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Variability in late outcomes: Reducing uncertainty

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Background & Hypothesis: Early exposures to environmental chemicals, such as lead and methylmercury, are reliably associated with late neurotoxicities in children. However, the substantial scatter of observations used to estimate dose-effect relationships seriously limits the ability to predict the impact of exposure on an individual child.

Methodology: In this presentation, three potential sources of variability are identified: 1) errors or imprecision in characterizing dose (and/or outcome); 2) incomplete characterization of endpoint variance attributable to factors other than the exposure of interest; and 3) inter-individual differences in susceptibility, attributable to biological and social-environmental factors. The latter source implies that the long-term impact of early exposure will not the same for all individuals, but will vary depending on host characteristics and the presence of other neurodevelopmental risk factors.

Results: Strategies are suggested for reducing the variability contributed by these sources, including the development of validated PBPK models and biomarkers of early biological effects, the development of more comprehensive models of outcome variance specifically, the application of multi-level models that incorporate supra-individual and supra-family risk factors, and the use of study designs that permit assessment of the effect modifying influence of contextual factors on the form and severity of neurotoxicity.

Implications: Decomposing and explaining the variability in the distribution of observed scores around the best-fit lines representing dose-effect relationships is a major research need with regard to efforts to link early exposures with late outcomes.