Reviewer's report

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

Version: 0 Date: 01 Oct 2019

Reviewer: Rebecca Dzubow

Reviewer's report:

This is a great topic for a paper as there is light to be shed here; however, there is much more detail, accuracy and clarification that needs to be added.

The author should read and cite: Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment (https://www.epa.gov/sites/production/files/2015-07/documents/determ.pdf). In particular, Figure 3 makes clear that the application of the FQPA safety factor reflects not only the susceptibility concerns related to toxicity and exposure of infants and children, but also may represent LOAEL-to-NOAEL uncertainty (UFL), Subchronic-to-Chronic uncertainty (UFS), or incomplete database (UFDB). (Note: modifying factors are not applied anymore.) In other words, even if the FQPA SF of 10X is retained, it may not represent any protection for infants and children. Therefore, the rationale for the value of the FQPA SF, when above 1X, should also be articulated.

Another document relevant to this topic is: Available EPA Information on Assessing Exposure to Pesticides in Food--A User's Guide (https://www.regulations.gov/document?D=EPA-HQ-OPP-2007-0780-0001). This document states: "It should be noted that OPP considers all of the factors listed above (except the interspecies and intraspecies uncertainty factors) to be responsive to the FQPA mandate."

The author should include additional explanation as to why chronic dietary exposure is being emphasized. There are many other routes of exposure to children that would also require consideration of the FQPA safety factor, such as residential exposure (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide) and spray drift (https://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2013-0676).

Please note the following are newer risk assessments than those cited in the draft manuscript.


Other specific comments:

* P.2, lines 5-6 - "account for pre- and postnatal toxicity and for data gaps regarding pesticide's effects on infants and children" - this sentence needs to also include data gaps related to exposure, as stated in FQPA.

* P.3, lines 2-3 - "Total pesticide bans" - one can argue that bans on certain uses, not necessarily total pesticide bans, are sufficient to protect human health and the environment.

* P.3, line 6 - "voluntary or mandatory pesticide use cancellation" - Voluntary cancellations are often because there is a risk identified by EPA in the course of review of the data, and the registrant agrees to cancel. Mandatory cancellations are generally when the registrant does not agree. Not sure if it matters which for the protection of children's health.

* P.3, lines 6-7 - "use cancellation" - it is not clear if a total pesticide ban or specific use cancellations is what is meant here.

* P.3, line 11 - "Developed on the basis of latest research on pesticide toxicity" - Note that EPA is required by FQPA to review the latest research for each registered pesticide every 15 years (https://www.epa.gov/pesticide-reevaluation/registration-review-process).

* P.4, line 1 - "agricultural spraying" - please clarify if this is referring to OPs, as is the rest of the sentence.


* P.4, line 11 - consider citing other relevant IG reports, including:
* P.4, lines 16 and 21 - "chronic exposures" should be "chronic dietary exposures"

* P.5, line 3 - "largest volume in US agriculture" - please cite USGS 2016 here and add to the reference list.

* P.5, lines 4-5 - "pesticides detected in people" - it would be a stronger argument to identify pesticides detected in infants, children and pregnant women. Also, it is not clear if these were the most commonly pesticides detected in people.

* P.5, line 5 - "biomonitoring studies" - please cite relevant studies here.

* P.5, lines 5-6 - "pesticides commonly detected on fresh produce" - it would be a stronger argument to state:
  
  o whether this list of pesticides are those most commonly detected, and

  o whether these are pesticides used on foods that are most commonly consumed by infants, children and pregnant women.

* P.5, line 6 - "testing conducted by the US Department of Agriculture" - please cite the years or specific reference document (PDP 2016-2017 is referenced in Table 3, footnote 1; please add to reference list)

* P.5, lines 6-7 - "of the 38 pesticides, 37 had a human health risk assessment published between 2011 and 2019" - again, this is because of the 15-year re-review requirement (https://www.epa.gov/pesticide-reevaluation/registration-review-process).


* p. 5, lines 18-23 - the author should include more on how the FQPA SF can differ between exposure scenarios for the same pesticide, as the toxicity data used for that scenario can differ.

* Table 1 - Pesticide risk assessments are challenging for the public to find online. Web citations for each of the cited risk assessments should be included in the reference list.

* Table 1 - noting that there is one developmental toxicity and two reproductive toxicity studies used for the derivation of the chronic reference doses in this table:
  
  o Consider putting more emphasis on endpoints relevant for early life exposures.
EPA presumes that if the endpoints selected for use in dose-response are early life endpoints, then there is no need to apply the 10X FQPA safety factor.

While typical chronic toxicity studies (used for the remaining 7 pesticides on this list) do not explicitly consider early life data, endpoints and doses selected from the chronic toxicity studies to be used in dose-response are chosen to be protective of all relevant endpoints from other available studies.

* Table 1, footnote 1 - "Use estimates listed for metalochlor…" should be its own footnote.

* P.7, lines 2-5 - the date of the laboratory studies are not relevant. Registrants are required to submit specific types of studies (https://www.epa.gov/pesticide-registration/data-requirements-pesticide-registration; https://www.epa.gov/sites/production/files/2016-01/documents/data-require-guide-principle.pdf) that comply with specific testing guidelines (https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/final-test-guidelines-pesticides-and-toxic; https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-870-health-effects-test-guidelines). Additional studies may be required to be submitted by the registrant if additional data gaps are identified by EPA. However, the registrant has no incentive to develop additional studies if they have met all data requirements identified by EPA. It should be noted that studies in the public literature should also be considered by EPA, and whether a literature review has been conducted and whether additional studies were identified should be noted in the human health risk assessment. See: Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (https://www.epa.gov/sites/production/files/2015-07/documents/lit-studies.pdf).

* P.7, line 4 - "based toxicity studies" should say "based on toxicity studies"

* P.7, lines 6-9 - It should be noted whether a literature review has been conducted for epidemiology studies in the public literature, and how they were considered in dose-response determinations. See: Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides (https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0316-0072).

* P. 7, lines 9-15 - While more sensitive endpoints may not have been examined in studies conducted decades ago, during the 15-year review cycle EPA should identify the data gaps and require additional studies when needed.

* Table 2 - it is not clear why table 1 includes estimated use and toxicity study used for derivation of chronic reference dose, but not this table.

* Table 2, Column 2 - please provide references for each of the human health risk assessments here, not in the additional file.

* Table 2 - chlorpyrifos 2017 is not a human health risk assessment, but rather a petition denial. Stating that the 10X FQPA SF was "replaced by 1X in 2017" is not entirely accurate, as a revised risk assessment has not been published indicating the use of a 1X. Similarly, while there is the
recent policy document indicating a 1X is sufficient for the pyrethroids, there are no published risk assessments with this revision. This nuance should be clear. Note also that this pyrethroids policy document is draft, and will be open for public comment (https://www.epa.gov/ingredients-used-pesticide-products/evaluation-fqpa-safety-factor-pyrethrins-and-pyrethroids).

* P. 8, line 10 - "partly restricted" - do you mean the residential ban of 2000? (https://www.epa.gov/ingredients-used-pesticide-products/chlorpyrifos#actions).

* P. 8, line 12 - "decision was reversed in 2017..." is not a completely accurate statement, as a revised risk assessment has not been published indicating the use of a 1X.

* Table 3 - not clear why table 1 includes estimated use and toxicity study used for derivation of chronic reference dose, but not this table.

* Table 3, footnote 1 - p.10, line 2 - "detectable levels of residues" does not indicate whether there are levels identified above the tolerance, or without a tolerance.

* Table 4 - it is not clear why the older cancer classifications are being referred to, if the more recent cancer classifications are assumed to be based on the most up-to-date data.


* P. 11, line 10 - "a rather unique descriptor" - please see the Guidelines for Carcinogen Risk Assessment, p. 2-52): "Multiple descriptors can be used for a single agent, for example, when carcinogenesis is dose- or route-dependent. For example, if an agent causes point-of-contact tumors by one exposure route but adequate testing is negative by another route, then the agent could be described as likely to be carcinogenic by the first route but not likely to be carcinogenic by the second. Another example is when the mode of action is sufficiently understood to conclude that a key event in tumor development would not occur below a certain dose range. In this case, the agent could be described as likely to be carcinogenic above a certain dose range but not likely to be carcinogenic below that range."

* P. 11, lines 11-12 - It is not clear why if the dataset is older it is presumed to be unreliable. See comment above.


* P. 11, line 19 - what is "Hallmarks of Cancer"?
"it cannot be taken for granted that a cancer risk determination, once made, will remain true decades later." FQPA requires the data to be reassessed every 15 years.

"lack of inclusion of relevant human epidemiology data for the development of chronic reference doses" - cite epi guidance which describes when epi data can be used in dose-response.

"harm to the endocrine system" - cite the endocrine disruptors screening program: https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-edsp-overview

"missed opportunity for the U.S. EPA to use the authority" of the FQPA - would rephrase using "fully use"?

Others may have reviewed this topic as well, including:


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