

Mechanistically Consistent PBTK Modeling Framework for Mixtures of Toxic Metals

Alan Sasso, Sastry Isukapalli, Panos Georgopoulos • UMDNJ-RWJ Medical School/EOHSI, Piscataway, NJ

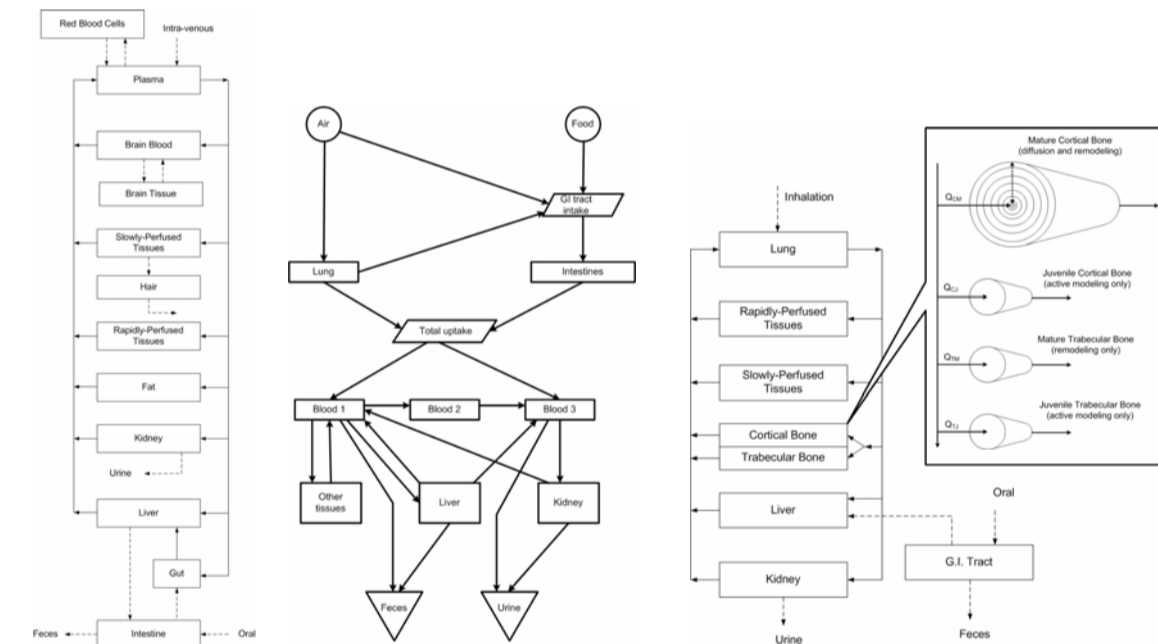
BIOLOGICAL MODELS

Introduction

Toxic metals are often found together in multiple exposure media (soil, food, and air) as mixtures, and interaction effects among these metals exist at the toxicokinetic and toxicodynamic levels in humans. Several physiologically based toxicokinetic (PBTK) models exist for metals. However, differences in the formulation of these models exist with respect to (a) physiological structure (e.g., body tissue volumes and blood flow ratios), (b) general modeling assumptions (e.g., for transport and transformation of the chemicals within the body), and (c) exposure-relevant parameters. The fact that certain assumptions that are appropriate for one metal or metal compound can be incompatible with the assumptions made for another metal makes consistent modeling of mixtures of toxic metals a challenging enterprise.

This work overviews progress towards the development and application of a novel, modular, "generalized" system: the Modeling ENvironment for TOrtal Risk (MENTOR) with Physiologically-based Pharmacokinetic modeling for Populations (3P). It provides an extensible framework that can accommodate new modules describing virtual tissues and organs at various levels of detail. Preliminary case studies using the multi-metals implementation of MENTOR-3P are presented in (a) "forward-mode" for characterizing target tissue doses for either individuals or (statistical) populations, and (b) "inverse-mode" for estimating exposures and PBTK parameters from biomarkers. MENTOR-3P provides the link between MENTOR, for source-to-dose modeling, and the Dose Response Information Analysis system (DORIAN), for dose-to-effect modeling.

PBTK modeling of toxic metals



a) Methylmercury (Shipp et al. 2000) b) Cadmium (Nordberg 1979) c) Lead (O'Flaherty 1993)

- **Methylmercury:** mixed flow/diffusion limited PBTK with hair excretion
- **Cadmium:** biokinetic with metallothionein binding, liver/kidney accumulation
- **Lead:** flow limited PBTK with complex bone diffusion

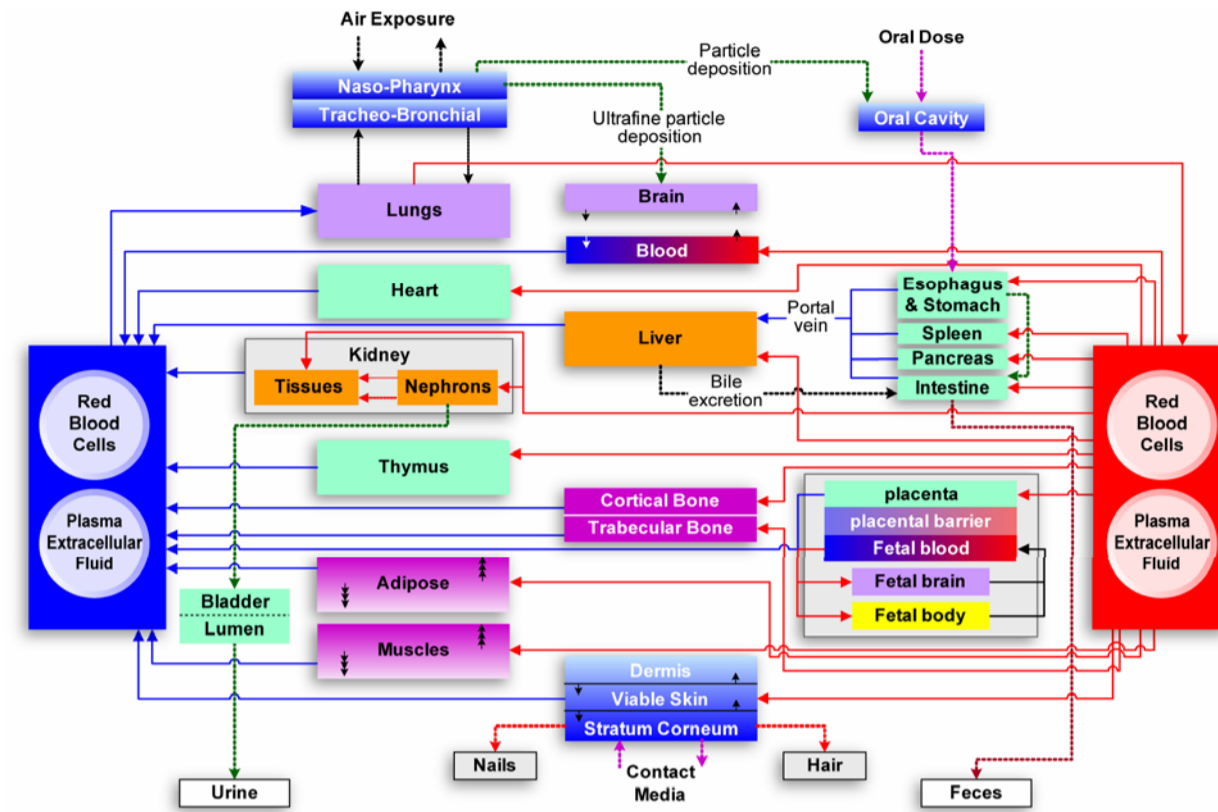
Subscripts i and j denote chemical species and model compartment, respectively; $C_{i,j}$ concentration; $V_{i,j}$ volume; $J_{i,j}$ net transport of chemical into tissue from blood; $R_{i,j}$ net reaction rate; $T_{i,j}$ net transport into tissue from another tissue; $PA_{i,j}$ is total permeation rate, C^{art} is arterial blood concentration; C^{ven} concentration exiting the compartment; $Q_{i,j}$ blood flow rate.

$$\frac{d(C_{i,j} V_{i,j})}{dt} = J_{i,j} + R_{i,j} + T_{i,j} \quad J_{i,j} = PA_{i,j} \left(C_{i,j}^{art} - \frac{C_{i,j}}{P_{i,j}} \right)$$

$$C_{i,j}^{ven} = C_{i,j}^{art} - \frac{J_{i,j}}{Q_{i,j}}$$

At the limit $PA_{i,j} = Q_{i,j}$ (high permeation), the system reduces to the common "flow-limited" assumption. If $J_{i,j} = 0$, the system reduces to a classic biokinetic/toxicokinetic model. Permeation rate $J_{i,j}$ may be defined by more complex models than that shown here.

Population PBTK model structure

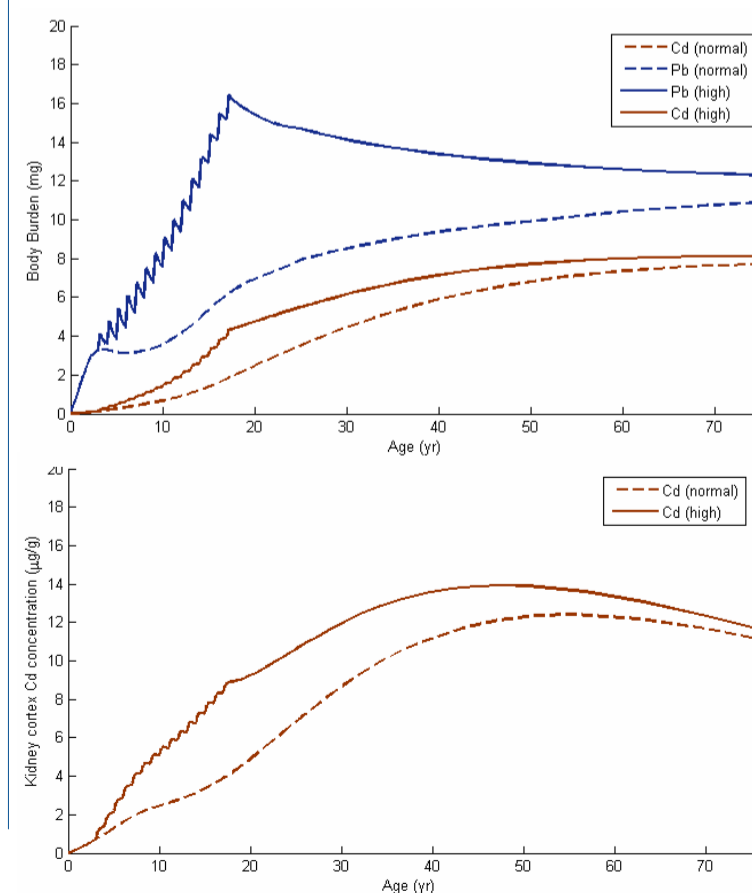


All chemical-specific toxicokinetic models are treated as subsets of the same whole-body model. Blood flow rates and volumes of common compartments are equal across models. Lumped compartments still vary by chemical, but parameters are consistent with the sum of remaining whole-body organs.

Susceptibility and toxicokinetics

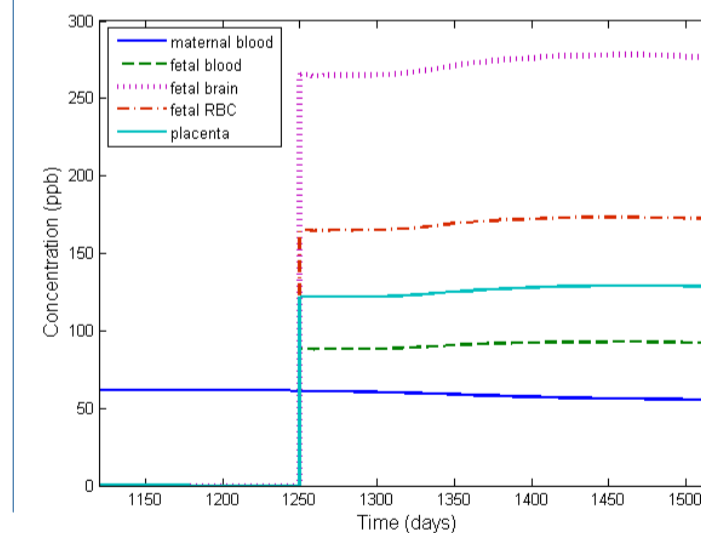
Malnutrition leads to high metal transporter levels (i.e. DMT1), increasing absorption of essential and toxic metals (Bressler et al., 2007).

Below: Exposure to lead (Pb) and cadmium (Cd) was simulated over the lifetime of a "standard individual" (O'Flaherty exposure scenario for Pb; dietary intake of 0.3 $\mu\text{g}/\text{kg}/\text{day}$ for Cd). Case 1: normal GI absorption; case 2: high childhood GI absorption fraction for 3 months per year (70% for Pb, 30% for Cd).



Developing fetal systems are highly susceptible to methylmercury (MeHg) toxicity.

Below: Dietary MeHg exposure was simulated for a 60kg female consuming 60 $\mu\text{g}/\text{day}$ MeHg (with increased intake during pregnancy). The toxicokinetic and pregnancy MeHg model of Shipp et al.(2000) was used.

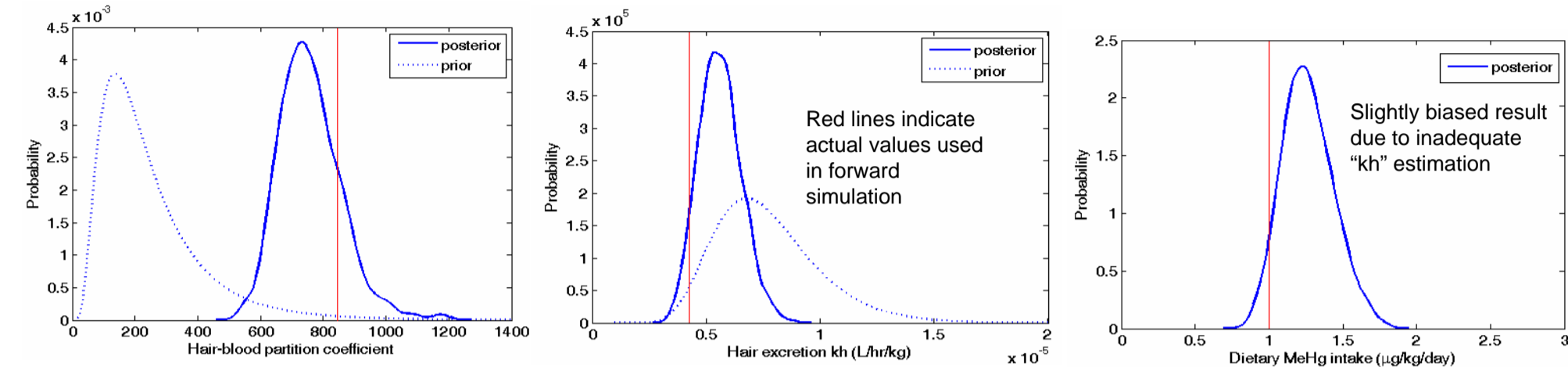


References

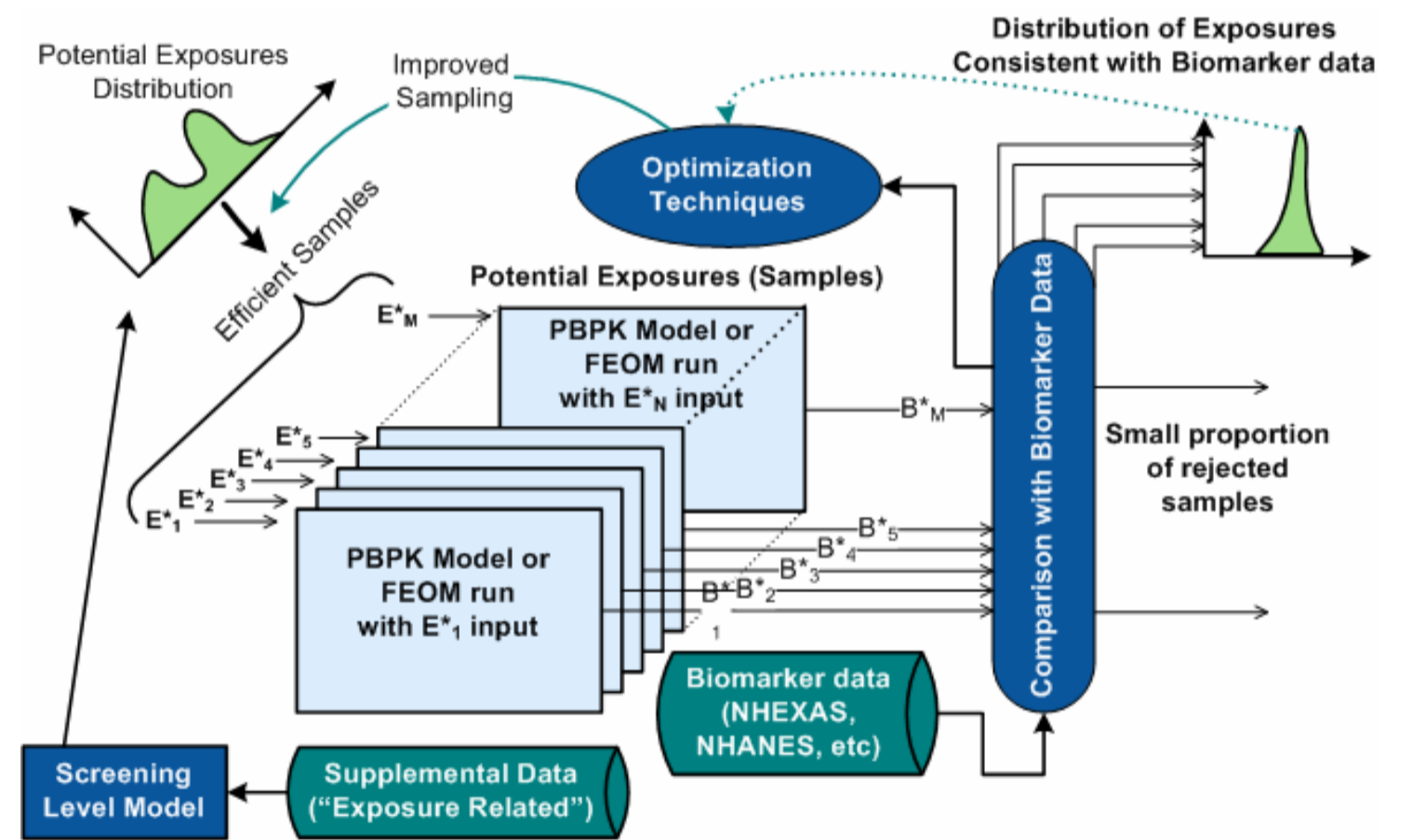
Bressler et al., 2007. "Metal transporters in intestine and brain: their involvement in metal-associated neurotoxicities". *Human & Experimental Toxicology* 26 (3):221-229.
 Nordberg and Kjellstrom (1979). "Metabolic model for cadmium in man." *Environ Health Perspect* 28: 211-7.
 O'Flaherty, 1993. "Physiologically based models for bone-seeking elements. IV. Kinetics of lead disposition in humans." *Toxicol Appl Pharmacol* 118(1): 16-29.
 Reddy et al., 2005. Physiologically based pharmacokinetic modeling : science and applications. Hoboken, N.J.: Wiley-Interscience.
 Shipp et al., 2000. "Determination of a site-specific reference dose for methylmercury for fish-eating populations." *Toxicol Ind Health* 16(9-10): 335-438.
 Acknowledgments: This work is funded in part by the US Environmental Protection Agency under Cooperative Agreement #EPAR-827033 (Center for Exposure and Risk Modeling) and STAR Grant number GAD R 832721-010 (environmental bioinformatics and Computational Toxicology Center). This work has not been reviewed by and does not represent the opinions of the funding agency.

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 physicochemical 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