Author's response to reviews

Title: Auditory dysfunction associated with solvent exposure

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Author's response to reviews: see over
Dear Editor

Re. “Auditory dysfunction associated with solvent exposure” MS: 9553587738081718

Thank you for forwarding to us the very thoughtful comments provided by the reviewers of this manuscript. We are pleased to submit the revised manuscript for possible inclusion in BMC Public Health. My co-authors and I have revised the manuscript carefully after considering the changes suggested by the reviewers.

The following changes have been made according to the comments previously received:

Reviewer: Dr Dimitrios Balatsouras

The analysis of TEOAEs in the Method section was changed as suggested “The presence of a TEOAE response was determined by analysing the amplitudes”.

Reviewer: Dr Ann-Christin Johnson

1. This study is very interesting and it addresses an important area of hearing research. The knowledge in this field is generally limited and information about ototoxicity of chemical substances is still needed. The question raised by the authors about how to test solvent induced hearing loss is clearly relevant and the results of this study gives suggestions of relevant test procedures that could answer some of these questions.

2. The Title is relevant and the Abstract covers the content of the study.
3. The English language could be a little more scientific and needs to be looked into (e.g. a lot of also, also is found).

R. The manuscript has been carefully reviewed by a native English-speaker and language changes have been made accordingly.

4. The Background and Introduction is very long. It gives a thorough review of the area, citing relevant literature, but with too many details. It could be shortened. In my opinion some of the references are better placed in the Discussion when the specific results are discussed.

R. The background section has been shortened and details about specific studies have been moved to the discussion section, as suggested by the reviewer.

5. This part is not very clear (see questions below) and the order of the descriptions should be considered. MER

R. The method section has been completely reorganised.

6. It is not clear how many subjects that were included from the start of the study, was it 100 + 100 before or after all the exclusions?

R. In the revised version of the manuscript, details about the initial number of participants is given in the method section. The number of subjects excluded from the sample and the reason of such exclusion are provided in the beginning of the results section. The selection criteria are mentioned in the method section.

Discretionary revisions:

Subjects

7. How was the educational background in the groups matched?

R. Educational level was defined as incomplete secondary education, complete secondary education or tertiary studies. This explanation has been added in the method section accordingly (see page 6).

8. How many in the exposed group worked in the paint factories and how many in the laboratory?

R. In the revised version only subjects from the paint-making factories have been included.
9. The part on Exclusions from the different groups (p7 ff) is partly a result since it is based on the answers from the questionnaire and the actual figures about which and how many subjects that were excluded should be moved to the results section.

R. This part has been moved to the beginning of the results section.

10. The number of subjects excluded and the reason could there be presented in a table.

R. The number of subjects excluded from each group and the reasons have been included in the beginning of the results section (in the body of the manuscript).

11. In the Method section it should be stated the criteria for exclusion that was (hopefully) decided before the study started.

R. The selection/exclusion criteria are explained in the beginning of the method section, which indeed was decided before collecting the data.

12. The definition of tympanometric results of Type A should be defined.

R. In the revised version of the paper an explanation for Type A results in tympanometry has been added: “tympanic peak pressure between -100 and +50 daPa and static compliance ≥ 0.2 mL” (see page 6).

13. The definition of non-sensorineural hearing loss as an exclusion criteria should be given

R. The definition of non-sensorineural hearing loss as an exclusion criterion is now provided in the manuscript: “Subjects with a conductive component in the audiogram (presence of an air-bone gap at two or more frequencies equal or higher than 10 dB HL) were excluded from the final sample” (see page 8).

14. The procedure of each of the audiological test methods are given later under Methods but I cannot find it a description of how the total procedure was performed.

R. A description of how the whole procedure was carried out is now provided in the method section of the revised manuscript.

14a. Were all tests in one subject done at the same time, in what order were the tests presented to the subjects etc?

R. All subjects were tested during one session and all tests were conducted in the same order (please see the method section).
14b. Was the questionnaire filled in by the project leader after interviews and was this done at the same time as the testing?

R. The questionnaire was conducted by the first author of this manuscript and it was done right before testing, as explained in the method section.

15. There are too much details about how the work in the paint factories and the laboratory was conducted. This part could be shortened and written more stringent.

R. This part has been shortened, as suggested. (see page 7).

16. However the part talking about the exposure assessment based on previous record should be more detailed.

16a. How many records?

R. In the revised version we have now mentioned the number of records (see page 7)

16b. How and when was the sampling done?

R. In the revised manuscript we have now mentioned how and when the records were obtained (see page 7)

16c. How was the means calculated?

R. The means were calculated based on 15 single measurements (see page 7).

17. Regarding Random Gap detection (p 10) it should be described how the threshold was established, as the gaps in ms or what?

R. In the revised version of the manuscript it has been included that thresholds in milliseconds were obtained: “thresholds were defined as the minimum difference in milliseconds between the onset of both stimuli that was detected by the subject” (see page 9).

18. Regarding TEAOE (p12) it is said that the reproducibility was an out-come but the in the results only the binaural average of the amplitude is discussed. How these amplitudes were calculated (which frequency bands etc) could be given in the methods.

R. “TEAOEs were analysed by deriving the mean response for each ear in dB SNR. Amplitudes at each frequency band were also examined. The binaural response of TEOAEs in dB SNR was then calculated and further used in the statistical analyses. The binaural average of the mean amplitude
of TEOAEs is expressed by the following formula: (mean TEOAEs dB SNR right ear + mean TEOAEs dB SNR left ear)/2”. (see page 8-9).

19. The definition of hearing loss based on the audiograms needs to be clarified.

R. In the revised manuscript, the results are not shown in terms of hearing loss, so this part has been removed.

19a. What was the definition for high-frequency HL?

R. In the revision version, high frequency hearing loss has been removed from the analysis.

19b. What is the definition used for unilateral HL?

R. Similarly as above, in the revised version the concept of unilateral hearing loss has been removed.

20. When defining the outcome measures from the different audiological tests (p12-13) the equations for each measure should be given in connection to each test.

R. The equations used for the statistical analyses that relate to each audiological test have been incorporated in the description of each test, as suggested by the reviewer.

20a. It is also hard to read maybe a small table would help for this? MER

R. A Table showing each equation has not been added, as the manuscript already contains too many Tables.

21. Language in this section is not very good. MER

R. The use of language in the section about analytical statistics has been improved.

22. The results here should be coherent to the definitions of different kinds of HL from the PTA that has to be stated in the methods.

R. This part has been removed.

23. It is hard to read and understand the numbers in this part, a table giving the % of the different groups PTA might help?

R. this part has been removed.
24. Figure legends for Figure 1 and 2 shall state that it is means for each separate frequency that is seen. MER

R. The legend of Figure 1 (previously figures 1 and 2) has been replaced with the following text: “Mean right and left ear pure-tone thresholds (250-8000 Hz) and standard errors for both groups of subjects. * denotes significant differences between solvent-exposed and non-exposed control subjects at p < 0.003” (Mann-Whitney test).

25. The figure legends or the figures could indicate which results that was significantly different between the groups?

R. This suggestion has been added in the revised manuscript (see legends for figures 1 and 2).

26. Was a Chi2 test done regarding past Noise exposure also in the controls? MER

R. The Chi2 analysis has been removed.

27. I cannot find that gender was associated with PTA in the multivariate model in Table 4? Is there something wrong with the table or with the text (p16)?

R. The text has been changed accordingly (no gender effect).

28. In the discussion (p17) it is said that past noise exposure was included in the multivariate model but this is not mentioned in the results (at least I cannot find it?)

R. Past noise exposure was indeed included in the multivariate regression models but did not appear significantly associated with any of the outcome measures, that is why it is not mentioned in the results section. However, the tables with the results of the multivariate regression models do include this variable (see tables 4 to 6). Finally, the inclusion of this covariate is mentioned in the Method Section under the subheading of “Data Analysis”.

29. The limitations of the study regarding the design and the groups including the exclusions need to be addressed.

R. A section addressing the limitations of the study has been incorporated in the discussion of the revised manuscript (see page 19-20).

30. The results are discussed but I think more references is needed to support some of the hypotheses.

R. References have been added to the discussion
31. This is particularly needed regarding; Other hearing outcomes (p19-20) and Effects on speech perceptions (p20-21).

R. References have been added to support to the discussion (see page 18-19)

32. Some literature references could also be moved from the Background sections MER.

R. Many references from the background have been moved to the discussion section in the revised version.

Reviewer: Dr Fabriziomaria Gobba

1. Controls are from two inhomogeneous subgroups: administrative employees of the University of Chile and male police officers. First of all, why use male police officers as “controls” in a study on auditory dysfunction? It is hard to suppose that previous exposure to noise due to fire-arm use (but also, possibly, motorbike use etc) is uninfluent. In addition, presumably there are several differences among police officers and the other groups (administrative employees of the University, laboratory workers and workers from the paint-making factories) in terms of life style (e.g. alcohol and smoking, both important for hearing loss, etc.).

R. Taking into consideration the heterogeneity of the groups, we have done new analyses after excluding “police officers” as part of the control group and “laboratory workers” as part of the “exposed-group”. Therefore, the analyses presented in the revised version of the paper are comprised of 72 solvent-exposed workers from two paint-making factories and 72 control group subjects. Control group subjects were employees of the University of Chile who performed different duties (from cleaning to administration). Control-group subjects were matched for educational level to exposed-group subjects. We believe that employees of the University of Chile represent an adequate non-exposed control group as they lived in the same city and had the same educational level as the exposed-group. Covariates such as alcohol consumption and smoking were included in the analyses as confounding factors.

2. But also the group of Exposed workers is composed by 2 clearly different subgroups: “workers from the paint-making factories” and “laboratory workers”: the former were exposed to a mixture of different solvents (MEK, toluene, xylene and varsol and many other including benzol, esters and alcohols), the latter mainly to one solvent only, xylene, at levels apparently low compared to the
occupational limits; furthermore, also the pattern of exposure was presumably different. Accordingly, the 2 subgroups should be considered separately.

R. As explained above, in the revised version of the manuscript we have only included workers from paint-making factories.

3. Another problem: were exposed (“workers from the paint-making factories” and “laboratory workers”) and controls (“administrative employees of the University of Chile and male police officers”) educational level matched, as stated by Authors?

R. Each solvent-exposed subject was matched with one control-group subject according to the educational level, as stated in the method.

4. The Background is too long.

R. The background has been shortened.

5. In the revision of the Background, please consider that the definition of “solvent” is not correct; compare e.g. the IUPAC definition.

R. The IUPAC definition has been incorporated in the revised version of the manuscript (see first paragraph of the introduction).

6. The Authors state that “In the occupational health and safety arena, solvents have been associated with dermal effects [1], neurobehavioral changes [2], and respiratory effects [3]”: but solvents have several other relevant effects, e.g. can be carcinogens, nephrotoxic, etc.

R. This statement has been removed.

7. Page 6-7: What about diseases and use of ototoxic pharmaceutical drugs

R. Subjects with specific health conditions such diabetes, neurological disorders and use of ototoxic drugs were not included in the final sample (see method section).
8. Table 1: the Authors state that the mean number of cigarettes per week in group 2 is 9.3: is so, why is the median 0?

R. The median has been re-typed, 0 was a typographical error in the previous version of the manuscript.

My co-authors and I would like to thank you and your review team for their careful reading of our manuscript and the valuable comments offered. We feel they have led to a much improved revised version and we look forward to receiving your further advice regarding the status of our manuscript.

Yours sincerely,

Adrian Fuente, Ph. D.