

EXHIBIT 75

From: em.pone.0.3bf209.f664ac0f@editorialmanager.com on behalf of PLOS ONE
[no-reply@editorialmanager.com]
Sent: Saturday, June 21, 2014 1:56 PM
To: Alavanja, Michael (NIH/NCI) [E]
Subject: PLOS ONE Decision: Revise [PONE-D-14-10356] - [EMID:ee47db29a5f419db]

PONE-D-14-10356

Non-Hodgkin Lymphoma risk and insecticide, fungicide and fumigant use in the Agricultural Health Study
PLOS ONE

Dear Dr. Alavanja,

Thank you for submitting your manuscript to PLOS ONE. After careful consideration, we feel that it has merit, but is not suitable for publication as it currently stands. Therefore, my decision is "Major Revision."

The reviewer made many important points. However, please feel free to make any rebuttal.

We encourage you to submit your revision within thirty days of the date of this decision.

When your files are ready, please submit your revision by logging on to <http://pone.edmgr.com/> and following the Submissions Needing Revision link. Do not submit a revised manuscript as a new submission. Before uploading, you should proofread your manuscript very closely for mistakes and grammatical errors. Should your manuscript be accepted for publication, you may not have another chance to make corrections as we do not offer pre-publication proofs.

If you would like to make changes to your financial disclosure, please include your updated statement in your cover letter.

In addition, when submitting your revision please include the following items:

- A rebuttal letter that responds to each point brought up by the academic editor and reviewer(s). This letter should be uploaded as a 'Response to Reviewers' file.
- A clean revised manuscript as your 'Manuscript' file.
- A marked-up copy of the changes made from the previous article file as a 'Revised Manuscript with Track Changes' file. This can be done using 'track changes' in programs such as MS Word and/or highlighting any changes in the new document.

For more information on how to upload your revised submission, see our video:
<http://blogs.plos.org/everyone/2011/05/10/how-to-submit-your-revised-manuscript/>

If you choose not to submit a revision, please notify us.

Yours sincerely,

Suminori Akiba, M.D., Ph.D.
Academic Editor
PLOS ONE

Additional Editor Comments (optional):

The reviewer made many important points. However, please feel free to make any rebuttal.

Minor comments:

P5, line 132

It is a good idea to explain more about the target population.

Response to request for more description of the target population: In the Agricultural Health Study analysis of NHL the target population included individuals who are either private applicators which included mostly farmers but some nursery operators, and commercial applicators which includes persons who apply pesticides as their job. This information is provided in reference 14 and 15 cited in our manuscript. In order to keep within the word limit of PLOS ONE we have kept our responses as short as possible: Thus we have added the following highlighted material to the sentence in the Material and Methods section that describes the target population: "The AHS is a prospective cohort study of 52,394 licensed private applicators (mostly farmers) in Iowa and North Carolina and 4,916 licensed commercial applicators (individuals paid for pesticide applications to farms, homes, lawns, etc.) in Iowa....."

P6, line 150

Authors should explain the method to identify migration more clearly. (I am afraid that it may be difficult for readers who are not familiar in the systems in the US to understand the entire picture of the follow-up of this study.

Response to identifying migration more clearly: In the Agricultural Health Study farmers and commercial applicators tend to be residentially stable. Nonetheless, if a cohort member moves their residence from Iowa or North Carolina to anywhere else they would be lost to cancer follow-up because the catchment area of state cancer registries is limited to that particular state. We are able to use several computerized files to ascertain the current address of an individual and to determine the year the individual left the state and would therefore be lost to cancer follow-up. In order to keep within the word limit of Plosone we have kept our responses as short as possible. Thus we have added the following highlighted material to the sentence in the Material and Methods section which describes how we identify migration i.e. "In addition, we linked cohort members to the state mortality registries of Iowa and North Carolina and

the nation-wide National Death Index to determine vital status, and to the nation-wide address records of the Internal Revenue Service, state-wide motor vehicle registration files, and pesticide license registries of state agricultural departments to determine residence in Iowa or North Carolina.” We have previously described this methodology in more detail and have reference this in this manuscript (references 14 and 15).

Journal requirements:

When submitting your revision, we need you to address these additional requirements.

1. Thank you for stating the following in the Competing Interests section: [The authors declared that no competing interests exist.].

We note that one or more of the authors are employed by a commercial company (IMS, Inc).

Please provide amended statements of Competing Interests and Financial disclosure that declare the affiliation(s) to this company, along with any other relevant declarations relating to employment, consultancy, patents, products in development or marketed products etc. Please confirm that this does not alter your adherence to all PLOS ONE policies on sharing data and materials, as detailed online in our guide for authors <http://www.PLOSone.org/static/editorial.action#competing> by including the following statement: "This does not alter our adherence to PLOS ONE policies on sharing data and materials." If there are restrictions on sharing of data and/or materials, please state these. Please note that we cannot proceed with consideration of your article until this information has been declared.

Response: Joseph Barker is employed by a commercial company (IMS, Inc) to provide computer support for National Cancer Institute studies. Agricultural Health Study (AHS) data are owned by the National Cancer Institute (NCI) and NCI is a component of the National Institutes of Health (a component of the US Government). An IMS employee's participation in the AHS research project does not alter our adherence to National Institute of Health or PLOS ONE policies which are consistent policies on sharing data and materials. Since there are no restrictions on sharing data and/or materials we expect PLOS ONE to complete the review of our article in a timely fashion.

This information should be included in your cover letter; we will change the online submission form on your behalf.

Please be assured that it is standard PLOS ONE policy for corresponding authors to declare, on behalf of all authors, all potential competing interests, for the purposes of transparency. PLOS ONE defines a competing interest as anything that interferes with, or could reasonably be perceived as interfering with, the full and objective presentation, peer review, editorial decision-making, or publication of research or non-research articles submitted to one of the journals. Competing interests can be financial or non-financial, professional, or personal. Competing interests can arise in relationship to an organization or another person. Please follow this link to our website for more details on competing interests: <http://www.PLOSone.org/static/editorial.action#competing>

Response: As corresponding author of this manuscript I can declare, on behalf of all authors, that there are no potential competing interests. I understand PLOS ONE defines a competing interest as anything that interferes with, or could reasonably be perceived as interfering with, the full and objective presentation, peer review, editorial decision-making, or publication of research or non-research articles submitted to one of the journals. Competing interests can be financial or non-financial, professional, or personal. Competing interests can arise in relationship to an organization or another person.

2. Please include the second paragraph in your ethics statement [At enrollment, subjects did not sign a written informed consent form. However, the cover letter of the questionnaire booklet informed subjects of the voluntary nature of participation and the ability to withdraw or to not answer a question, and provided an assurance of confidentiality (including a Privacy Act Notification statement). The letter also included a written summary of the purpose of research, time involved, benefits of research, and a contact for questions about the research. Finally, subjects were specifically informed that their contact information (including Social Security Number), would be used to search health and vital records in the future. The participants provided consent by completing and returning the questionnaire booklet.] in the Methods section of your manuscript, as we note it is currently missing.

Response: In the second paragraph of my ethics statement and in the Methods section of our manuscript, at your direction, I have added the following statement: "At enrollment, subjects did not sign a written informed consent form. However, the cover letter of the questionnaire booklet informed subjects of the voluntary nature of participation and the ability to withdraw or to not answer a question, and provided an assurance of confidentiality (including a Privacy Act Notification statement). The letter also included a written summary of the purpose of research, time involved, benefits of research, and a contact for questions about the research. Finally, subjects were specifically informed that their contact information (including Social Security Number), would be used to search health and vital records in the future. The participants provided consent by completing and returning the questionnaire booklet".

3. We note that you stated "data are available upon request" at submission. Could you please confirm that all data underlying the findings in your study are freely available in the manuscript, supplemental files, or in a public repository? If this is not the case, and your data are available upon request because of an ethical or legal restriction or because you obtained data from a third party, please include the following in your revised cover letter:

Response: As corresponding author of this study I confirm that all de-identified data underlying the findings in the study manuscript and supplemental files are freely available as per NIH policy, which is consistent with PLOS ONE policy.

- a. The reason why your data cannot be made available in the manuscript, the supplemental files, or a public repository;
- b. The name(s) of the individual(s) that readers may contact to request the data;

We will make changes to your data availability statement on your behalf, based on the information you provide. For more information about our data policy and acceptable reasons for not making your data fully available, please refer to: <http://www.plosone.org/static/policies#sharing>

[Note: HTML markup is below. Please do not edit.]

Reviewers' comments:

Reviewer's Responses to Questions

Comments to the Author

1. Is the manuscript technically sound, and do the data support the conclusions?

The manuscript must describe a technically sound piece of scientific research with data that supports the conclusions. Experiments must have been conducted rigorously, with appropriate controls, replication, and sample sizes. The conclusions must be drawn appropriately based on the data presented.

Reviewer #1: Yes

2. Has the statistical analysis been performed appropriately and rigorously?

Reviewer #1: Yes

3. Does the manuscript adhere to the PLOS Data Policy?

Authors must follow the [PLOS Data policy](#), which requires authors to make all data underlying the findings described in their manuscript fully available without restriction. Please refer to the author's Data Availability Statement in the manuscript. All data and related metadata must be deposited in an appropriate public repository, unless already provided as part of the submitted article or supporting information. If there are restrictions on the ability of authors to publicly share data—e.g. privacy or use of data from a third party— these reasons must be specified.

Reviewer #1: Yes

4. Is the manuscript presented in an intelligible fashion and written in standard English?

PLOS ONE does not copyedit accepted manuscripts, so the language in submitted articles must be clear, correct, and unambiguous. Any typographical or grammatical errors should be corrected at revision, so please note any specific errors here.

Reviewer #1: Yes

5. Review Comments to the Author

Please use the space provided to explain your answers to the questions above. You may also include additional comments for the author, including concerns about dual publication, research ethics, or publication ethics. (Please upload your review as an attachment if it exceeds 20,000 characters)

Reviewer #1: A) General comments

This manuscript is well written with a detailed analysis based on a very important prospective agricultural cohort already providing many articles on the field.

However, some limits (large number of different statistical tests realized, correlation of the use of different active ingredients, no data provided on the potential effect of functional types of pesticides, imputation method not used on all missing data...) are not well underlined and discussed. Moreover the originality of the approach is limited.

Response to potential effects of functional types of pesticides: Our manuscript tables 2 and 3 indicate the chemical and functional class of each insecticide, fungicide and fumigant evaluated. In the discussion (lines 337-431) we discussed each pesticide showing a significant association with NHL or an NHL subtype and identified the pesticide's chemical and functional class. These tables (and the accompanying discussion) show no functional or chemical class was solely responsible for the excess risk of NHL or an NHL subtype. In summary significant associations were observed for selected organophosphate insecticides, selected organochlorine insecticides and a pyrethroid insecticide. We observed that individual pesticides and not pesticide groupings by functional class or chemical class provide the strongest analytic method to study etiology, particularly when the individual pesticide is evaluated by NHL subtype. As per your recommendation we added the following sentence to the discussion: "Our results show pesticides of different chemical and functional classes are associated with an excess risk of NHL and NHL subtypes, and all of the individual members of any single class of pesticides were not all associated with an elevated risk of NHL or its subtypes."

Response to imputation methods not used on all missing data: On lines 179-184 we explain that multiple imputation methods were used to impute use of specific pesticides for those who did not complete the phase 2 questionnaire (n=20,968). 36,342 did complete the phase 2 questionnaire, giving a total of 57,310 individuals with phase 1 and phase 2 information. However, we do have some missing data in the cohort database since the phase 1 take-home questionnaire was not completed by some cohort members resulting in missing years of specific pesticide use (duration) and missing the number of times per year the specific pesticide was used (frequency). However, we have information of ever/never use on the vast majority of these individuals since the question was asked in the enrollment questionnaire. On lines 171-178 we explain the extent of the missing data from the phase 2 questionnaire. As per your recommendation

we have added the following as a study limitation on lines 466-468: "We also had reduced statistical power to evaluate some pesticides for total days of use and intensity-weighted days of use because some cohort participants did not complete the phase one take-home questionnaire."

Response- to originality: We disagree with the comment that the originality of the approach is limited. The Agricultural Health Study is one of only a very few large prospective cohort studies (worldwide) of pesticide applicators with regular occupational exposures to a variety of pesticides. Exposure histories were collected from everyone enrolled in the study prior to the onset of an incident cancer. In this study we updated pesticide exposures approximately 5 years after enrollment, so that for many/most cohort participants we have a working lifetime of pesticide exposure history. The cohort has experienced little loss to mortality or cancer incidence follow-up because of the use of the nation-wide National Death Index and population-based cancer registries in Iowa and North Carolina. In addition, we have conducted field studies in which we compared questionnaire-based exposure history to actual dermal and urinary measurements (Reference 50 Thomas et al; Reference 20 Coble et al). We believe the combination of methods used to mitigate measurement error and eliminate case-recall bias is uncommon and possibly unique. These strengths are discussed in the paper. Respectfully, we have made no change to the manuscript.

Authors focused on part of the pesticides (all those that are not herbicides, 20 insecticides, 5 fungicides and 1 fumigant) for which they have information on in the Agricultural Health Study. They studied association between self declared use of these specific pesticides and risk of NHL overall and risk of up to 5 subtypes of NHL conducting to 156 RR in table 2, 52 RR in table 3 and less than 110 RR in table 4 (no sufficient number of cases for many active ingredients for the subtype "Other B-cell types") conducting to more than 300 RRs... How authors take into account the possibility of chance finding. They only made a short comment in the discussion (line 462-463).

Response: In response to the reviewers comment we have added the following statement to the study abstract. "...and, because 26 pesticides were evaluated for their association with NHL and its subtypes some chance findings could have occurred."

Authors should also justify more what was their rationale to group results from insecticides, fungicides and one fumigant into one paper and exclude herbicides from this analysis, the sensitivity analysis with adjustment on total herbicides excepted?

Response: We believe, that since the existing literature linking pesticides to NHL [and other cancers] is judged by the International Agency for Research on Cancer and other pesticide regulatory bodies to be suggestive, but inconclusive, it is of paramount scientific importance to do a comprehensive evaluation of pesticides and their potential role in the etiology of NHL and NHL subtypes in a prospective cohort study. In order to report on this extensive evaluation comprehensively but within the editorial guidelines

of PLOS ONE, we focused on widely-used and economically important insecticides, fungicides and fumigants here, while adjusting for the potentially important confounding effect of total herbicide use. The precedent for evaluating a subset of pesticides by functional class or chemical class is well established in the literature. We do plan to do a related analysis for herbicides and NHL and NHL subtypes. Respectfully, we have made no change to the manuscript.

B) Specific comments

The authors claim in the “Novelty and Impact” section that their findings “on exposed pesticide applicators with high quality exposure information”. Authors should specify that their exposure algorithm (Coble et al, ref 20) was mainly based on the type of Personal Protective Equipment that applicators used and not on other determinants of pesticide exposure like type of sprayers within a particular agricultural setting, hygienic conditions, high exposure events... The reviewer suggests to moderate their emphasis on this point.

Response: The reviewers comment on the AHS exposure algorithm is incorrect (see reference 50 Coble et al.). The AHS exposure algorithm has four exposure determinants: 1) whether the applicator mixed pesticides prior to application (a relatively high potential source of exposure) 2) the method used to apply the pesticide (varying from relatively low exposure methods to relatively high potential exposures method). 3) whether the applicator repaired the application equipment him/herself 4) what type of protective equipment, if any, was worn/used by the pesticide applicator. Other sources of potential exposure (e.g., high pesticide exposure events) were evaluated separately. Respectfully, we have made no change to the manuscript.

Material and Methods section

1) Line 133: The reviewer agrees with some of the exclusion criteria: for example exclusion of individuals living outside one of the 2 states. But, why did authors exclude individuals with some missing data (1,509 individuals excluded because of missing data for potential confounders), but not all people with missing data on at least one variable of interest (for examples. missing information on pesticide from the take home questionnaire for phase 1, see point 4 below or for missing data for exposure metrics, see line 212)?

Response: Both race and total herbicide application days were used in our analytical model because they were both observed to have a small but measureable (>10% change) on the risk of NHL or an NHL subtype. Individual pesticides from the take-home questionnaire were not found to have a meaningful confounding effect on other pesticides evaluated, so there was no need to exclude these pesticides from the analysis. Respectfully, we have made no change to the manuscript.

2) Why did authors exclude applicators with prevalent cancer what ever the type of cancer? What is (are) the source(s) of information on prevalent cancers ? Cancer registries? Self report?

Response: The basic source of information on cancer-prevalence was the population-based cancer registries in Iowa and North Carolina. With the methods we used in this study it would have been impossible to determine if the NHL resulted from a metastasis from an earlier cancer or resulted from the residual effects of treating the earlier cancer. We also avoided potential case-recall bias since prevalent- cancer cases might be expected to recall exposure histories differently than non-cases. Finally, we also avoided the possibility of survival bias with pesticide-induced cancers being either more or less likely to result in death. It was, therefore, deemed reasonable/ preferable to use our approach and avoid the potential consequences of getting a biased result from including prevalent-cancers. Respectfully, we have made no change to the manuscript.

3) Line 150: Authors should provide numbers of individuals for each cause of censored, how many applicators were censored because of death, diagnosis of cancer...between enrolment and the end of follow-up?

Response: Between enrollment and the end of follow-up, 6,195 individuals were diagnosed with an incident cancer other than NHL, 4,619 died without a record of cancer in the registry data, and 1,248 cohort members left the state and could not be followed-up for cancer. Person-years of follow-up accumulated for all of these study participants after enrollment until they were censored for the incident cancer, death or moving out of the state. This information is now included in an additional appendix table since we do not want to exceed the PLOS One word limit for research papers.

4) Line 176: Why authors did not mention any tentative to imput data, in this present paper, from the take home questionnaire for phase 1 or at least discuss the potential bias related with this lack of data for more than 50 % of applicators?

Response: Information on ever use of all 50 pesticides in the AHS was obtained in the phase 1 questionnaire. For all those who did not complete the phase 1 take-home questionnaire, duration of use (i.e., number of years of use) and frequency of use (i.e., number of days per year of use) were missing on 13 insecticides, 4 fungicides and 3 fumigants. However, information on exposure was collected before incident cancer so case-recall bias could not occur. In a paper by Tarone (Tarone et al, American Journal of Industrial Medicine 31:233-242 [1997]) the authors observed that 'the characteristics of farmers who completed only the enrollment questionnaire were quite similar to those of farmers who also completed and returned the take-home questionnaire.' "Although statistically significant differences between respondents and non-respondents were observed, most were small in magnitude and would not be expected to compromise etiologic inferences based on prospectively ascertained health outcomes." Also, we stated the following in our paper "... misclassification of pesticide exposures can occur and can have a sizeable impact on estimates of relative

risk, which in a prospective cohort design would tend to produce false negative results.⁴⁹”

The lack of evidence for case-recall bias, substantial selection bias or random misclassification of exposure is reassuring and suggests the missing data associated with failing to complete a take-home questionnaire should not bias NHL risk estimates. Nonetheless we caution in the paper [in line 458-460]: “A small number of cases exposed to some specific pesticides could lead to false positive or negative findings.” Respectfully, we have made no change to the manuscript.

5) Line 183: Authors should clarify for how many individuals of the phase 2 (from the MM section) did they impute data? It should not be all the 20,968 applicators because some of them died, others stopped pesticide use, some others were lost from follow-up between enrolment and phase 2?

Response: Imputation was performed on all 20,968 applicators as stated in our manuscript because these applicators all completed the enrollment questionnaire and contributed at least some person-time after enrollment. Among the 20,96, the exposures imputed after enrollment were applied until the person was newly diagnosed with cancer, died or move out of the catchment area of the cancer registries or through the end of the study period December 31, 2011 in Iowa and December 31, 2010 in North Carolina. Respectfully, we have made no change to the manuscript.

6) Line 186: How the authors manage potential change in the variable used for the exposure metrics between enrolment data and phase 2 data, especially for PPE use. Fortunately, PPE use changes over time among farmers! And also for the number of days of use per year for specific active ingredient? For example, how authors dealt with a farmer with 20 days per year at phase 1 and 0 days per year at phase 2 with a diagnosis of cancer between the 2 time points?

Response: On lines 197-198 we explain follow-up time is divided into 2-year intervals to accumulate person-time and update time-varying factors (e.g., PPE use and days of use of specific active ingredients). Time varying pesticide exposure data was update by administering our follow-up questionnaire (phase 2) approximately 5 years after enrollment. Therefore, if we use the reviewer’s example- If a farmer with 20 days per year of exposure {multiplied by years of exposure let’s say 10 years, resulting in 200 exposure days to a particular chemical} than responds that they did not use the pesticide during the period of the phase 2 questionnaire they would accumulate no additional days of exposure before the cancer occurred. On the other hand if they used 20 days per year of exposure for 2 additional years during the interval of the phase 2 questionnaire before their cancer they would have 240 days of total exposure in the regular analyses. We also used lagged exposure analysis to discount recent exposures which may not have biological relevance as explained on lines 245-246. Respectfully, we have made no change to the manuscript.

7) Line 215: Authors should clarify at which step of the analysis they tried to take into account their long (and not hierarchised) list of confounders? Initially or only for statistically significant results in order to identify modification of association?

Response: The procedures used to identify potential confounding factors are described in lines 213-228. Briefly, possible confounders were identified from the NHL literature and then examined as potential confounders in the AHS data, with individual pesticide. Line 221 "However, since most of these variables did not change the risk estimates for specific pesticides, we presented results adjusted for age, race, state and total days of herbicide use, which impacted risk estimates by more than 10 % for some subtypes." Respectfully, we have made no change to the manuscript.

8) Line 215: How authors justify to study "State" as a potential confounder in their analysis? Is there no risk to over adjust since agricultural activities and certainly pesticide use are different from the 2 States? What are the different license types? Private and Commercial? Do authors know how the type of license can change relationships with exposure?

Response: In the Agricultural Health Study the two license types are private applicators which included mostly farmers but some nursery operators, and commercial applicators which include persons who apply pesticides as their job. Farmers are generally older than commercial applicators and generally have fewer applications per year but, farmers generally have more years of pesticide application experience. We have added to the sentence on line 127 in the Material and Methods section i.e. "The AHS is a prospective cohort study of 52,394 licensed private applicators (mostly farmers) in Iowa and North Carolina and 4,916 licensed commercial applicators (individuals paid for pesticide applications to farms, homes, lawns etc.) in Iowa, and 32,346 spouses of private applicators.

The variable 'state' demonstrates the two essential attributes of a confounder, namely, 'state' is related to the use of some individual pesticides and it is also related to the risk of some NHL subtypes in our AHS data. The mechanism by which this operates is not completely clear, but we believe there are some work practices that we have not captured in our questionnaires that may influence some exposures and these work practices may vary by state. Since 'state' acts as a confounder it is appropriate to treat the variable as a confounder in our models. On the other hand we believe it is unlikely that 'over adjustment' would be possible since it is unlikely that 'state' is an intervening variable lying along the causal pathway between the exposure and the NHL. Respectfully, we have made no change to the manuscript.

9) Authors could realized polytomous regression after exclusion of other B lymphoma because of diluted effect or loss of statistical power when comparing the different sub-types of cancers (table 4) ?

Response: We believe it is important to show the significant associations of specific pesticides with individual cell types in table 4, but to also temper the finding by showing the results of polytomous regression which demonstrate that no statistically significant cell type effects have been demonstrated. Respectfully, we have made no change to the manuscript.

Results section

The reviewer thinks that providing data for all analyses in the tables 2 to 4 is not necessary and could be replaced by 2 tables: one summarized table on NHL overall with data for yes/no and with the 2 exposure metrics for some of the active ingredients (since data for all NHL are not that new for AHS and not the main interesting results from this paper) with meaningful information according to the authors and the other one with data for subtype analyses without all data (since all homogeneity tests were not statistically significant at least at the 0.05 level) but only meaningful ones from tables 3 and 4. Authors could provide complete results in appendix?

Response: We respectfully disagree with the reviewer. The reviewer is not correct to say "data for all NHL are not new and not the main interest of the paper". Both NHL and its subtypes are very important and have not been previously reported from the AHS for pesticides. International bodies such as the International Agency for Research on Cancer (IARC) among others would benefit greatly in receiving both a comprehensive review of the association of pesticides with NHL and its subtypes. Combining tables to reduce the number of tables from 4 to 2 makes the resulting table very complex or forces us to reduce the content of the table so that the sample size of each analysis is not included in the table. We know, we tried it. In the interest of complete transparency in reporting the data we respectfully choose to leave the tables unchanged in our revised draft.

1) Lines 262 and 263: How authors explained the effect of State for NHL overall and race for multiple myeloma?

Response: African heritage is an established risk factor for multiple myeloma but the biological reason for this excess risk among those with African heritage is not known. Since NHL has been associated with immunosuppression, race and ethnicity, family history of lymphoma, some occupations, animal exposures and other exposures, these factors may be related to 'state'. It is beyond the scope of this paper to discuss these risk factors that do not appear to confound the associations between specific pesticides and NHL. Respectfully, we have made no change to the manuscript.

2) Line 281: there is a typo for coefficient of "determination"?

Response: "coefficient of determination" is now listed in the manuscript without a typo.

3) Other exposure indicators not usually used by authors (available in their questionnaires) like duration of use in years and time since the year (or period) of first use could be presented or at least discussed.

Response: As mentioned in our response above "The AHS exposure algorithm has four exposure determinants: 1) whether the applicator mixed pesticides prior to/during the application (a relatively high potential source of exposure) 2) the method used to apply the pesticide (varying from relatively low exposure methods to relatively high potential exposures methods). 3) whether the applicator repaired the application equipment him/herself 4) what type of protective equipment, if any, was worn/used by the pesticide applicator. So, many determinants of exposure including duration are included in the algorithm. Moreover, we have lag the exposures to exclude the most recent 5 years of exposure as mentioned in the Methods section line 245-251 and found no significant effect. Information on the first use of a pesticide is limited in the questionnaire data so analysis on this variable could not be performed. Respectfully, we have made no change to the manuscript.

Discussion section:

1) DDT was only used by applicators at least 20 years before the enrolment phase of the AHS since it was banned from agricultural use in the USA in the early 70s? Authors could provide percentage of use prior to enrolment among applicators from AHS as they did for lindane. It could be interesting to provide the data on frequencies of use per decades in the AHS cohort or at least the mean duration of use among users and discuss the interesting finding that the possibility that DDT could induce NHL tumors more than 30 years after cessation of use!

Response: Ever use data are available for DDT. In response to the reviewers comment we have added the sentence: "In our study, 12,471 people reported ever using DDT (21 %) prior to enrollment, but only 1 at the phase 2 questionnaire". For organochlorine chemicals which were banned prior to the onset of the AHS field work in 1993, we do not have information on decades of use and cannot provide any additional information in our discussion.

2) Permethrin results: Will authors provide information about the frequencies or at least the respective part of use between uses on animals or crops and discuss the potential effect on exposure metrics to mix the two ways of exposure?

Response: The animal and crop use of permethrin had to be combined here to provide adequate numbers of exposed cases to complete the analysis of the permethrin effect on the multiple myeloma cell type. Essentially all pesticides are applied by a variety of techniques, in that regard permethrin use is not very dissimilar from any other pesticide. At a later time when even more multiple myeloma cases are generated in the cohort we may be able to do an analysis by type of application. Respectfully, we have

made no change to the manuscript.

3) Authors could discuss the impacts of their results on public health policies. For at least, organochlorine insecticides which are banned since many years for some of them and for pesticides still in use in USA.

Response: In the conclusion of our paper (lines 473-475) we state "The epidemiological literature on NHL and these pesticides is inconsistent and although the findings from this large, prospective cohort add important information, additional studies that focus on NHL and its subtypes and specific pesticides are needed." While we understand this is a cautious statement, we believe it is appropriate for any single research paper since we believe a decision on public health policy should be based on the totality of the relevant literature in exposure assessment, toxicology, and epidemiological. In previous review papers by co-authors of this manuscript, recommendations have been made for public health action. We believe that review papers are the appropriate forum for discussing public health policies. Respectfully, we have made no changes to this research manuscript.

Tables 1 and 3

Authors could provide lower and upper bounds for the number of days of use

In Tables 1 and 3 lower and upper bounds have been added to the table for the number of days of use.

6. If you would like your identity to be revealed to the authors, please include your name here (optional).

Your name and review will not be published with the manuscript.

Reviewer #1: (No Response)

[NOTE: If reviewer comments were submitted as an attachment file, they will be attached to this email and accessible via the submission site. Please log into your account, locate the manuscript record, and check for the action link "View Attachments". If this link does not appear, there are no attachment files to be viewed.]