Reviewer’s report

Title: Maternal occupational exposure and oral clefts in offspring

Version: 0 Date: 22 Dec 2016

Reviewer: CM Rocheleau

Reviewer's report:

Overall, this is an interesting paper that reads very well and adds useful information to the literature, but there are some issues in the adjusted analysis that I believe must be addressed. Although they are important, I consider them minor because I do not think these would be very time-consuming to correct.

Major issues in the adjusted analysis:

1. Effect modification is completely ignored. Specifically: infant gender was different between the malformed control and case infants. Previous research on the association between herbicides and oral clefts has shown effect modification by infant gender, as the authors note in their background section. These are excellent reasons to examine results stratified by infant gender, not merely adjust for infant gender. Did the authors consider this?

2. The authors defined family history as a positive history of a chromosomal or genetic disorder for controls, not a family history of orofacial clefts. This is unusual; family history is usually defined as family history of the outcome under study (i.e. oral clefts) for both cases and controls. Please explain the rationale and how this would impact interpretation of results.

3. There are more degrees of freedom than exposed cases in most comparisons in table 2. These results are overadjusted, and there will be positivity violations that can cause errors in estimates (even though models will converge in a logistic regression). Common tactics to prevent unnecessary adjustment are backwards selection and/or using a criteria of “change in the estimate of the main effect” criteria.

4. I am not clear on how the adjusted models shown in table 2 were developed. Were the terms for fungicides, insecticides, and herbicides included simultaneously in the same model or separate models? At lines 246-249, it sounds like terms were simultaneously added to the model for pesticide and organic dust, but all cases were co-exposed to organic dust-- again, this can cause biased effect estimates due to positivity violations.

5. I suggest a more thorough evaluation of the potential bias that can be introduced by using malformed controls. One relatively quick and easy approach I've seen in registry-based
studies is to use two control groups (one is infants with chromosomal/genetic disorders, the other is infants with non-chromosomal/genetic disorders other than the defect under study). This might be a useful approach; otherwise I suggest including some mention in the methods of steps the authors took to address these.

Minor suggestions:

6. Please give a brief background of the ALOHA+ JEM. A few sentences should be sufficient.

7. Line 133, typo: divided, not dived.

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