Mechanistically Consistent PBTK Modeling Framework for Mixtures of Toxic Metals

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BIOLOGICAL MODELS

Estimation of exposures from biomarkers through inversion

PBTK models can be useful in back-calculating exposure from measured biomarker data. To test inversion approaches, a synthetic biomarker (hair+blood) dataset for dietary methylmercury exposure was generated through known exposure and PBTK parameters. Bayes rule and Markov-Chain Monte Carlo (MCMC) using Metropolis sampling was used to estimate: dietary intake rate of methyl mercury; time duration of the exposure; 20 physiochemical and biochemical PBTK parameters.

Existing approaches for reconstruction of exposures from biomarker data at the population level require sampling from the entire range of the population distribution, typically hundreds of thousands of model simulations. An optimization-aided approach (below) can significantly reduce the number of required model simulations when compared to brute-force Monte Carlo inversion. The computational efficiency of the inversion process can further be improved through the use of Fast Equivalent Operational Models (FEOMs) of the PBTK system.

Future and ongoing work

- Forward and inverse simulation using the integrated PBTK modeling system for mixtures of multi-timescale chemicals
- Sensitivity, uncertainty, and robustness analysis of PBTK inversion approaches
- Incorporation of "omics" data and biochemical metabolite data into the framework
- Population parameter estimation and model refinement
- Linking of toxicokinetic and toxicodynamic models, with attention to molecular biomarkers and toxic interactions

References


May 21–23, 2007 • Research Triangle Park, North Carolina