Reviewer's report

Title: Efficacy of N,N’bis-(2-mercaptoethyl)isophthalamide on mercury intoxication: A randomized controlled trial

Version: 0 Date: 10 Oct 2017

Reviewer: Nadine Steckling

Reviewer's report:

In this paper, a new chelating agent (N,N’bis-(2-mercaptoethyl)isophthalamide, NBMI) for mercury intoxication was successfully tested in a pilot project in artisanal small-scale gold mining in Ecuador. Several indicators were used to test the efficacy of NBMI. Although the sample size is small, significant reductions of fatigue (physical, total) are the result.

My overall impression is, that the results are important and highly relevant and needs to be published, however, at some points the paper should be clarified to enhance the understanding. The paper contains a huge amount of information. Especially the text in the results section contains too many information. Be more precise. However, the discussion section should be more extensive. Please find my comments below:

- The results section is very long. Do not repeat detailed results in the text which are presented in the tables. It is complicated and the reader is lost in details. E.g., prefer <0.05, <0.01, <0.001 and not significant for the p-value in the text rather than the exact value. Chapter "Mental and physical fatigue score" contains too many information. Suggestion: delete the information about the changes of the points. This could be content of a table. Just mention the proportional change. E.g., "...the mean Total Fatigue Score was reduced by 52%.”

- The discussion should be more extensive. E.g., give more information about the exposure to mercury. Is there an ongoing exposure to mercury during/after the treatment phase? Is it assumable that the miners have not stopped the use of mercury? Is there a sustainable effect assumable if the mercury exposure was not stopped? Discuss the group differences of mercury concentration in urine prior the treatment. Start the discussion by answering the research question. line 537ff: The optimal dose in relation to the body weight should be ascertained to safe resources. line 330f: Discuss it. It would be interesting to know if the severity of the symptoms changed. line 345f: discuss the high decrease in the placebo group. Maybe a psychological effect. line 535: Is overweight common in this group? The sentence could be changed; e.g.: In future studies, the dose of the product should be adapted to the workers body weight. Is it the first study testing NBMI? Mention it.
- The amendments of the protocol are confusing. Please try to reduce this information. E.g., lines 175ff, line 606: It is confusing, that there were different criteria for inclusion applied. If I understand correctly, first, participants were included if the MIS reached a value of at least 5 points. In a second phase, participants were also included if a value of at least 3 points was reached. Thus, all participants finally included have a value of at least 3 points. This should be mentioned in the methods. A limitation of the study is that due to the change of the inclusion criteria, some individuals were not included although they have fulfilled the final inclusion criteria. Try to describe it easy. First, describe the final methods applied. Then, describe variations of the final rules applied and mention the reasons of the variations.

- Please mention the sample size in the abstract.

- Please correct typing errors (e.g., line 435: replace "ad" with "and". Page 22, line 438: delete "in"")

- I recommend moving the text from lines 74 to 82 on page 5 into line 65 on page 4.

- Figure 1 is not mentioned in the text.

- line 120: please replace "…100 mg, 300 mg…" with "…100 mg NBMI, 300 mg NBMI…". line 130: "The subjects were prohibited to drink energy drinks…” rather "The subjects were asked to abstain from energy drinks…"? line 143: please add "either filled with NBMI or placebo capsules or both". line 114: 12 subjects per arm is not correct. Its 12, 11, and 13 subjects per arm.

- lines 102/103: repetition. Delete "After obtaining the informed consent of all interested miners…” Line 7: please replace "…miners with elevated mercury urine levels…” with "…miners with mercury urine levels above 15 µg/l…” Line 10: Please add an explanation in the methods section for the health outcomes mentioned in the results section (line 14). E.g., "…the medical intoxication score and its single health outcomes(e.g. sleeping problems) included, …" Line 49: Recommended change: "A recent study determined the severity of chronic mercury intoxication in terms of disability weights and found the most severe case of intoxication even to be more serious than severe depression and quadriplegia."

- Table 1: The rows for "Sex" and "Ethnic Origin" can be deleted. Mention it in the text.
- Table 2: The rows titled with "No" can be deleted.

- line 308: "...the majority of..." all participants or all treated participants?

- line 318: 0.19 for which group?

- line 374f: "...in all treatment groups" or "...in both treatment and the placebo group"?

- line 399f: The chapter should not start with the information about similar results of the sensitivity analysis. Remove it to the end of the chapter or even to the end of each topic.

- lines 417f: "I should be noted..." Replace "I" with "It" and remove the sentence to the discussion section.

- Table 4: include a column with the total points at screening.

- Table 4: explain abbreviations (e.g., LSmean)

- line 441: I do not understand how a value below 0 is possible.

- Table 5: I do not understand the columns "Change from baseline" "Median", "Min", "Max". E.g., NBMU 100 mg, baseline, median, 66.67 plus 8.21 (change from baseline) is not 64.36 (NBMU 100 mg, day 15).

- line 139: "randomization was done in blocks of six". I do not understand.

- Figure 2: Please define "#Amd. No. 3". Please clarify the brackets in the box "Inclusion". If 12 subjects were screened on protocol version 4.0, how is it possible to include 17?"
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