Author's response to reviews

Title: Low Level Methyl Mercury Exposure Affects Neuropyschological Function in Adults

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Re: MS 1789929710138457

Thank you for the excellent reviews of our ms, and the for the opportunity to improve its quality by revising the text in response to the reviewers' comments. A revised text is uploaded separately; in this letter we wish to note the changes and responses to the reviewers.

Dr Lucchini:
1. we thank the reviewer for this comments; we know that the analysis of dose:response in epidemiological studies is limited, but the data do support a dose-related effect of mercury on the outcomes measured.
2. The concept of treating each settlement separately was considered by us. However, given the small populations in each community and the similarities among them [based on our experience in field work], the aggregation of data has been done by many researchers in Brazil. Within each town, as noted in the paper, there was a similar distribution of mercury exposures and demographic variables. We have added references on prior studies of these populations, which document the similarities in sociodemographic and other characteristics. We have also added a statement to emphasize the potential hazards of aggregation.
3. Data on gender and age were included; each town was assessed and the sample drawn to represent the age/gender distribution for each town. This is stated more clearly in the methods section, with references to the other surveys conducted in these towns.
4. Alcohol consumption was considered as a covariate. Based upon self-report [as well as our familiarity with the communities], there were no heavy consumers of alcohol in the sample (e.g., more than 5 times per week). Alcohol consumption was not a predictor of hair mercury levels. The only significant predictor of hair Hg was fish consumption, as stated in the text.
5. We are planning further analyses of these data using other metrics for estimating dose and effect.

Minor comments from Dr Lucchini:
1. Concentrations of mercury in fish were measured by Yokoo et al in a separate publication (Yokoo et al (2001) Envir Res 86: 88-93); data from this paper are now included in this ms.
2. Exposure levels for hair Hg are now mentioned in the abstract
3. All participants were tested within the same time range in the day and over the same total time

period. This is now stated in the methods.
4. Reference to the WHO is now included in the stat section
5. There is no particular reason why the refusals did or did not differ from the participants, since "time" was the major reason given. Age, gender, diet, and hair Hg were similar.

Dr Malm:
We have re-read the paper for grammar and punctuation. It is the senior author's practice to allow students to write the first version, especially if they are not native English speakers.
1. Dr Malm must not have received the full statement of support as included in the text submitted by email. Full details were provided.
2. We checked the list of abbreviations for consistency
3. References have been changed and additional references provided, with more clarity as to which papers describe data from Amazonia, and which are relevant to Mato Grosso. It should be noted that there are dozens of papers on the topic of Hg exposures in Amazonia; thus, a selection was made of some of the larger studies.
4. The text is changed
5. This citation has been corrected
6. Several references to the census have been included in the text and in the bibliography.
7. The text is corrected
8. There was no recent insecticide spraying in the area of the study

Dr White:
1. Dr White correctly notes that the pattern of neurocognitive deficits was not exactly the same as the prenatal studies, and not all of the domains covered by the developmental studies were assessed in this project. We note this is the abstract and the text. For one reason, in the pediatric studies, appropriate attention was given to assessing developmental milestones in neuropsychological performance, which is not germane to studies of adults. Because the Boston Naming Test has not been validated in this adult population, it was not applied in this study. The difference in results for visual memory may be due in part to the fact that different tests and procedures were used. The Bender Gestalt Test has been used for children and an immediate reproduction score has been used for memory. In our study the Virual Reproduction subtest of the WMS was used, with a delay in reproduction. Thus Dr White is correct in avoiding direct comparison of results between adults and children. We have revised the text to respond to this cogent criticism.
2. This is another excellent point, in that there have been relatively few studies of MeHg exposures in adults at these low doses. Thus inferences as to mechanism have been expressed with more caution in the text, as well as the limitations on inferences from occupational studies of inorganic mercury.
3. The age range was wide and was selected primarily to represent the population distribution in the census. We did use age as a covariate in our analyses, which is probably the most conservative approach given the relatively small size of this study. Over 50% of the total sample is within the range of 25-54 yrs.
4. Education was utilized as a covariate in the analyses, and the definition of educational attainment is presented in the Table 1.
5. As noted above, the similarities were based upon (a) deliberate sampling strategy, so that age/sex distributions reflected the population of each village; we also reported similarities in diet and education. As noted in the response to Dr Malm, we have added further references on the studies of these populations.
6. The dichotomizing was done for illustrative purposes, since there is no "gold standard" for evaluating risks of MeHg to adults. We believe this analysis is informative, and suggests that further studies of dose:response would be valuable.
7. We have added material to respond to the question as to which measures we would predict to be affected by MeHg in adults.
8. We cannot determine the role of chronic vs current MeHg exposures in this cross-sectional study, as we noted in the text. Absent a longitudinal study, we believe that such a conclusion would be

highly speculative.
9. Dr White's comments are well taken, and we have revised this section appropriately.
Minor comments:
1. text is revised to ensure consistency
2. editorial changes, along with those noted by Dr Malm, have been made.