Physiologically Based ToxicoKinetic (PBTK) models have become the tools of choice for predicting the fate of environmental contaminants in humans. While there are several PBTK models that have been proposed for different environmental chemicals, many of them are not mechanistically consistent (especially for toxic metals). There exist several differences in the formulation of these models with respect to (a) physiological structure (body tissue volume and blood flow ratios), (b) general modeling assumptions (for transport and transformation of the chemicals within the body), and (c) exposure-relevant activities. The varying formulations pose a challenge when attempting to model individuals and populations as they are exposed to mixtures of chemicals from the environment. This paper introduces a mechanistically consistent, general PBTK modeling framework for toxic metals.

PBPK models for different metals

Three PBTK models of varying complexity for toxic metals (above)d


Integrated multi-chemical PBPK modeling system

- 10,000 “virtual individuals” were generated to match the demographic characteristics of Oswego County, NY (Data: US Census Survey 2000)
- Food consumption surveys (e.g. CSFII) provided short-term consumption rates (24 hour)
- Food frequency questionnaires (e.g. NHANES data from 1999 onwards) provided qualitative information on long-term (1 month) food consumption patterns
- CSFII and NHANES dietary seafood consumption data were merged to estimate month-long consumption of different seafood categories for each individual (method adapted from Tran et al., 2004)
- Dietary predictions were combined with on-methylmercury levels in each seafood category to produce total month-long methylmercury consumption estimates
- The PBTK framework was used to estimate hair and blood levels of methylmercury (below)

Population-based methylmercury exposure

The dominant exposure route for mercury and methylmercury compounds is dietary ingestion of seafood. Seafowl contamination is a global atmospheric and ecological problem (left).

References

Acknowledgment

This work has not been reviewed by and does not represent the opinions of the funding agencies.

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 special attention to molecular biomarkers and interactions

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Development of a Physiologically-Based Toxicokinetic (PBTK) framework for toxic metals and applications to inhalation and dietary exposure pathways

Abstract

Physiologically Based Toxicokinetic (PBTK) models have become the tools of choice for predicting the fate of environmental contaminants in humans. While there are several PBTK models that have been proposed for different environmental chemicals, many of them are not mechanistically consistent (especially for toxic metals). There exist several differences in the formulation of these models with respect to (a) physiological structure (body tissue volume and blood flow ratios), (b) general modeling assumptions (for transport and transformation of the chemicals within the body), and (c) exposure-relevant activities. The varying formulations pose a challenge when attempting to model individuals and populations as they are exposed to mixtures of chemicals from the environment. This paper introduces a mechanistically consistent, general PBTK modeling framework for toxic metals.

Relative contribution of the inhalation pathway for lead

Ingestion is usually the primary pathway for lead intake. However, the inhalation pathway can become significant for the case of high air lead concentration.

The lead exposure model of O’Flaherty (1993) was run assuming an ambient air lead concentration of (a) half the NAAQS* (top) and (b) twice the NAAQS (bottom). For case (b), the dietary and inhalation exposure contributions are almost equivalent. The burden predicted by the PBTK model reflects the air lead increase (below).

Data:

For other chemicals and multi-pathway cases, these techniques may be helpful in determining dietary vs. inhalation contributions to exposure.

Focus: Methylmercury dose-reconstruction using inversion of the PBTK model

The Bayesian MCMC inversion produced a slightly biased result for dietary intake. The dataset was not sufficient enough to “overwhelm the prior” for hair excretion rate, resulting in an overestimation of exposure. Red lines denote the actual values.

Mean PBTK model values used for all parameters with exception of hair excretion parameters. For case (b), the dietary and inhalation exposure contributions are almost equivalent. The burden predicted by the PBTK model reflects the air lead increase (below).

Population-based methylmercury exposure

The domestic exposure route for mercury and methylmercury compounds is dietary ingestion of seafood. Seafood contamination is a global atmospheric and ecological problem (left).

Population parameter estimation and model refinement

Linking of toxicokinetic and toxicodynamic models, with special attention to molecular biomarkers and interactions

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* NAAQS = National Ambient Air Quality Standards

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