Reviewer's report

Title: Mercury in human brain, blood, muscle and toenails in relation to exposure

Version: 1 Date: 16 July 2007

Reviewer: Alan Stern

Reviewer's report:

General
This is a worthwhile MS that addresses the relationships among various tissues and biomarkers (as well as toenails and dental amalgams) with regards to Hg concentration on autopsy with an emphasis on inorganic Hg. Of particular importance is data on the levels of cumulative inorganic Hg in brain. The study appears to have been well designed and carried out. The authors seem to be unaware, however, that to date, there are very few data on the relationship between toenail Hg and blood Hg. Such data is important for understanding methylmercury (MeHg) exposure in several key studies that employed toenail Hg as their only biomarker of exposure. This MS provies one of the only databases that allows a useful statistical description of this relationship. While it is clear that the authors’ main intent is to assess inorg. Hg relationships, the importance of relationships for the toenail data makes it important to either expand the description and discussion of these data, or to provide an expanded treatment in a separate paper. With that in mind and with several specific comments (see below), I believe that this MS is worthy of publication.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

pg. 7 - Nothing is said with regard to wet weight vs. dry weight concentration of Hg in the tissue samples. This is an important consideration for standardizing such data among studies. This should be specified in the Methods section and reiterated in the Results section.

There is no information regarding the specifics of the toenail sampling. What length of toenail was used? What toe was the nail taken from? How, if at all, were the toenail samples cleaned prior to analysis?

pg. 10, par. 2 - The MeHg/total Hg ratio seems low especially given the fact that the mean MeHg concentration while not high, is not trivial. This should be addressed in the Discussion section.

pg. 11, par. 2 - The significant correlations referred to in the text between total Hg in toenails and MeHg in blood should be given in the text.

pg. 16, par. 1 - The explanation for the lack of significant correlation between inorg. Hg in blood and inorg. Hg in brain is probably correct as far as it goes, but
is an unnecessarily complicated explanation and possibly not the main factor explaining the lack of correlation. Rather, blood inorg. Hg reflects the balance between the rate of intake and the elimination rate of inorg. Hg (approx. 35 days) from both MeHg metabolism and from dental amalgams (largely elemental Hg), and is subject to temporal variation resulting from changes in MeHg intake and short-term disturbance of dental amalgams. Brain inorg. Hg reflects the mercuric Hg that accumulates in the brain due to Hg transported to the brain as elemental Hg and Hg transported to the brain as MeHg that is subsequently oxidized slowly in situ to mercuric Hg. Mercuric Hg is retained longer in the brain than it is in the blood. Thus, the difference in toxicokinetics of inorg. Hg in blood and brain can explain the lack of correlation.

pg. 18, par. 1 - This explanation for the lack of significance of age in the model for brain inorg. Hg concentration is counterintuitive. Wouldn't you expect that high affinity sites would bind preferentially at lower concentration rather than at higher concentration? Alternatively, it may be that MeHg-derived inorg. Hg binds at different sites in the brain than inorg. Hg derived from elemental Hg due to the differences in metabolism to mercuric Hg.

pg. 20, par. 2 - The point about the low correlation between toenail total Hg and brain MeHg is an important observation for the use of toenail Hg for future studies as well as in the interpretation of existing studies using toenail Hg (e.g., cardiovascular studies). This point has not been made in the text and warrants more discussion. Would this biomarker be useful for studies of non-neurological endpoints (i.e., cardiovascular)? To what extent does the reduced correlation between toenail Hg and blood or brain Hg reflect temporal offsets (i.e., moderate half life in blood and brain(?), but long term retention in toenails) that would influence blood and possibly brain concentration more than toenail concentration reflecting an extended period of incorporation?

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Why is the page with the correlations data separate from the main text? These data are an integral part of the MS rather than a "footnote" or appendix and should be included with the tables.

pg. 8, paragraph 1, last line - "Calculated" should be changed to "estimated," since determination by difference incorporates errors from two different measurements.

pg. 11, par. 3 - As worded, the text implies that information about the ratio of inorg. Hg in blood to dental amalgams with the exclusion of case #28 is given in the additional table. Since this is not the case, the wording should be changed.

pg. 13 par. 2 - The authors should give the regression model for toenail Hg in addition to the correlation data. The ability to predict blood levels of Hg (and thus
intake) from toenail data would be very valuable.

pg. 14, par 2, sentence 2 - It is unclear as to what this means or why it is pertinent to the text. This should either be more clearly explained or eliminated.

pg. 16, par. 2 - Give the case number of referred to indirectly.

par 3 and ff. - What about variability in brain inorg. Hg resulting from differences in Se exposure and variability?

pg. 20., par. 1, last sentence - Add the words "as well as fish consumption) after "dental amalgams."

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.