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May 2, 2013

Honorable Luis A. Alejo
Chair of the Assembly Environmental
Safety and Toxic Materials Committee
California State Assembly
P.O. Box 942849, Room 2117
Sacramento, CA 94249-0030

Scientists' Response to Epidemiologic Critique of Gemmill et al. 2013

Dear Assembly Member Alejo:

As you know, we have recently published a paper finding that women who lived near higher methyl bromide (MeBr) applications during pregnancy had babies with reduced birth weight. This paper was published in *Environmental Health Perspectives*, one of the most respected peer-reviewed journals in its field.

A report conducted by a consulting firm (Exponent, Inc) has been submitted to your committee criticizing this paper. We would appreciate the opportunity to address Exponent, Inc's criticisms. We would also like to remind the committee that the paper by Gemmill et al. was conducted by university scientists funded by federal research dollars, with no industry or advocacy funding. The paper underwent rigorous review by both a selection of anonymous peer scientists and the journal editors before publication. Many of Exponent, Inc's criticisms were acknowledged by us in the published paper. Other criticisms were reviewed by the journal's scientific peer-reviewers and editors but found not to undermine the validity of the paper.

As we state in our paper, we present evidence that living near applications of methyl bromide may be associated with poorer fetal growth. This is only one study and additional research is needed. However, this paper is currently one of the only published studies on the subject and it raises important issues about the safety of methyl bromide. We can confidently address each of Exponent Inc's criticisms. We hope the committee will not dismiss this important research.

We respond to each specific criticism from Exponent, Inc. below:

- Lack of direct exposure measurements: There is no good measure of MeBr in the human body. Thus, we used residential proximity to MeBr application as the best available proxy of exposure.

This is a valid exposure proxy because inhalation is the primary route of exposure and, due to the high volatility of this fumigant, proximity to agricultural use is a strong predictor of air concentrations. In fact, a peer-reviewed study conducted by the California Department of Pesticide Regulation (CDPR) and cited in the Exponent review found that agricultural use of MeBr within a 7x7 mile area (~ 5 km radius) explained 95% of the variability in air concentrations (Li et al, 2005), suggesting that residential proximity in this geographical range is a reasonable proxy of ambient exposure in the absence of biomarker measures.

- Dose-response trend that does not appear to be supportive of increased risk: The authors of the Exponent report question our finding that a larger buffer zone resulted in stronger associations. However, a larger radius (5-8 km) from the source of MeBr use actually produces a more accurate estimate of concentrations, as demonstrated in the CDPR study (Li et al.).
- Inconsistencies in associations by trimester: The Exponent authors appear to misunderstand this issue. The fact that we have detailed information on all moves during pregnancy is a strength of this study allowing us to only include women with accurate information on residential exposure at each trimester of pregnancy. Additionally, it is biologically plausible, or even likely, that exposure during certain points in pregnancy would have greater effects on fetal growth. This is not an inconsistency.
- Exposure misclassification: As all epidemiologists know, a certain level of exposure misclassification is inevitable, despite the best efforts to reduce it. As mentioned previously, the extremely high correlation between agricultural MeBr use and air concentrations demonstrated by CDPR *and* accounting for the residential mobility of participants would limit misclassification in our study. Accounting for wind patterns and dispersion has not improved the agreement between fumigant use and air concentrations in previously published studies in the peer-reviewed literature (Honaganahalli and Seiber 2000), and information on MeBr applications to specific fields instead of a square-mile section used in our analyses has little impact on estimated exposure when a radius greater than 3 miles around the home is used.
- Potential for confounding: We controlled for potential confounding by a number of factors, including maternal age, income, education, parity, week of initiating prenatal care, mother's country of birth, and pre-pregnancy BMI. As noted in our paper, we tested smoking, environmental tobacco smoke exposure, and alcohol, caffeine, or illicit drug use but found that they were not confounders in this association. It is important that readers understand that for a factor to act as a confounder, it must be associated with the exposure *and* the outcome and many of the suggested "confounders" mentioned in the Exponent review do not meet this criteria. Of course, residual confounding is a possibility in all epidemiologic studies, but we have done our best to minimize it.
- Lack of independent evaluation of MeBr: The Exponent authors are concerned that we have published many papers looking at other chemical exposures in this population. We want to emphasize that the CHAMACOS study was specifically designed to look at multiple environmental exposures. The fact that we have found associations with other chemicals (e.g. organophosphate pesticides with child development) in no way invalidates our finding of an association of MeBr with birth outcome. All of us are exposed to multiple chemical exposures.

The CHAMACOS study has the advantage of being able to examine these chemical exposures as part of a larger picture.

- Lack of information on MeBr update: We fail to see how this is relevant to our findings.
- Focus on statistical significance and Lack of public health relevance and/or recommendations: We note that living near high use of methyl bromide during the second trimester is associated with a 113 g decrease in birth weight, which is about half of the 250 g birth weight decrease generally associated with maternal smoking (Kramer 1987).
- Lack of information on delivery type: Cesarean vs. vaginal delivery was not seen to be an important issue by the journal reviewers and was not mentioned in the paper. Although it is not reported, we did include delivery type in the analyses and found that it made no difference to our findings.
- Issues with external validity or generalizability: Participants of the CHAMACOS study are similar to residents of farmworker communities in California – a group at particular risk of MeBr exposure. Most women in the study were Latina and born in Mexico. As a group, Mexican immigrant women are at low risk of low birth weight – thus, we observe declines in fetal growth parameters among a more "robust" maternal population. We agree that future studies should analyze the potential effects of MeBr exposure on other populations, particularly those at higher risk of poor birth outcomes. We welcome future studies.

Sincerely,

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