Reviewer’s report

Title: Pesticide exposures and chronic kidney disease of unknown etiology: an epidemiologic review

Version: 0 Date: 13 Feb 2017

Reviewer: Rebecca Laws

Reviewer’s report:

Review of "Pesticide exposures and chronic kidney disease of unknown etiology: an epidemiologic review"

Overall, this is a good review of the existing literature on the association between pesticide exposure and CKD of unknown etiology. This is much needed in the context of this epidemic, making it an important and timely summary of the state of the pesticide hypothesis.

I have some questions about how the qualitative assessment of the articles was assigned, and would like to see a more formal assessment of each article, providing rankings in several categories (i.e. study design, exposure assessment, outcome definition, statistical methods, bias and confounding) that, together, would form the basis of the "explanation value." Though I think the validity comments in the Supplemental tables are well reasoned, it appeared that at times, the validity comments did not match the final explanation value, and I wonder how the value itself was derived for each article.

I find that the Results and Discussion sections are well organized, and guide readers through the literature review. Table 3, in particular, is excellent. Conclusions are well-founded.

Overall, this is a timely and needed review. However, I have some concerns, primarily in regards to how the explanation values were derived, which I have detailed below. I think that incorporation of these comments will result in a stronger review article.

Major compulsory revisions:

* Abstract

  o Lines 44-45: Unclear what "different pesticides in different regions" means in the context of the abstract
    - Because overall goal is not to assess pesticide exposure in relation to other exposures, may not be necessary to mention that no studies investigated interactions in the abstract (but can be discussed in Discussion)

  o Line 50: Was the goal to "discard" this hypothesis or further elucidate it?

* Background
Overall, I think the Background could be framed more clearly. It is unclear from the Background how MeN relates to CKDu. When discussing CKD mortality in Nicaragua and El Salvador, is this MeN or CKDu, or both? One possible way to frame Background is to start with unique features of disease, then describe geography, then describe epidemiology (of MeN/CKDu).

To the reader unfamiliar with this epidemic, it may be unclear how "production of uric acid" is an etiology.

Are there any studies that could be cited to document high exposure levels to pesticides in Central America and/or Sri Lanka?

Line 109: what other regions? Only Egypt?

Lines 119-121: Are you describing authors of this paper, or authors of the papers that you are reviewing? If the former, I would exclude this statement because it may be viewed as speculation.

Lines 123-124: Please elaborate on the aim. The review does more than is stated here - you not only evaluate the current evidence, but you also draw conclusions about the strength of each study to make an overall assessment about pesticides as a causal agent of the CKDu/MeN epidemic. Additionally, here and several other places in the article, it is confusing whether you are interested in only CKDu/MeN, or also in CKD of traditional causes. At times, they are referred to as separate endpoints, but in the review itself, they are lumped together. It may help to elucidate why you included studies not in hotspot areas and to be more clear throughout the review when you use CKD and CKDu in the same sentence.

Methods

Please provide full search query/terms, either in main text or supplemental material

Why was the search started in the year 2000 (out of curiosity) - if there is a reason, it should be noted in text

I recommend expanding comprehensive search beyond 2014 to present-day, to capture studies that may have been published in past 3 years. Please clarify how some articles after 2014 were included - the "manual inclusion" described in Figure 1. It seems that inclusion of articles post-2014 should be included in the same systematic way that articles pre-2014 were included.

Was search further filtered to only include human epidemiological studies?

Unclear how a thesis and a second unpublished work were included - did these appear in search, or were they later added?
As described above, I would recommend designing a ranking system for each article on the basis of various key components of validity, such as study design, exposure assessment, outcome definition, statistical methods, bias and confounding. This would allow for a somewhat more objective determination of explanation value.

* Included in this assessment should be how the outcome was defined and whether exposure assessment was based on self-report, which could introduce the possibility of recall bias, depending on the study design. Currently these two factors do not seem to be considered much in validity comments.

* Clarify how explanation value was assigned

* There seems to be some discrepancy for some articles on validity comments and explanation value. Having a more systematic way of assigning explanation value would resolve this issue. Some examples are below:

  * Garcia-Trabanino 2005 (validity comments: interpretation difficult, unclear adjustment for confounders)
  
  * Laux 2012 (Authors themselves state that conclusions cannot be made about pesticides and CKD)
  
  * Wanigasuriya 2007 (validity comments: multivariate regression models not well described, and adjusted ORs not presented)
  
  * Athuraliya 2011 (validity comments: diagnosis based on proteinuria may have under-detected CKDu cases in the population)
  
  * Jayasumana 2015 (validity comments: exposure variables are crude, no details on cumulative pesticide use and application was collected)
  
  * Aroonvilairat 2015 (validity comments: scant description of selection of controls)

Discretionary revisions:

* Recommend not including prevalence results in Tables, as it takes away from association results

* Consider incorporating Supplemental Table material into main Tables 1 and 2, as there is already much overlap. If authors feel strongly that they be separated, do not including redundant information; however, it would be useful to include validity comments in main tables.

Why are hypothesis-generating studies included in Supplemental tables? How are these different from studies that received an explanation value of "None"?

Minor issues not for publication:
* Minor grammar/punctuation errors, some use of colloquial language (i.e. "on the one hand")

* Did authors consider adding search terms to capture AKI outcomes? If so, what is the rationale for not including these?

* Do authors mean eGFR using the CKD-EPI equation instead of eGFR-EPI?

* Supplemental table

  o #19 and #20 include results in description of Exposure assessment

  o #23 is not included in Table 2

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Please indicate how interesting you found the manuscript:

An article of importance in its field

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Please indicate the quality of language in the manuscript:

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