## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | The Prospective Investigation of Pesticide Applicators' Health (PIPAH) Study, a cohort study of professional pesticide users in Great Britain |
| **AUTHORS** | Harding, Anne-Helen; Fox, David; Chen, Yiqun; Pearce, Neil; Fishwick, David; Frost, Gillian |

## VERSION 1 - REVIEW

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| **REVIEWER** | Beyene Negatu<br>PhD Candidate , Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands. E-mail; b.negatu@uu.nl / Beyene.negatu@gmail.com |
| **REVIEW RETURNED** | 26-Dec-2016 |

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| **GENERAL COMMENTS** | Comments to the Author<br>Abstract<br>Any tentative date for completion of data collection was not included.<br>Main document<br>Minor comments/suggestions<br>- Page 1, line 16 first time use of an abbreviation.<br>- Many of the sentences in the introduction, though they are well-known it is better to add some published references.<br>- It would be better to include the number of participants flow in figure 2.<br>- Page 23 line 17-19 in the STROBE Statement it is better to delete the page no and replace it with " not applicable " since the authors only did a descriptive study not yet done an estimate adjustments for potential confounders. Similarly page 23 line 22 in the STROBE Statement also "not applicable".<br>- Page 22 line 32-35 STROBE Statement, it would be better to include a statistical method used in the Cohort description part of the manuscript and add a page number.<br>Major concerns<br>In order to study associations of pesticide exposure and health effects in occupational epidemiology, a detailed exposure assessment by taking into account a variety of factors that can possibly influence occupational pesticide exposure is required.<br>- The authors did not separately consider mixing/loading and spraying stages of pesticide application process in exposure assessment in any of the pesticide related works or class of pesticides why is that?<br>- In assessing of application method only types of application methods was considered but not use frequency of each of the methods? Was frequency of use equally distributed among the application methods?<br>- Intensity of pesticide use might be different among the mentioned pesticide related works or class of pesticides but was not assessed? |

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| | - In assessing PPE use in all of pesticide related works/class of pesticides, questions were written as “did you usually use personal protective equipment?” Did it mean using a full gear of PPE including chemical resistant overall, boots, gloves, or respirators and goggles? Or just one or a group of PPE? This non specificity might imply a range of potential exposure protection that is 10% to 90%, which can considerably affect the final exposure estimate/ exposure–effect association?<br>- The authors mentioned workers from pesticide manufacturing sector were included in the study (9.6 %) , how was questionnaire based pesticide exposure assessment done in those workers ? was that different from the rest of selected mainly agriculture related workers ? |

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| **REVIEWER** | Monika Meyer-Baron<br>Leibniz Research Centre for Working Environment and Human Factors, Germany |
| **REVIEW RETURNED** | 13-Jan-2017 |

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| **GENERAL COMMENTS** | The manuscript provides descriptive data of a study on occupational health of pesticide users. It is most obviously not appropriate to provide the rationale for the study and the chosen approach so I think the description is the only outcome and I feel this is somewhat too little for a paper.<br>The rationale for presenting this part of the data should be made clearer. Was the idea to analyze the comparability of the sample? Then the comparability should be analyzed for the health outcomes as well; not only for some of the other variables.<br>If the intention was to provide the first results, then also some kind of summary of independent and dependent variables should be provided. The occupational characteristics e. g. (not only history and pesticide but also application methods and other things) could be summarized and an idea could be provided which things might be important/are striking/are unexpected for the JEM.<br><br>Other comments<br>Page 4, line 13: The share of neurological conditions was not 6 but 11%.<br>Page 5, line 5: “Individuals obtaining certificates of competence in the safe use of pesticides” I think this is an important bias for the outcomes and should be part of “Strengths and limitations” unless there is a law in Great Britain that uneducated people are not allowed to use pesticides. It can be assumed that the study recruits only those people who are aware that there is a risk in using pesticides and who are inclined to consider it or avoid it.<br>Page 8, line 34ff: Does this mean that the questionnaire was developed, validated and employed in the current study? This paragraph is not overly clear.<br>Page 12, line 39: Why “particulary with respect to their smoking status”? The difference as regards alcohol consumption is almost identical. And the difference regarding their diet is also striking.<br>Page 12/page 13: The size of the portion is not important here since the collected/reported data do not refer to size just to frequency.<br>Page 18, line 15: “greater than 10%” …. asthma (10%)” This is a contradiction.<br>Page 22f: If one applies the attached STROBE statement to the manuscript the following shortcomings should be resolved:<br>Abstract … what was found … : your introduction gives plans for the |

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| | future analyses but almost no information on outcomes.<br>Introduction … prespecified hypotheses: not given.<br>Methods … Results: not clearly separated, outcomes are already mentioned in what could be a methods chapter.<br>Discussion: there is none |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name: Beyene Negatu
Institution and Country: PhD Candidate , Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands.
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Comments to the Author
Abstract
Any tentative date for completion of data collection was not included.

*This cohort was established as a long term study in order to monitor the exposure and health of professional pesticide users in Great Britain. Although the type and frequency of data collected may change over time, currently no end date has been set for the collection of data.*

Main document
Minor comments/suggestions

- Page 1, line 16 first time use of an abbreviation.

*We have added 'Great Britain' before 'GB'*

- Many of the sentences in the introduction, though they are well-known it is better to add some published references.

*We have added some references to this section, as suggested.*

- It would be better to include the number of participants flow in figure 2.

*We have included the number of participants invited and recruited in figure 2.*

- Page 23 line 17-19 in the STROBE Statement it is better to delete the page no and replace it with " not applicable " since the authors only did a descriptive study not yet done an estimate adjustments for potential confounders. Similarly page 23 line 22 in the STROBE Statement
a so "not applicable".

*We have replaced the page number with 'not applicable' as suggested.*

- Page 22 line 32-35 STROBE Statement, it would be better to include a statistical method used in the Cohort description part of the manuscript and add a page number.

*We have added a page number and a brief description of the statistical methods.*

Major concerns
In order to study associations of pesticide exposure and health effects in occupational epidemiology, a detailed exposure assessment by taking into account a variety of factors that can possibly influence occupational pesticide exposure is required.

*The authors agree that exposure assessment is critical in observational studies but at the same time it can also be very difficult to accurately assess complex exposures retrospectively.*

*For the purpose of our response, we have grouped the reviewers' following four comments together because they all deal with queries about additional information on pesticide exposure.*

*The baseline General Questionnaire which participants were invited to complete on joining the study included questions on the respondent's history of pesticide use. These questions had to be appropriate for respondents who had used pesticides for many years. This meant that it was not possible to ask very detailed questions. The question set was based on those used in similar studies of professional pesticide users to facilitate cross-cohort comparisons.*

*In the baseline General Questionnaire, we asked for a simple history of pesticide use which had sufficient information to develop a Crop/Job Exposure Matrix. The study team felt it would be unrealistic to expect respondents to accurately recall detailed information about frequency of application, application rates, application method, and exact PPE used for each application method and stage of pesticide application, for every type of pesticide used over a period which could, in some cases, have lasted for more than 50 years. Recall bias can arise in retrospective assessment, but is likely to become more of an issue the further back in time the work history goes. Such detailed questions might also have affected response rates.*

*The study team recognised the fact that the baseline General Questionnaire did not ask for any details about specific pesticide use. Since enrolling into the study, the study participants have been invited to complete a pesticide use questionnaire every year. For three years, we piloted a detailed questionnaire. In this questionnaire we request information relating to the past year on the main areas where pesticides were used, use of individual pesticide products, frequency and duration of pesticide product use, and application methods and PPE used for different types of pesticide product. The study participants will be invited to complete the full pesticide use questionnaire periodically and to complete a shortened version of the pesticide use questionnaire in the intervening years. In this way the study will be able to track changes in pesticide use over time as well as fill in the details about individual pesticide use.*

*The authors trust that this explanation addresses the following four reviewer comments satisfactorily.*

- The authors did not separately consider mixing/loading and spraying stages of pesticide application process in exposure assessment in any of the pesticide related works or class of pesticides why is that?

- In assessing of application method only types of application methods was considered but not use frequency of each of the methods? Was frequency of use equally distributed among the application methods?

- Intensity of pesticide use might be different among the mentioned pesticide related works or class of pesticides but was not assessed?

- In assessing PPE use in all of pesticide related works/class of pesticides, questions were written as "did you usually use personal protective equipment?" Did it mean using a full gear of PPE including chemical resistant overall, boots, gloves, or respirators and goggles? Or just one or a group of PPE? This non specificity might imply a range ofpotential exposure protection that is 10% to 90%, which can considerablyaffect the final exposure estimate/ exposure–effect association?

- The authors mentioned workers from pesticide manufacturing sector were included in the study (9.6 %) , how was questionnaire based pesticide exposure assessment done in those workers ? was that different from the rest of selected mainly agriculture related workers ?

*We think there may be a misunderstanding here. There are no workers from the manufacturing sector in the PIPAH study. The amenity sector in which 9.6 % of participants work includes those involved in weed, pest and disease control in for example parks, sports grounds, urban areas, highways, rail network, etc. Consequently, all participants completed the same questionnaire.*

Reviewer: 2

Reviewer Name: Monika Meyer-Baron
Institution and Country: Leibniz Research Centre for Working Environment and Human Factors, Germany

Please state any competing interests or state 'None declared': None

declared

Please leave your comments for the authors below

The manuscript provides descriptive data of a study on occupational health of pesticide users. It is most obviously not appropriate to provide the rationale for the study and the chosen approach so I think the description is the only outcome and I feel this is somewhat too little for a paper. The rationale for presenting this part of the data should be made clearer.
Was the idea to analyze the comparability of the sample? Then the comparability should be analyzed for the health outcomes as well; not only for some of the other variables.

If the intention was to provide the first results, then also some kind of summary of independent and dependent variables should be provided. The occupational characteristics e. g. (not only history and pesticide but also application methods and other things) could be summarized and an idea could be provided which things might be important/are striking/are unexpected for the JEM.

*This manuscript was prepared as a 'Cohort Profile', which the BMJ describes as filling 'the space between a study protocol and a results paper'. The profile should 'describe the rationale for a cohort's creation, its methods, baseline data and its future plans'. The BMJ instructions for authors provide the structure and typical content for these Cohort Profiles and the authors followed these when drafting the manuscript. The structure is quite different to that usually found in research papers reporting the results of a specific investigation.*

*We compared some of the cohort characteristics, such as smoking status, with national data. However the study team has not formally analysed any health outcomes and is not planning to do this until we can estimate pesticide exposure from the Crop/Job Exposure Matrix.*

*The reviewer suggested providing more occupational characteristics and we have added summary data relating to the repair or maintenance of application/mixing equipment (see table 5).*

Other comments
Page 4, line 13: The share of neurological conditions was not 6 but 11%.

*Thank you, this has been amended.*

Page 5, line 5: "Individuals obtaining certificates of competence in the safe use of pesticides" I think this is an important bias for the outcomes and should be part of "Strengths and limitations" unless there is a law in Great Britain that uneducated people are not allowed to use pesticides. It can be assumed that the study recruits only those people who are aware that there is a risk in using pesticides and who are inclined to consider it or avoid it.

*The 1986 Control of Pesticides Regulations required all professional pesticide users in GB to be certified in the safe use of pesticides, unless they were born before 1965 in which case they could spray pesticides under 'grandfather rights'. Since November 2015, 'grandfather rights' were revoked and now all professional pesticide users must be certified. The target population for this study are professional pesticide users so there was no bias in the selection of the sampling frames for recruitment into this occupational cohort and the results will be generalizable to professional pesticide users. However the study findings will not be applicable to the general population which includes non-professional pesticide users and bystanders.*

Page 8, line 34ff: Does this mean that the questionnaire was developed, validated and employed in the current study? This paragraph is not overly clear.

*We have added some more information about the baseline questionnaire to clarify this.*

Page 12, line 39: Why "particularly with respect to their smoking status"? The difference as regards alcohol consumption is almost identical. And the difference regarding their diet is also striking.

*The absolute difference between the percentage of non-smokers and smokers and between drinkers and non-drinkers is 9 %. However the relative difference is greater for smoking status: 9 % compared to 18 % for smoking status and 94 % compared to 85 % for alcohol consumption. So we mentioned smoking status in particular because of this higher relative difference and because of the known associations between smoking and a large number of negative health outcomes.*

Page 12/page 13: The size of the portion is not important here since the collected/reported data do not refer to size just to frequency.

*We have removed the portion sizes from the text as suggested.*

Page 18, line 15: "greater than 10%" …. asthma (10%)" This is a contradiction.

*This contradiction arose because of rounding. Lifetime prevalence for asthma is in fact 10.4. We have amended the text to remove this contradiction.*

Page 22f: If one applies the attached STROBE statement to the manuscript the following shortcomings should be resolved:
Abstract … what was found … : your introduction gives plans for the future analyses but almost no information on outcomes.
Introduction … prespecified hypotheses: not given.
Methods … Results: not clearly separated, outcomes are already mentioned in what could be a methods chapter.
Discussion: there is none

*The structure and typical content described in the BMJ's author guidelines for this 'Cohort Profile' category of manuscript means that some of the normally important parts of the STROBE statement are not applicable to this type of manuscript.*

**VERSION 2 – REVIEW**

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| **REVIEWER** | Monika Meyer-Baron<br>Leibniz Research Centre for Working Environment and Human Factors, Germany |
| **REVIEW RETURNED** | 19-Jun-2017 |

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| **GENERAL COMMENTS** | I would appreciate several of your answers would be part of the paper to make it clearer also for other readers. I am not sure EVERY reader is familiar for example with the requirements of a cohort profile set up by BMJ. |

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| **REVIEWER** | Beyene Negatu<br>Institute for Risk Assessment Sciences, Utrecht University, The Netherlands |
| **REVIEW RETURNED** | 04-Jul-2017 |

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| **GENERAL COMMENTS** | The study focused on explaining the cohort profile of a prospective study on long-term health effects of occupational pesticide exposure in certified pesticide applicators in Great Britain (GB). Though the study has still some limitations e.g. a very low response rate (20%) and with a shallow exposure assessment. As it is a cohort study it is |

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| | expected that the limitations will be remedied, and it can contribute a lot to the field occupational epidemiology. |

## VERSION 2 – AUTHOR RESPONSE

**Reviewer: 1**
Reviewer Name: Monika Meyer-Baron
Institution and Country: Leibniz Research Centre for Working Environment and Human Factors, Germany
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
I would appreciate several of your answers would be part of the paper to make it clearer also for other readers. I am not sure EVERY reader is familiar for example with the requirements of a cohort profile set up by BMJ.

We have added a sentence at the end of the Introduction indicating that this paper presents a profile of the cohort study. We have not added more than this because the previous comments and responses will be published along with this paper.

**Reviewer: 2**
Reviewer Name: Beyene Negatu
Institution and Country: Institute for Risk Assessment Sciences, Utrecht University, The Netherlands
Please state any competing interests or state 'None declared': NON

Please leave your comments for the authors below
The study focused on explaining the cohort profile of a prospective study on long-term health effects of occupational pesticide exposure in certified pesticide applicators in Great Britain (GB). Though the study has still some limitations e.g. a very low response rate (20%) and with a shallow exposure assessment. As it is a cohort study it is expected that the limitations will be remedied, and it can contribute a lot to the field occupational epidemiology.