Evaluating Risk in Older Adults Using Physiologically Based Pharmacokinetic Models

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1. Introduction

- The rapid growth in the number of older Americans has many implications for public health, including the need to better understand the risks posed by environmental exposures to older adults
- Physiological and biochemical changes that occur during aging may affect chemical absorption, distribution, metabolism and elimination (ADME).
- A few examples of known changes are in the table below

Absorption	• Reduced gastric acid production • Changes in dermal absorption, barrier function • Reduced lung volume, elasticity
Distribution	• Decreased total body water in older adults • Decreased muscle mass, increased relative adipose level • Plasma protein levels associated with binding • Potential for altered permeability of blood-brain barrier with concurrent disease
Metabolism	• Reduced liver volume and liver blood flow • Decline in specific cytochrome P450 content • Polypharmacy
Elimination	• Reduced renal function • Reduced biliary excretion • Reduced pulmonary excretion

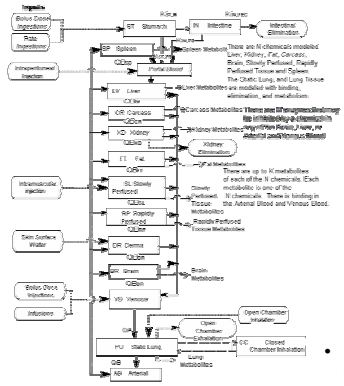
2. Methods

- Investigate prototype toxicants with diverse physical, pharmacokinetic, and toxicological properties, including

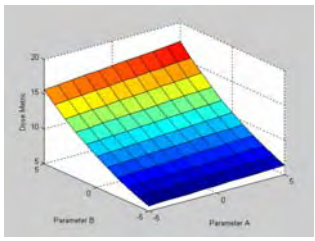
Chemical class and properties	Toxicity	Dose metrics
• Volatile organics • Metals • Pesticides • Air pollutants • High and low lipophilicity	• Receptor mediated • Metabolic activation • Endpoints, including cancer, neurological, immune, reproductive	• Parent chemical and metabolites • Peak concentrations • Integrated amounts (area under the curve)

- Candidate chemicals currently include trichloroethylene, benzene, toluene, ozone, arsenic, dioxin, chlorpyrifos, and pyrethroids
- Physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) models mathematically represent the biological processes associated with chemical ADME.
- This enables the incorporation of the changes associated with aging.
- Sensitivity analyses allow for systematic investigation of PBPK models to reveal the biological processes associated with risk.
- Identification of the important biological processes provides focus for future research efforts.
  - Literature search
  - Laboratory experiments

Disclaimer: Although this work was reviewed by the U.S. Environmental Protection Agency (U.S. EPA) and approved for publication, it may not necessarily reflect official Agency policy.



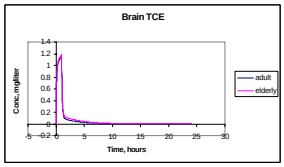
- Schematic representation of a PBPK model from EPA's Exposure Related Dose Estimating Model (ERDEM).
  - Subject-specific organ/tissue volumes, respiration volumes, and blood flows are represented
  - Distribution characteristics can be changed based on changes in tissue and blood composition
  - Rates associated with metabolism and clearance pathways are modeled



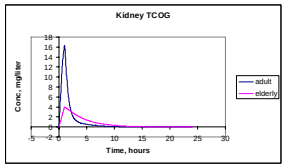
- In this 2-dimensional example (2 parameters), the slope of the dose metric is steeper as the value of Parameter B is changed, compared to the slope of Parameter A. These relations indicate a greater impact on the dose metric for the biological processes associated with Parameter B.
- Stochastic Response Surface and Reduced Model methods enable the investigation of the N-dimensional parameter space of a PBPK model more efficiently than deterministic or traditional Monte-Carlo investigations.

3. Illustration

- PBPK models of trichloroethylene (TCE) were developed for aged and adult rats



The healthy aged rat shows similar brain TCE concentrations as the adult



The impact of changes in blood flow to the kidney are illustrated by the time course of the metabolite TCOG in kidney

- Research is ongoing to
  - Compile physiologic data, including variability, for parameters required for PBPK modeling of the aged population that include:
    - Cardiac output
    - Blood flows to organs
    - Blood lipid content
    - Ventilation rate
    - Organ volumes
    - Glomerular filtration rate
  - Develop PBPK models for the prototype chemicals
  - Perform formal sensitivity analyses to highlight the important biological processes

4. Future Directions

- Create a broadly accessible database for PBPK/PD modeling of older adults
- Develop models to account for disease states and polypharmacy
- Design experiments to address specific hypotheses identified in the sensitivity analysis, including
  - *In vitro* experiments to address specific biochemical pathways
  - Animal experiments, where the comparison of models and results allows for the selection of the most representative animal for human extrapolation