Reviewer’s report

Title: Prevalence and Mortality of Cryptococcal Disease in Adults with Advanced HIV in an Urban Tertiary Hospital in Sierra Leone: A Prospective Study

Version: 0 Date: 06 Jan 2020

Reviewer: Lianne Sheppard

Reviewer's report:

General comments

This paper completely and thoroughly accomplishes the statement in its title: a comprehensive analysis of the animal carcinogenicity data for glyphosate from chronic exposure rodent carcinogenicity studies. Overall this is important work that needs to be published as soon as possible. The paper makes key contributions to the literature and existing regulatory reviews by providing complete analysis results and a summary of all animal toxicology analyses of glyphosate carcinogenicity in one place, and clear documentation of the inclusion and exclusion of available studies in the in-depth analyses conducted.

However, paper should be strengthened to make its contribution even more powerful and comprehensible. While the analysis is thorough and complete, the documentation, organization, and clarity of the messages can be substantially improved. It is important that this paper bring along readers with less expertise in the statistical methods used or in animal carcinogenicity testing procedures so that there is better and broader appreciation of the contribution of this work and the completeness of its documentation. I provide many details in my specific comments below. In addition, I compile here some broad recommendations for revision; I elaborate on most of these below.

(Note: the paper had no page numbers so I numbered them sequentially starting with page 1 for the abstract page.)

1. Try to maintain a consistent ordering of presentation of various studies throughout and help the reader keep track of details by adding liberal cross-referencing of this paper's study reference number, study authors and year, alphabetic label used in the summary tables, and supplemental appendix table number. For instance, Table 1 column 1 should also include the study year, and supplemental appendix table number.

2. Readers need to better understand which cancers were investigated in each study, even if they aren't discussed in the text or presented in the tables. This can either be covered in the methods section (if the list of cancers is the same for all studies) or added to the description of each study in supplementary appendix.

3. The organization, presentation, and flow should be improved:

   a. Some text that belongs in the methods appears in the results

      i. Signposting (i.e. subsection headers) is needed throughout. This includes helping readers less familiar with all the cancer endpoints to navigate the paper.
b. Tables need to be more clearly labeled (see some specific suggestions below)

c. Some work should be summarized in new tables. Specifically there should be a new table that summarizes all studies discussed in the methods but not analyzed in this paper. Also a summary results table should be added that captures the key results currently only presented in the last paragraph of the discussion.

d. Please rewrite so that all work done by Dr. Portier is presented using active voice. This will greatly improve clarity of the paper, particularly in the discussion section.

4. Revise the Discussion section to make it more powerful and help the reader see the overall message of the paper more clearly, namely that there are many more cancers attributable to glyphosate exposure than have been documented previously.

a. Make sure Dr. Portier's work is described using active voice so the reader doesn't get confused about what results are reported here vs. elsewhere.

b. Consider adding an overview paragraph at the beginning of the discussion section describing the results, documenting for instance the number of cancers that have been shown present in more than one species or sex, a list of important cancers identified, etc. (I realize this suggestion duplicates some of the information provided in the summary paragraph at the end of the paper. Thus a key consideration may be the placement of the overview of the results in addition to the additional information I suggest adding.) As noted above, I suggest a table that summarizes the key findings of this paper be added.

c. Endpoint/organ (system) discussions:

i. Use headers to call out the discussion of each endpoint/organ (system) and revise the wording to allow the reader to easily distinguish the new information being introduced in the text.

ii. This section will be more powerful if flows more like a story rather than providing a list of related results, which is how the text currently reads (see e.g. p 15 discussion of the kidney results).

iii. I think it is important to also mention the species (and sexes as relevant) that don't show results and to help the reader put the findings in context. Many readers of this work may not understand which species are most useful for understanding endpoint-specific carcinogenicity in humans. It also seems more balanced to put the results in context of all the species and sexes, and not to merely focus on the statistically significant results. If addressing this comment will introduce too much redundancy in the text, then an alternative approach would be to discuss this point in a new paragraph or integrate it into the p. 17 discussion of the number of tests conducted.

d. The mention of the use of mouse models as surrogates of NHL is an important point that should be brought out more powerfully. I suggest bringing it forward to the beginning of the discussion of lymphomas. (p 16 l 30+)

e. P 17 l 8+: The contrast in results between pure glyphosate and GBH is an important point. Please bring out this point more clearly here and/or revisit it later in the discussion section.
Specific comments

1. P 2. Much of the text about data sources (lines 14-20 and 35-41) is duplicative and should be collapsed. I suggest that the background section be revised to cover high-level comments about the data considered and the details be moved to the methods section.

2. P 3: Table 1 should be revised to be easier to understand and to provide the cross-referencing discussed above.
   
a. Divide the duration, strain column into 3 columns: 2 for strain (rats vs. mice being in different columns) and one for duration.

b. Add a column for glyphosate purity and any other compound-related details.

c. Include any other details that tend to be repeated across studies in the text

d. Consider whether the comments section can be replaced with columns with check boxes for survival differences and weight differences, perhaps with footnotes to provide the details below the table.

3. Individual study discussion (pp 4-6): This should be revised to be easier to follow and read.

   a. There is quite a bit of repetition in text suggesting reorganization would be more effective. A few key points should be made up front, such as which studies were used in this review. I suggest dividing the section into studies used in this review and those not used. There should be a new table that summarizes all the studies not used in the review. I suggest this new table be formatted as similarly to Table 1 as is justified by the available information. Once there are two tables that summarize all studies, it may be possible to shorten this section considerably to highlight key details and observations across studies, using the tables to convey the rest of the details that are currently in the text.

   b. The order of the studies presented in the text should correspond to the order in the summary tables (Table 1 + new table). Also the order of the supplementary tables should correspond to Table 1 and the letter ordering used in this paper.

   c. Consider enhancing readability by removing details from the text that can appear in the tables and also to elaborate on aspects not covered well in the tables. For instance, what does "inconsistency in the data" mean in the discussion of Reyna & Gordon [16] & [27]? (See also point a. above)

   d. Clarify the point about the tumor data in the discussion of Pavkov & Turner [26] since the text seems somewhat contradictory.

4. Data analysis discussion (starts on p 6)

   a. Clarify which endpoints were analyzed with the Cochran-Armitage test. It is possible this should be supported with details here or in the Supplement. Also the discussion notes that 436 tests were conducted, but without further work by the reader, it is impossible to know how this number was obtained. This should be clearly documented in the paper, presumably in this section.
b. Use active voice to make it clear what the author did throughout this section. For instance, p 6 lines 34-35, 39-42.

c. For clarity, it would be helpful to provide all three models in notation. This could be added here or in the supplement. For instance, the notation will make it much clearer what is meant by "individual background responses". It will also clarify the handling of the individual background in the third model (which I think the text implies is included, but complete clarity provided by the notation would be helpful).

d. Add text, e.g. in parentheses, to link the wording in this section to the column headings in Tables 2-4.

e. P 7 l 8+: The discussion of the historical control data analysis should be expanded for clarity and with an eye towards the discussion section. Somewhere there should be mention of the source of the historical control data and the sample sizes considered. It would also be helpful to indicate the tumors where this assessment is expected and/or used in this paper.

5. Results overview p 7:

a. Lines 24-32 belong in the methods section. Also clarify why there are rows with all non-significant p-values in the tables since my reading of the text suggests this should not be the case.

b. Line 36: Clarify whether this criterion is within a subgroup (by species and/or strain) or across all studies

c. It would be helpful in this section to indicate which cancers were considered, whether or not they appear in Tables 2-4. The full set of cancers considered needs to be documented in the paper and should be touched on in the results overview.

6. P 7 l 46-47: This sentence belongs in the methods section. Also similar mention of OECD guidelines on p. 10, 13.

7. P 7 l 50-53: This text duplicates earlier mention and should be consolidated in the methods or at the beginning of the results section. Also the consolidated text should more clearly indicate how the selection was made (see comment 5.b. above)

8. Tables 2-4 should be reformatted for greater clarity. Here are some suggestions:

a. A clearer title is needed, e.g. "p-values for the trend test and logistic regression analyses by tumors with at least one study yielding a statistically significant trend test result [ADD subgroup as appropriate] in male and female CD-1 mice"

b. Here or in the text (presumably in the results overview or methods), clarify why there are cancers shown with no statistically significant p-values in the entire row

c. Consider presenting statistically significant p-values in boldface type

9. Species, sex, and tumor-specific results reporting

a. Add sub-headers to the text to indicate sex and class of tumors being discussed
b. Indicate the results being reported that are beyond those shown in the tables

c. P 9 l 44: This source of historical control data is not referenced.

d. P 9 l 56: insert "and no evidence of heterogeneity in response" or similar after "(p=0.031)"

e. Consolidate duplicative text into one place, such as selection of studies reported in Table 3, mentioned on p 10 and for Table 4 on p 13

10. More specific comments on the discussion

a. P 17 l 46: Add a header such as "Results in context and perspective on existing regulatory evaluations"

b. P 18 l 36: replace "in the analyses" with something clearer w.r.t. the reference being to this paper, such as "Tables 2-4" or "results section"

c. P 18 lines 42-3: This sentence deserves to be supported by references!

d. Please use active voice for discussion of all the work reported in this paper. For instance, the sentence that starts at the bottom of p 18 presumably refers to the work done in this paper, but as written it is unclear.

e. P 19 l 8+: Paragraph should be expanded/revised to increase clarity

f. P 19 l 20-21: This sentence should be referenced

g. P 19 l 23+: This text should be revised/expanded to increase clarity.

h. P 19 l 40+: It would be worth having a statistical appendix or the model notation in the methods section to strengthen this statement

i. P 19 l 47: clarify the meaning of the word "proper" here, by providing (reference to) sufficient technical details.

j. P 20 l12-14: This statement is important, but leaves too much unsaid. A reader will wonder how this review identified the significant trends but the study reports did not. (Presumably this is obvious to the author and is because the study reports never conducted the tests. Still it should be stated.) It is probably also worthwhile commenting that this observation implies that the regulatory agencies are not doing a thorough enough review of study reports if they are relying exclusively on the results that the study reports choose to present rather than conducting their own trend tests.

k. P 20 summary paragraph: In addition to relevant comments above about this summary, revise "can be categorized" to use active voice and generally rewrite the text to make the points more powerfully.

11. Additional reference: To anticipate other likely criticisms of this paper, and if it is possible to track this unpublished paper down, the author should mention a recently referenced paper and its relevance to this work: Crump, K., Crouch, E., Zelterman, D., Crump, C., & Haseman, J. (2019).
Accounting for multiple comparisons in statistical analysis of the extensive bioassay data on glyphosate. Submitted to Toxicological Sciences.

12. Supplement: Include more pertinent study-specific information as appropriate and make sure to provide all cross

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No, I declare that I have no competing interests. I do have a great interest in good research on glyphosate health impacts being published.

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