Statistical Methods for Evaluating Exposure-Biomarker Relationships

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Levels of exposures and biomarkers vary greatly within and between persons; these levels are subject to measurement error, exposure-biomarker relationships can be nonlinear, and levels of exposures and biomarkers can lie below analytical limits of detection. This combination of factors has limited useful applications of biomarkers for characterizing human health risks. The purpose of this project is to develop and evaluate appropriate statistical models for elucidating the true relationships between exposures to organic toxicants, notably volatile organic compounds, and biomarkers. We apply toxicokinetic theory and models to propose a regression model relating the mean-individual-biomarker level to the mean-individual-exposure level, while allowing both exposure levels and biomarker levels to vary within and between persons. The model permits questions related to saturable metabolism, low-dose linearity, and interindividual variability to be explicitly evaluated. Then, we develop maximum likelihood methods, and the associated computational algorithms, for estimating key regression model parameters, with appropriate adjustments for measurement errors in levels of exposure and biomarkers and with provisions for handling levels below analytical limits of detection. We investigate the validity and precision of these methods using a combination of simulation studies and regression diagnostic methods. Finally, we apply these maximum likelihood methods, and related regression diagnostics to existing exposure-biomarker data sets involving a host of chemical contaminants and biomarkers.

Implications: The methods developed in this study should provide the structure required for useful applications of biomarkers to investigate the nature of risks associated with organic contaminants.

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