Reviewer's report

Title: Combining Newborn Blood Concentration and Questionnaire Data to Estimate Individual Cumulative Prenatal Methylmercury Exposure

Version: 2 Date: 29 May 2014

Reviewer: Alan Stern

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GENERAL

This is an interesting study that investigates potential associations between gestational MeHg exposure and autism and developmental delay by construction of a pharmacokinetic model that attempts to utilize self-identified consumption data from 3, 2 and 1 month prior to conception as to refine estimates of MeHg during various gestational stages based on the single post-partum infant blood spot Hg concentration.

MAJOR COMPULSORY REVISIONS

In theory, this is an interesting approach. However, it suffers from the unsupported assumption that dietary recall of fish consumption is a highly reliable tool under the best of circumstances (overall correlations between MeHg intake reconstructed from recall and MeHg biomarkers generally fall around 0.3-0.4), much less, 2-5 months post-partum. This means that participants were asked to recall specifics of fish consumption up to 17 months prior to the interview and to distinguish the specifics of fish consumption patterns at that time from the patterns one and two months subsequently. This seems beyond any reasonable use of dietary recall data. This conclusion is supported by the finding that the model's prediction of unrealistically low MeHg concentrations for the categories of fish for which consumption data were collected. The authors attempt to address this by collapsing the fish categories. This results in an estimate of an overall average MeHg concentration in the fish of 42 ppb. However, this also seems unrealistically low since the FDA's reported mean value for canned tuna (which, depending on the study, is either the most commonly consumed seafood, or the second most commonly consumed seafood after shrimp - all other fish rank much lower) is 350 ppb for albacore and 128 ppb for light tuna (http://www.fda.gov/food/foodborneillnesscontaminants/metals/ucm115644.htm). Furthermore, this corrective procedure addresses only the recall for the type of fish consumed. It does not address inaccuracy in recall of the amount of fish consumed during each of the distant recall periods. This creates a fundamental problem in the overall analysis since the study, in part, was designed to refine the investigation of the association between gestational MeHg exposure and autism/developmental delays from the single post-partum blood spot measurement by estimating exposure separately for the second and third trimester. However, this temporal parsing of exposure rests on the temporal
specification of exposure prior to conception. If the estimates of exposure during the pre-conception period as a whole are not reliable, and the separate estimates for individual months pre-conception all the more so, I do not see how the single post-partum infant blood Hg concentration datum can be used to support a trimester-specific estimation of exposure or association with autism/developmental delay. The much more simple and direct analysis that the authors carry out of investigating associations between the blood spot Hg concentration and the autism/developmental delay diagnoses is certainly worthwhile. However, for that analysis, all of the model building in this paper is unnecessary. Since the model building approach is conceptually innovative and obviously required considerable effort, I am reluctant to recommend abandoning the attempt to estimate temporal changes in MeHg intake during gestation. However, given the problems discussed above, I can see no valid way to address the temporal aspects of exposure. I therefore recommend that the authors rewrite this paper to focus only on the investigation of associations between the blood spot Hg measurement and the diagnosis directly.

The title of this paper addresses only the estimate of MeHg exposure. However, the
MS, itself, in addition to constructing the model and using he model to estimate temporal trends in exposure, significantly addresses associations between exposure and the autism/developmental delay diagnoses. The title is, therefore misleading and needs to be rewritten to reflect the key epidemiological aspect of the MS.

MINOR ESSENTIAL REVISIONS

Line 89 - "High doses" is not defined here and associations have been found between what are generally considered low-moderate levels of MeHg exposure and neurologic developmental effects.

Lines 199-212 - The analytical method is not adequately described here. Is this analytical method laser ablation? It is not clear exactly how the laser was used and the connection between the laser and Hg quantitation.

Lines 216-217 - Why were the blood spot Hg concentrations log-transformed? This is not obvious and needs explanation. Log-transformation should not be an a priori default approach. Most statistical procedures do not require normality and log-transformation comes at a price in terms of interpretation of the results.

Lines 238-240 - It should be stated that this is the Cb at steady-state.

Line 243 - "a" is not defined in words. Based on the equation that follows, it is a weighting variable, but that is not sufficiently descriptive and it is not clear what quantities it is weighting and why.

Lines 248-249 - "Notably, the blood mercury concentration is thus expected to be a linear function of the fish mercury concentration." This is only the case at steady, and if the intake rate does, in fact, vary by the month pre-conception (and
if the data collected can, in fact, reflect that variation). then the assumption of achieving steady-state is questionable. Given the relatively long half-life of MeHg in mother and fetus and given the fetal homogenation of blood Hg over time, this may not be critical, but it needs to be discussed.

Line 274 - The value assigned to f requires a citation.

Lines 300-314 - Stern (2005), ""A revised probabilistic estimate of the maternal methyl mercury intake dose corresponding to a measured cord blood mercury concentration." Environ Health Perspect. 2005 Feb;113(2):155-63. Provides a detailed discussion of the appropriate values for the variables in the one-compartment model. Furthermore, as discussed in that paper, these quantities are distributed in the population. At a minimum, this should be acknowledged and its implication addressed.

Lines 351-352 - In addition to the structural problems underlying these estimates of fish MeHg concentration that result in extremely low estimates (discussed above), the relative concentration among the fish types produced by the model doesn't make sense. Tuna Hg concentration tends to be higher, not lower than average ocean fish.

Line 366 - Table 4 and Fig. 2 are presented in terms of "exposure," but the estimates are given in pbb (i.e., concentration.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare that I have no competing interests