Computational Approaches and Tools for Exposure Prioritization and Biomonitoring Data Interpretation

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The ability to describe the source-environment-exposure-dose-response continuum is essential for identifying exposures of greater concern to prioritize chemicals for toxicity testing or risk assessment, as well as for interpreting biomarker data for better assessment of exposure or risk. To link each element in this continuum, scientists at the National Exposure Research Laboratory (NERL) and the National Center for Computational Toxicology (NCCT) are collaborating to develop, evaluate, and apply various computational approaches and tools including predictive environmental fate modeling (*i.e.*, Environmental Fate Simulator (EFS)), exposure modeling, physiological based pharmacokinetic (PBPK) modeling, and pharmacodynamic modeling, and biologically based dose-response modeling. Specifically, NERL currently directs research activities in the following areas: (1) EFS; (2) screening level PBPK modeling; and (3) interpretation and use of biomonitoring data. The components of EFS include: a computational tool for calculating physical and chemical properties based on chemical structure; a reaction pathway simulator for predicting transformation pathways and products; linked databases populated with measured/calculated molecular descriptors necessary for predicting physical transport and chemical reactivity; an expert system for environmental characterization data needed to estimate partitioning behavior and reactivity; and the EFS software that provides seamless linkage of disparate models and databases. Screening level PBPK models are used to link external exposures to tissue dosimetry for improved dose response assessment. NERL scientists utilize a combination of results from *in vitro*/*in vivo* studies and QSAR/computational chemistry techniques to estimate chemical-specific parameters required for PBPK models. This knowledge and expertise are especially important for chiral chemicals, which exist as mixtures of stereoisomers having different physical and/or biological properties but are frequently treated in toxicity testing and risk assessment as single chemicals. For interpreting biomonitoring data, NERL is developing a framework to use the same computational approaches (e.g., PBPK modeling) to assess the quantitative relationships between biomarkers and human exposures. For example, an exposure study is underway to estimate non-occupational exposure to pyrethroids based on urinary biomarkers. This framework will identify the critical data gaps and uncertainties in estimating human exposures and will help in designing future exposure and epidemiological studies.