Author’s response to reviews

Title: Lifetime occupational exposure to metals and welding fumes, and risk of glioma: a 7-country population-based case-control study

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Author’s response to reviews:
July 20, 2017
Dr. Leslie Stayner
Editor 
Environmental Health

Dear Dr. Stayner, 

We are pleased to submit a revised version of our paper entitled “Lifetime occupational exposure to metals and welding fumes, and risk of glioma: a 7-country population-based study”, ENHE-D-17-00113.

We would like to sincerely thank the Reviewers for their thoughtful review of our manuscript which we have now revised in light of their comments and suggestions. We provide below our response to the reviewers’ comments and references to changes made in the manuscript. We believe that we were able to successfully respond to all comments.

Reviewer #1
Comment 1: The authors report the findings from a well-designed, large, multi-center, population-based case-control study on occupational exposure to metals and welding fumes and the risk of brain cancer glioma. Advantages of the study include (1) reasonable numbers of exposed cases and controls for each type of exposure, which allowed for more detailed analyses, (2) lifetime occupation history and the use of JEM to assign exposure by duration, probability, and level, and (3) sensitivity analyses evaluating different exposure categories, tumor type, type of interview, and other variables. The manuscript is well written with adequate reporting of study details to evaluate the quality of the study and the results. Findings from the sensitivity analysis is reported in the supplementary table. Minor suggested edits or comments are below.

Response 1: Thank you. We appreciate that our manuscript was well received.

Comment 2: Page 1, line 10: Change "more developed countries" to "high-income countries" (or more economically developed countries).

Response 2: We did.
Comment 3: Page 1, lines 29 to 39. Risk factors for brain tumors. Consider adding radiofrequency electromagnetic fields (including form wireless phones) based on IARC's conclusion of limited evidence.
   Response 3: This has been added.

Comment 4: Page 1, lines 50 -36: Clarify citations for occupational exposure to brain cancer; e.g., reference 13 (cited for chromium) also found an association with iron, lead, cadmium, etc.; other citations should also be checked.
   Response 4: We checked citations for accuracy and completeness, and edited the text when necessary.

Comment 5: Page 4, lines 40 to 45; clarify that the association with extremely low-frequency magnetic fields (cumulative exposure) and glioma was positive in the INTEROCC study (whereas risks were close to null for most of the other occupational exposures).
   Response 5: This has been clarified.

Comment 6: Table 1. Suggest reporting p values if there were significant differences between cases and controls for a specific variable (e.g., are differences in sex, center, asthma and proxy respondent significant?)
   Response 6: We have added this information in the footnote of Table 1.

Comment 7: Table 2. For welding fumes, clarify whether the exposures to other metals (e.g. iron, chromium, nickel) are from welding activities (such as welding on stainless steel) or co-exposures resulting on the job as a welder or from multiple jobs held by the same subject or a combination of these.
   Response 7: We have added a footnote in Table 2 clarifying that for welding fumes, exposures to other metals could come from welding activities, from other activities in the same job and/or from activities in other jobs.

Comment 8: Some of the sensitivity analyses for exposure to cadmium also found ORs greater than one (in addition to the suggested association for the 2nd tier of exposure reported in Table
3) and could be briefly mentioned. In addition, not all the sensitivity analyses seem to be reported in the supplementary tables and it would be of interest to see the actual ORs for cadmium for those analyses. The prevalence of cadmium exposure was lower than the other occupational exposures, resulting in fewer exposed cases and controls for each exposure category, which may result in greater imprecision and/or lower statistical power. Cadmium can cause cytotoxicity in glioma cells.

Response 8: Sensitivity analyses for cadmium (restriction to males, high grade cases, glioblastomas and self-respondents) are shown in Table 3. Additional analyses for several values of lag, probability and duration, including for cadmium, are shown in the Supplemental table. We now raise, in the results and discussion, the suggestive excesses in risk observed in some of the sub-analyses for cadmium. However, we are reluctant to put further emphasis on these findings which were often based on small numbers as elevated risks may not be meaningful. We added a few sentences documenting the cytotoxicity of cadmium.

Comment 9: Page 10, lines 10 to 18. Add welding fumes to the list of IARC carcinogens (cancer sites others than lung, http://monographs.iarc.fr/ENG/Meetings/index1.php; Guha et al. 2017; Lancet Oncol 10-April DOI:10.1016/S1470-2045(17)30255-3

Response 9: We did.


Response 10: We have added these studies in the discussion.

Comment 11: Page 13, Expand a little more on non-differential exposure misclassification and JEM, and discuss the strength and limitations of the specific JEM used in this study. For example, are there outstanding concerns in applying this JEM to other (non-Scandinavian) countries (although there have been attempts to cross-talk to other countries)?

Response 11: The paragraph has been edited as follows:
JEMs consist in assigning the same set of exposures to all subjects holding a given occupational title. They thus overlook idiosyncratic jobs circumstances that can influence exposure levels. This typically leads to non-differential misclassification of exposure, diminishing the opportunity to detect a true association [50]. In a case-control study of occupational exposure to lead there was moderate agreement in exposure estimates between an expert assessment of detailed work history versus a JEM approach, with the JEM demonstrating higher specificity (~0.9) than sensitivity (~0.5) [51]. Several steps were undertaken in the study to adapt FINJEM for application to the INTEROCC study, including peer review by an international panel of occupational hygienists to ensure that INTEROCC JEM estimates better reflected the prevailing exposure patterns in the seven participating countries [35]. A comprehensive comparison of FINJEM exposure estimates to those potentially encountered other countries could not be carried out. However, assessments were found to be reasonably comparable to those in a large population-based case-control study in Montreal, especially for metals and welding fumes [52].

Comment 12: Page 13, lines 24 to 26. While spouses would most likely know some occupational history, such as dates and occupational titles, if is not clear whether they would know detail information on job tasks. A stronger argument against bias from proxy interviews might be that sensitivity analysis restricted to non-proxy interviews found similar findings as analysis including proxy interviews.

Response 12: We agree. This argument is now brought up.

Comment 13: Page 13, limitations. Are there any concerns that the study population is a somewhat young population (30 to 59 years) for some countries?

Response 13: As a whole, our study covers the ages from 30 to 69, with some countries limited to age 59. Based on the SEER registry, the median age at diagnosis of glioma (all subtypes combined) is 59 years. For all subtypes other than glioblastoma and gliosarcoma, the median age is below that [53]. It is possible that the low numbers for older age groups in our study limited our ability to detect associations for exposures longer than those covered here and for subtypes than tend to develop at more advanced ages. We added this to the discussion.
Comment 14 : Supplementary table : All the different sensitivity analyses discussed in the methods do not appear in Table 1, for example, only analyses for two categories of exposure duration are provided whereas the methods state that analyses were done for three categories of exposure duration (e.g. 1-4 years, 5 to 9 years, and 10 years). Other examples of analyses described in the methods but not provided in the supplementary table are analyses using a referent category as never exposed to any metal or welding fumes and the detailed analyses on a priori confounders.

Response 14 : Our Supplementary Table indeed present several, but not all results from the many sensitivity analyses we carried out and described in the methods. We do indicate in the text that the results not shown are consistent with those from the main (presented) analyses. The bulk of findings largely depicts a picture of no association for all agents under study. We believe that adding more results showing ORs around one in the Supplementary Table are not essential. Should the Editor think differently, we can add these. Nevertheless, as results based on categories of duration of exposure (1-4, 5-9, ≥10 years) might be of interest for comparison with other studies, we added these in our main table (Table 3).

Reviewer #2
Comment 1 : This is a very well written manuscript. Just a few comments.
Response 1 : Thank you.

Comment 2 : Page 5 line 23: presumably only primary glioma or meningioma cases are included?
Response 2 : Yes, we now specify this.

Comment 3: Page 5 line 33: although methods are described elsewhere in more detail, it is important to state here whether the controls were hospital or population controls.
Response 3: Controls were randomly selected from electoral lists (Australia, Canada-Montreal, France, New Zealand), population-based registries (Canada-Vancouver, Germany, Israel), patient lists (UK), or random digit dialing (Canada-Ottawa). This information has been added to the text.
Comment 4: Page 8 line 45: what is the SIOPS variable based on? Occupation presumably? If so, what occupation in the occupational history is chosen to base SIOPS on?

Response 4: We now indicate that it was expressed as a time-weighted average across all jobs.

Comment 5: Page 8 line 54: for what reasons would the SIOPS variable be missing? Is this the case for participants that never had a job?

Response 5: This occurred when the occupation was unknown. It is now specified.

Comment 6: Page 9 line 31: what was the smoking status variable based on? Current smoking status or smoking status prior to diagnosis?

Response 6: We now clarify that the smoking status refers to the time of diagnosis or interview.

Comment 7: Page 9 line 55-58: this is a strange sentence: the sentence suggests that participants were generally never smokers, while the table suggests ½ were never smokers.

Response 7: This sentence was indeed unclear. We have reformulated it.

Comment 8: Page 11 line 16: this sentence suggests that iron and steel founding is classified as a Group 1 carcinogen for all cancers other than brain cancer, which is not the case.

Response 8: This sentence was also unclear and it has been edited.