 2,4-D. Given the length of the manuscript, an in-depth discussion of all the RfDs for the pesticides reviewed in this study would need to await the next study. The sentence noted by the reviewer has been edited to read, “Yet, in the 2019 assessment, the EPA proposed to establish the reference dose for metolachlor based on an older rather than a newer animal toxicology study, which would increase the exposure limit to metolachlor by 2.7-fold”.

Reviewer comment: p. 18, lines 13-16. In Table 2, it would be helpful to add a footnote or other indication for which pesticides are pyrethroids and neonics.

Author’s response: Information added to Table 2 as requested.


Author’s response: The EPA document added as reference 118.

Reviewer comment: Replace citation 29 for Ametoctradin scoping doc with the 2017 risk assessment which finds there are no adverse effects, and therefore the FQPA SF is not needed. https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0518-0005
Author’s response: Reference 29 updated to refer to 2017 document. Text in the manuscript and entry for ametocradin in Table 2 were updated accordingly. Additionally, reference for chlorantraniliprole [34] was updated.

Reviewer comment: Consider deleting citation 94, as citation 95 as the primary reference should be sufficient.

Author’s response: Citation list updated as requested.

Reviewer comment: Consider citing the publication "Toxic Hangover" by the Center For Biological Diversity that was published on January 7, 2020: https://www.biologicaldiversity.org/campaigns/pesticides_reduction/pdfs/Toxic-Hangover.pdf

Author’s response: Author is familiar with the study; findings from this research project were described in an earlier publication by Donley (already cited as reference 1 in the manuscript), which spurred the author to submit the present article to the Environmental Health journal.