

## **Mechanistically Consistent PBTK Modeling Framework for Mixtures of Toxic Metals**

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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. Although several physiologically based toxicokinetic (PBTK) models exist for different environmental chemicals, using them in assessing risks to co-occurring contaminants is often impractical. This is especially true for the case of toxic metals, where half-lives in the human body range from a few days (e.g., arsenic) to a few decades (e.g., lead, cadmium). Several 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. Since certain assumptions made for one metal or metal compound can be incompatible with the assumptions made for another metal, current formulations are inadequate for use in health assessing risks from mixtures of toxic metals. Therefore, there is a need for a mechanistically consistent framework capable of modeling multiple metals and metal compounds.

This work overviews progress in 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. Preliminary case studies using the multi-metals implementation of MENTOR-3P are presented at both the individual and population level 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.

*The viewpoints expressed in this work are solely the responsibility of the authors and do not necessarily reflect the views of USEPA or its contractors.*

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