

## A MODEL-BASED APPROACH TO LIMIT OF DETECTION IN STUDYING ENVIRONMENTAL CHEMICAL EXPOSURES AND TIME TO PREGNANCY

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**Background:** Human exposure to persistent environmental pollutants often results in a range of exposures with a proportion of concentrations below laboratory detection limits. Growing evidence supports that inadequate handling of concentrations that are below the limit of detection (LOD) may bias health effects in relation to chemical exposures. We sought to quantify such bias in day specific probability of conception during the fertile window, and propose a model-based approach to reduce the biases.

**Methods:** We assumed a flexible multivariate skewed generalized  $t$  distribution constrained by LODs, which realistically represents the underlying shape of the chemical exposures. Correlations in the multivariate distribution provided information across chemicals. Simulating 1000 datasets with three chemicals exposures having 40-60% below LODs, we compared results from the proposed approach to those from naïve substitution by  $\text{LOD}/\sqrt{2}$  for concentrations below LODs. We further applied the proposed approach to data from the Longitudinal Investigation of Fertility and the Environment (LIFE) Study adjusting for age, parity, daily usage of cigarettes and alcohol.

**Results:** Simulations revealed relative biases 25%, 94%, and 96%, respectively for the three chemicals using substitution, while the proposed approach results are 8%, 9%, and 5%. In LIFE data, polychlorinated biphenyl (PCB) #105, #209, perfluorooctane sulfonamid (PFSA), and cadmium had 26%, 77%, 91% and 43%, respectively, below the LODs. Posterior means (95% credible intervals) for these chemicals are 0.073(-0.303,0.457), 0.240(-0.132,0.604), -0.25(-0.690,0.124), and -0.120(-0.559,0.299) using substitution and -0.015(-0.397,0.407), 0.137(-0.193,0.477), -1.179(-1.929,-0.491), and -0.169(-0.746,0.380) using proposed approach. Substitution yields no significant chemical effects, where the proposed approach shows PFSA is significant and negatively associated with fecundity.

**Conclusions:** In estimating effects of chemical exposures on conception probabilities, the substitution can lead to biased estimates while the proposed method yields more accurate estimates. In LIFE study data, we found a statistically significant negative association between PFSA and day specific conception probabilities.