

Biomonitoring Equivalents – Current Activities and Use of Toxicokinetic Modeling

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Lesa L. Aylward
Sean M. Hays

Overview

- Update on current BE activities
 - Recent BE development activities
 - Use of biomonitoring data and BE values in public health and regulatory activities
- Use of toxicokinetic models in BE development and biomonitoring data interpretation
 - Empirical human data
 - Simple TK models
 - Steady-state PBPK models for VOCs
 - Fully-developed PBPK models

Recent BE Development Activities

- BE development continues under contract to Health Canada
- New or recently developed BEs
 - Selenium
 - Fluoride
 - 3-PBA
 - Silver
 - Molybdenum
- Additional compounds anticipated for late 2015-2016
 - Parabens
 - Other metals (vanadium)

Recent BE Development

Chemical	Human TK data	PBPK model	Analogue data
Selenium	✓		
Fluoride	✓		
3-PBA	✓		✓
Silver		✓	
Molybdenum	✓		

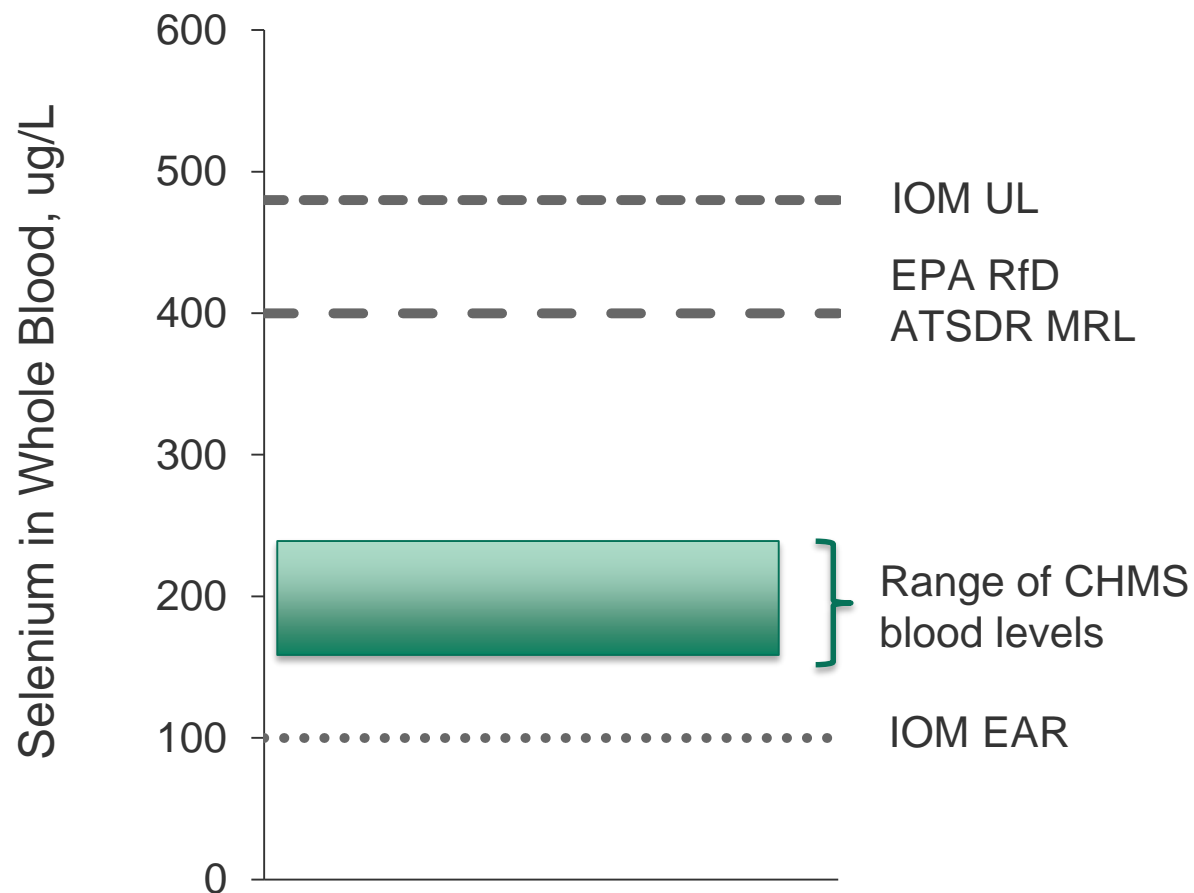
- BE values for selenium, molybdenum, and fluoride consider both potential toxicity AND nutritional essentiality or recommended minimal intake levels
- 3-PBA is a non-specific metabolite of numerous pyrethroids
- Silver evaluation addresses both ionic and nano silver exposure

Selenium

(Hays et al. 2014, Reg. Toxicol. Pharmacol. 70:333)

- BE values for selenium in whole blood, blood plasma, and urine
- Considers both nutritional essentiality and potential toxicity (selenosis)
- Human data on biomarker concentrations as a function of exposure
 - Same datasets used to identify NOAEL for selenosis

Selenium Whole Blood BE Values

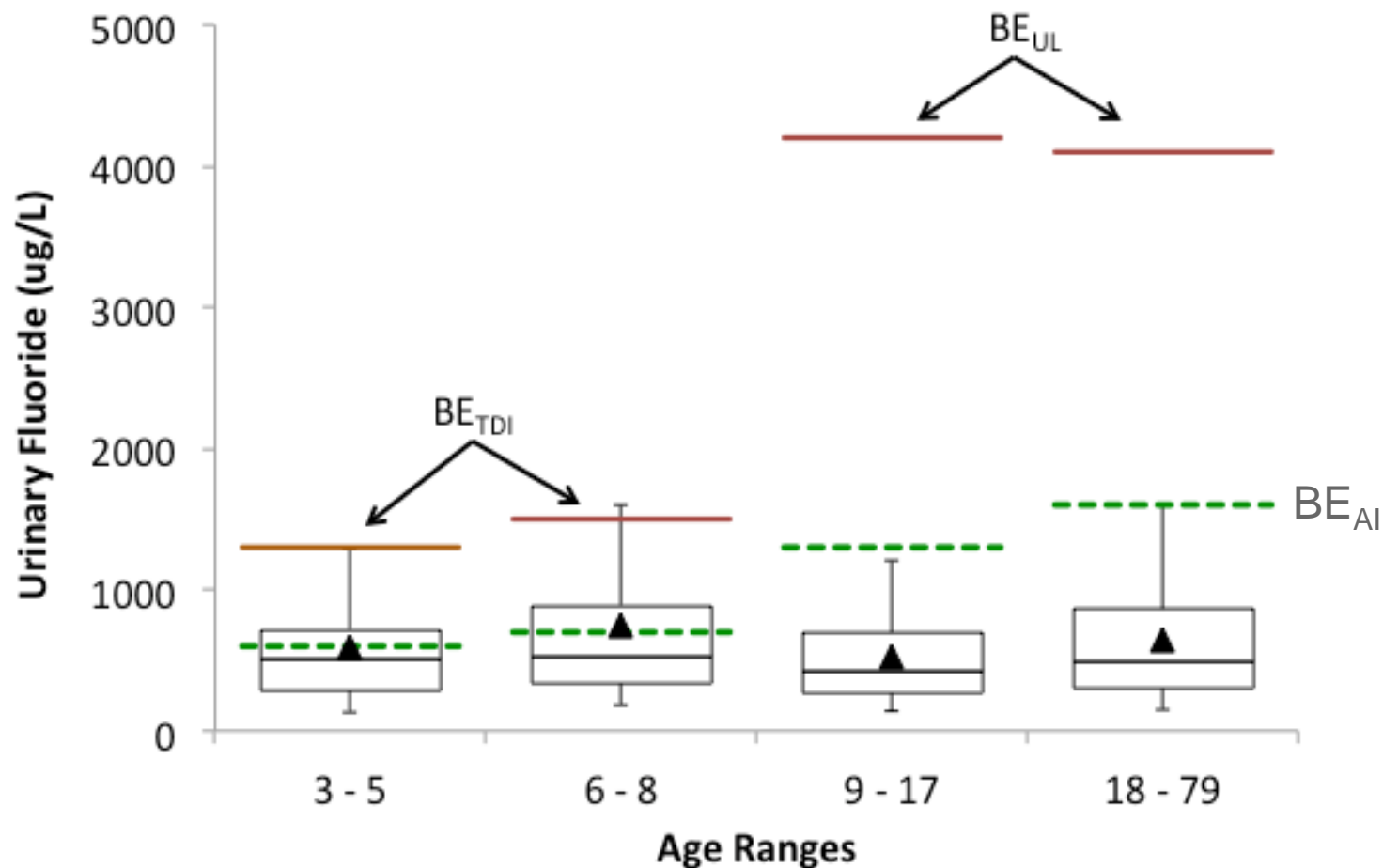


Fluoride

(Aylward et al., provisionally accepted, Reg. Toxicol. Pharmacol.)

- BE values for urinary fluoride
- Considers both benefits of fluoridation for prevention of dental caries and aesthetically undesirable dental fluorosis or skeletal fluorosis following excess exposure
- Human data on urinary fluoride vs. exposure levels; consideration of age-specific relationships in fluoride excretion data

CHMS Urinary Fluoride Compared to BE Values



Silver

- BE values for urine and whole blood derived
- Current RfD and other values are based on protection against argyria (discoloring accumulation of silver in tissues) following ionic silver exposure.
 - Human data from therapeutic use of silver compounds
- Nano-silver is now widely used, but governmental exposure guidance values have not been developed
 - BE was also derived for a literature-proposed TDI
- PBPK model addressing both ionic and nano-silver was used (*Bachler et al. 2013, International J Nanomedicine 8:3365*)

Bachler et al. 2013 Model

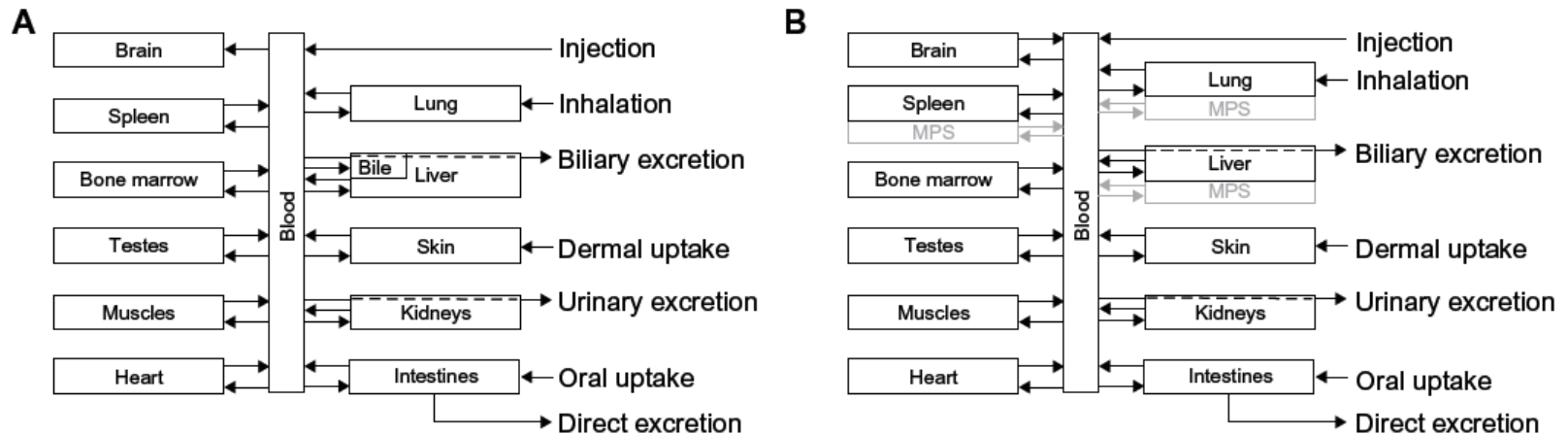


Figure 2 Schematic diagram of the PBPK model structures for (A) ionic and (B) nanoparticulate silver, which were used both for rats and humans.

Note: In the ionic silver model no transport of silver from the brain to the blood was modeled, to consider the blood–brain barrier.

Abbreviations: MPS, mononuclear phagocyte system; PBPK, physiologically based pharmacokinetic.

- Parallel model structures to address both ionic and nanoparticle silver
- Run to steady-state at human POD
- Manuscript in preparation (with Bachler and von Götz)

Molybdenum

- BE values for blood and urine
- Considers nutritional essentiality and potential toxic responses (increased serum uric acid in humans- USEPA; kidney alterations in rats – RIVM)
- Extensive human controlled dosing data gives empirical relationships between exposure and blood and urine concentrations.
- Manuscript in preparation.

Use of BE Values and Biomonitoring Data in Regulatory and Public Health Contexts

Health Canada

- Extensive support and use of BEs
 - Funding continues for BE development
 - BEs applied in HC Chemicals Management Plan (CMP) assessments
 - Biomonitoring data also being used with reverse dosimetry in evaluation of chemicals without BE values
- Cross chemical evaluation publication (Tox Letters 2014 231:126)



Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

Screening of population level biomonitoring data from the Canadian Health Measures Survey in a risk-based context

Annie St-Amand^{a,*}, Kate Werry^a, Lesa L. Aylward^b, Sean M. Hays^c, Andy Nong^a

BE Review Paper

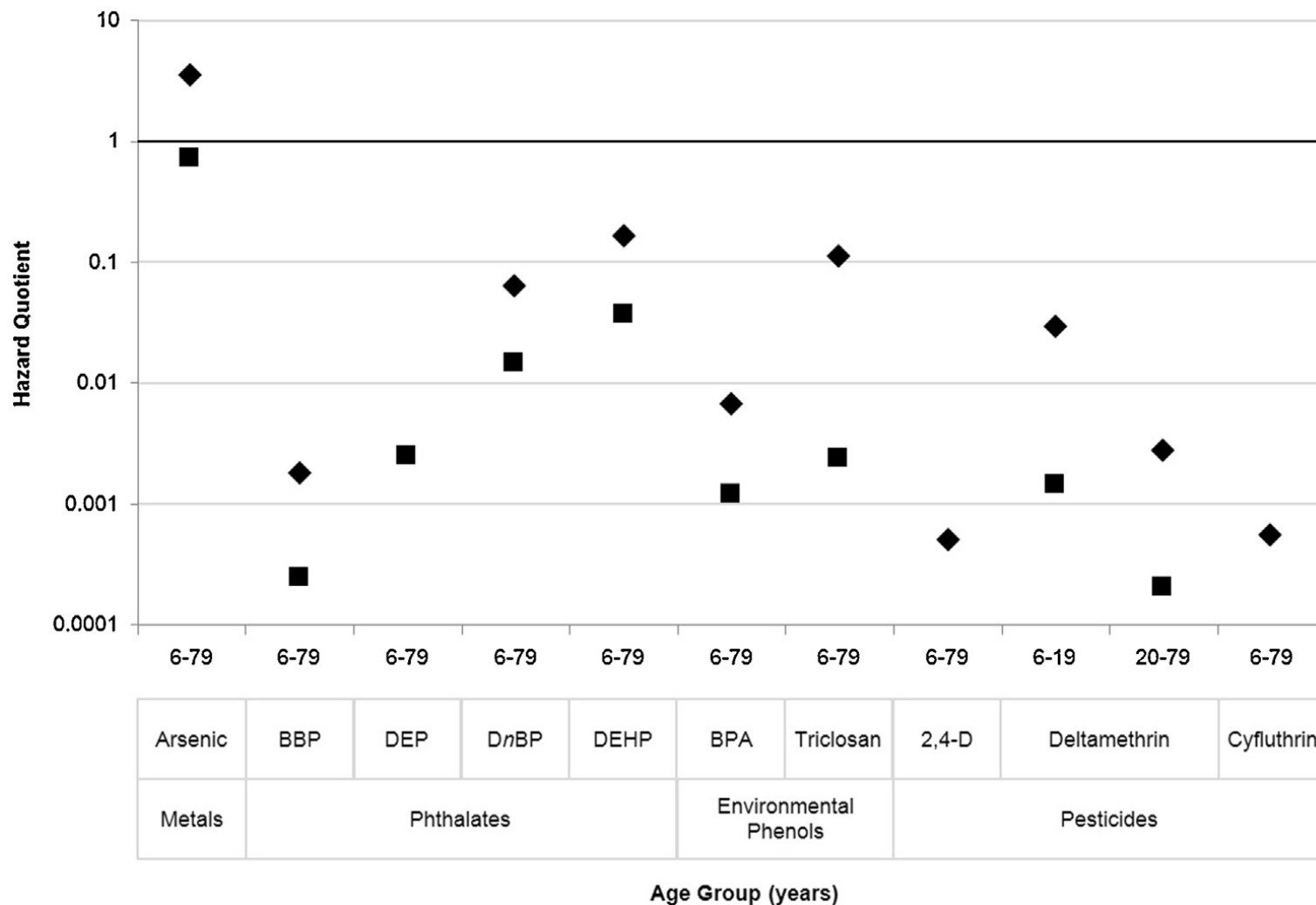
- Place CHMS biomonitoring data into a risk assessment (hazard quotient) perspective

$$HQ = \frac{[Biomarker]}{BE_{RfD}}$$

- Allows evaluation of both detected and non-detected analytes, and evaluation of both blood and urinary biomarkers
- Provides a cross-chemical perspective
- Similar to previous publication for US NHANES biomonitoring data

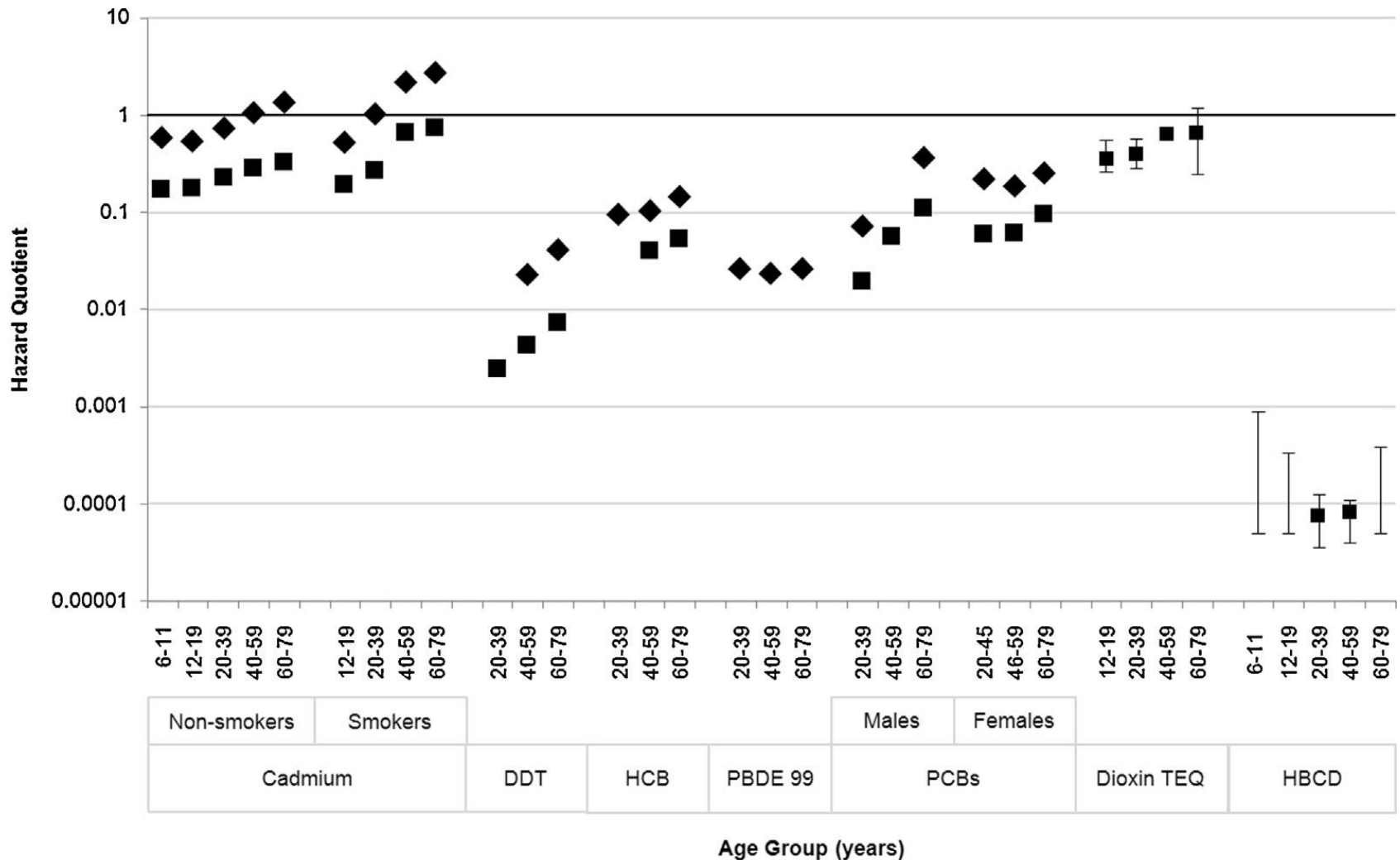
Cross-Chemical Evaluation Using BE Values - CHMS

Chemicals with Short Elimination Half-Lives, St-Amand et al. 2014



Cross-Chemical Evaluation Using BE Values - CHMS

Persistent Chemicals, St-Amand et al. 2014



USEPA

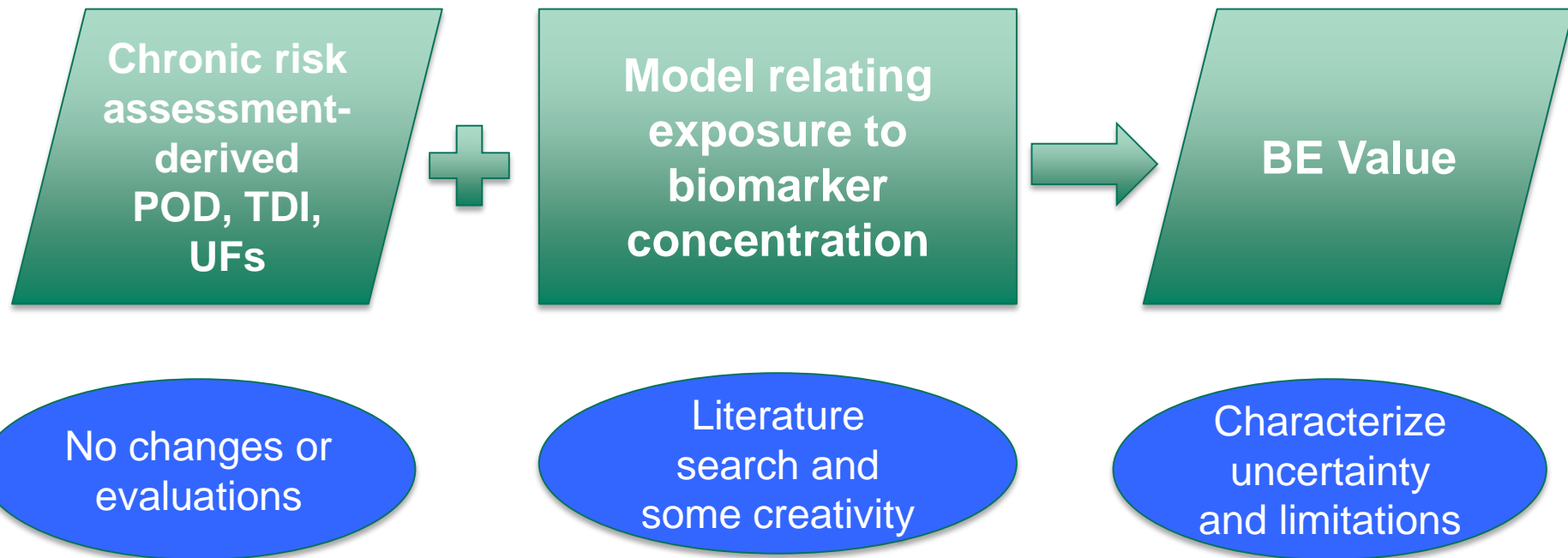
- No aggregate risk assessment activities outside of Office of Pesticide Programs
 - Hazard assessment (e.g., RfD) separate from exposure and risk assessment
 - Exposure assessment done by separate offices (e.g., Office of Water, Office of Air)
 - No cross-chemical prioritization mandate or activity
 - No mandate to use or examine biomonitoring data
- Office of Pesticide Programs does address aggregate exposure, but have not assessed chemicals with available BE values
 - OPP has highly prescribed external exposure assessment paradigms in place – no direct way to inject biomonitoring data into that process

US Consumer Product Safety Commission

- Recent evaluation of phthalate esters (PEs) which relied on NHANES urinary sampling data
 - Cumulative assessment including multiple PEs based on common toxicological endpoint
 - Applied reverse dosimetry rather than a BE or HBM approach

Use of Models in BE Development

BE Derivation: Fundamental Approach



- *Assumption of steady-state, consistent with chronic risk assessment guidance values*
- *Risk assessment interpretation for population evaluation, parallel to purpose of guidance values*

Models

“Essentially, all models are wrong, but some are useful.”

- George Box

- Model: A graphical, mathematical (symbolic), physical, or verbal representation or simplified version of a concept, phenomenon, relationship, structure, system, or an aspect of the real world. The objectives of a model include 1) ***to facilitate understanding by eliminating unnecessary components***, 2) ***to aid in decision making by simulating ‘what-if’ scenarios***, 3) to explain, control, and predict events on the basis of past observations.

Approaches Used in BE Development

- Direct extrapolation from measured biomarker concentration at POD
 - HBCDD
 - PCBs
- Empirical datasets and regressions for relationships between external exposure and biomarker concentrations
 - Molybdenum, selenium, fluoride, benzene in urine
- Simple one- or two-compartment toxicokinetic models
 - Multiple short-lived analytes for urinary excretion
 - Dioxins
 - Acrylamide
- PBPK models of varying complexity
 - VOC compounds
 - Silver

Example – Simple 1 or 2 Compartment Models

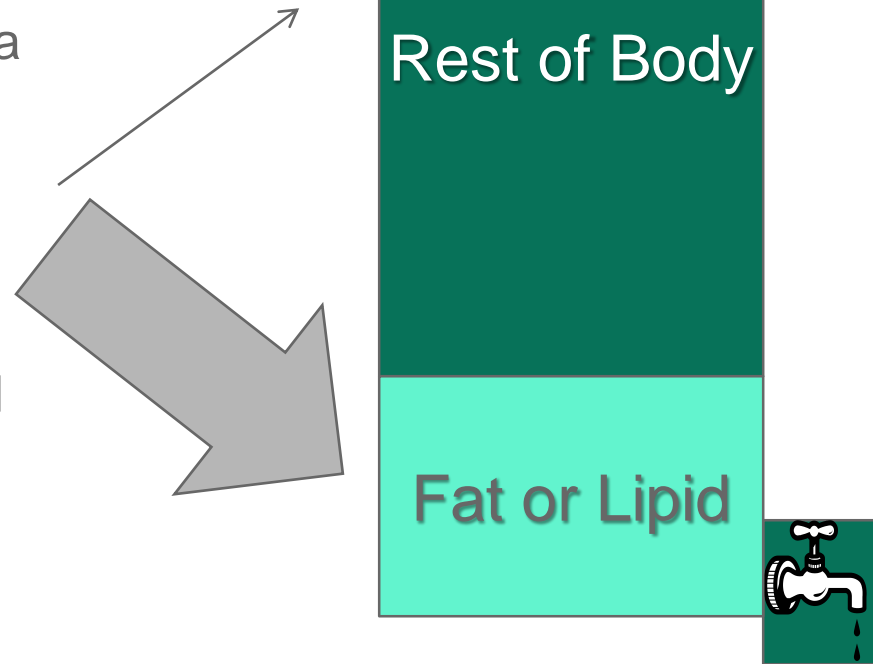
Hexabromocyclododecane (HBCDD)

- Distributes largely on the basis of lipophilicity into lipid throughout the body
 - Similar to many other persistent organochlorines
- Peak lipid concentration resulting from a single dose easily calculated:

$$C_{lipid} = \frac{AbsDose}{LipidVolume}$$

- Est. half-life for elimination can be used to calculate long term steady state concentration:

$$C_{lipid_ss} = \frac{AbsDaily\ Dose}{LipidVolume * k}$$



Example - Use of PBTK Modeling for VOCs - Toluene

VOC Model

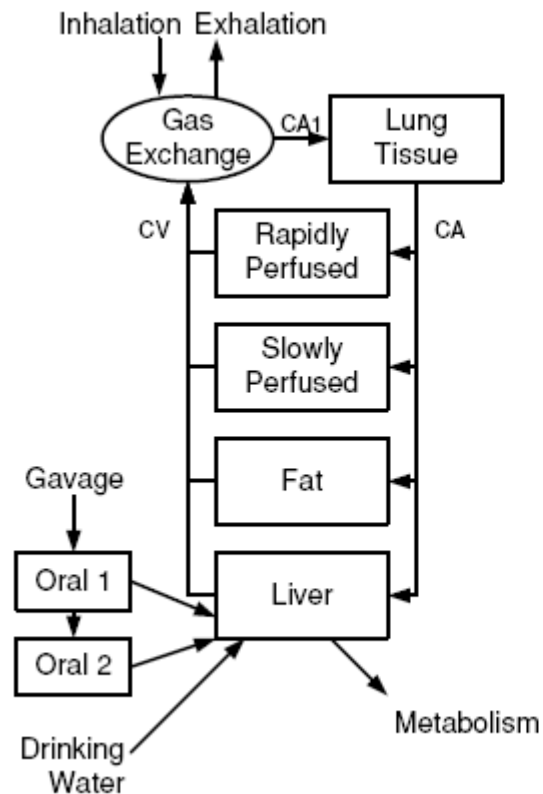
- Steady-state solutions to the generic VOC PBTK model
(Chiu and White 2006)

Risk Analysis, Vol. 26, No. 3, 2006

DOI: 10.1111/j.1539-6924.2006.00762.x

Steady-State Solutions to PBPK Models and Their Applications to Risk Assessment I: Route-to-Route Extrapolation of Volatile Chemicals

Weihsueh A. Chiu^{1*} and Paul White¹



Mass Balance Solution at Steady State

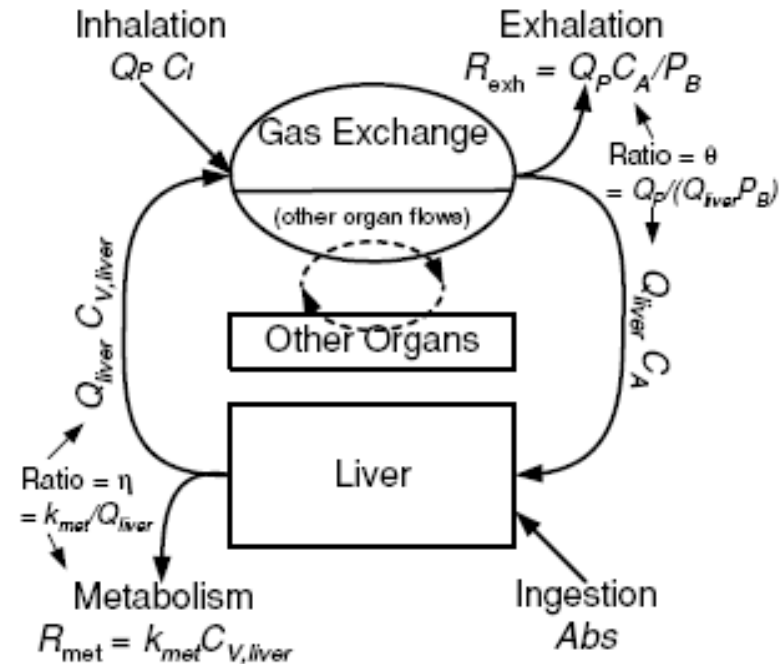
Inhalation concentration

$$Q_P C_I + Q_L C_{VL} = (Q_P / P_B + Q_L) C_A$$

Chemical-specific parameters

$$Abs + Q_L C_A = (Q_L + \frac{V_{max}}{K_m}) C_{VL}$$

Oral absorbed dose rate



$$C_{Vss} = C_A(1 - QLC) + C_{VL} * QLC$$

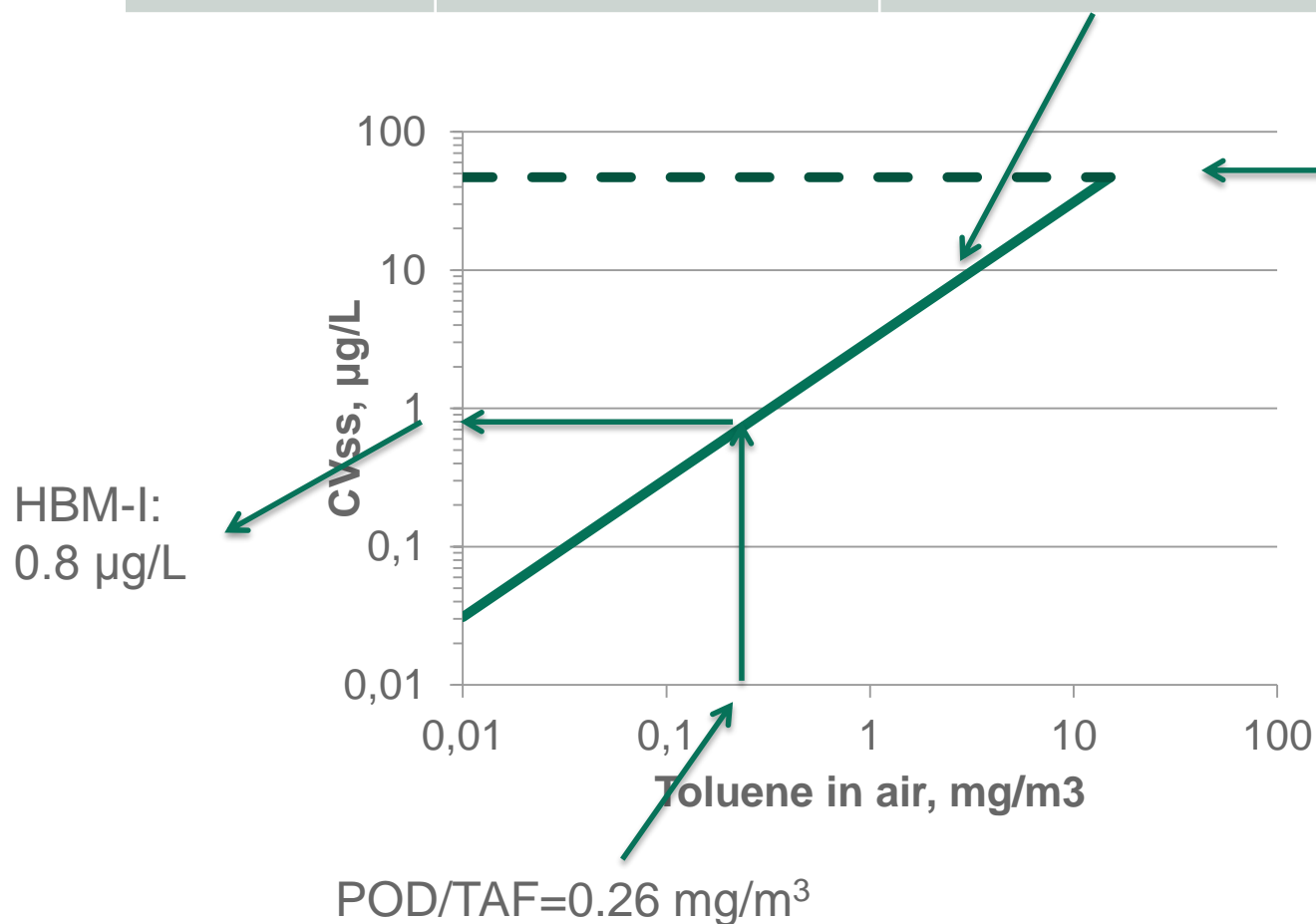
Physiologic parameters: Q_P , Q_L and QLC

Comments

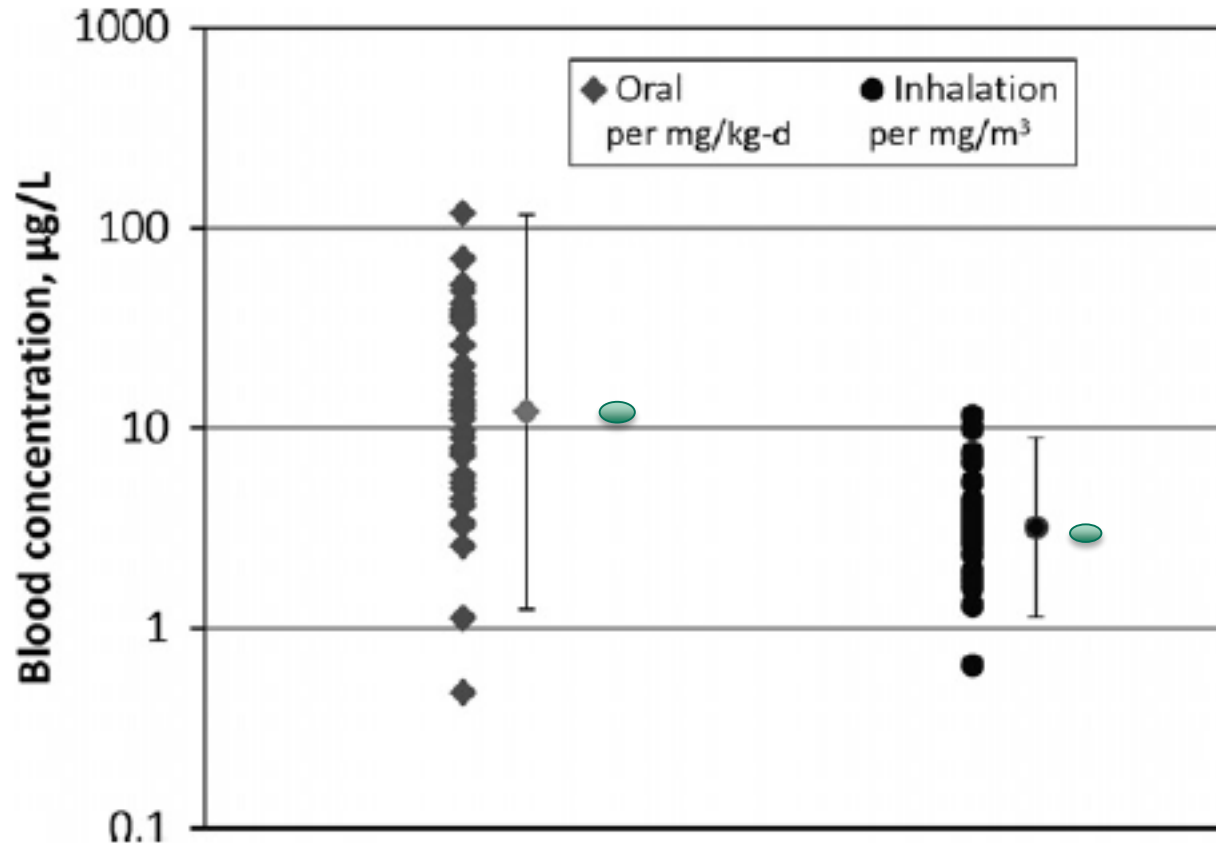
- **Solutions require that exposures remain in the linear range of the saturable metabolism**
 - Generally not exceeded for guidance values; can be exceeded at POD
- Intra-individual variability can be examined easily:
 - 3 physiological parameters: Q_p , Q_L and Q_{LC}
 - Chemical-specific parameters:
 - *Metabolic parameter: V_{max}/K_m*
 - *Phys/chem parameter: P_B*
- Steady-state slopes relating blood concentration to exposure easily calculated ***and can be applied to any selected guidance value:***
 - $\mu\text{g/L per mg/m}^3$ or $\mu\text{g/L per mg/kg-d}$

Toluene Steady-State Solution

	Oral slope $\mu\text{g/L per mg/kg-d}$	Inhalation slope $\mu\text{g/L per mg/m}^3$	Upper Limit $C_{VSS}, \mu\text{g/L}$
Toluene	11	3.1	47

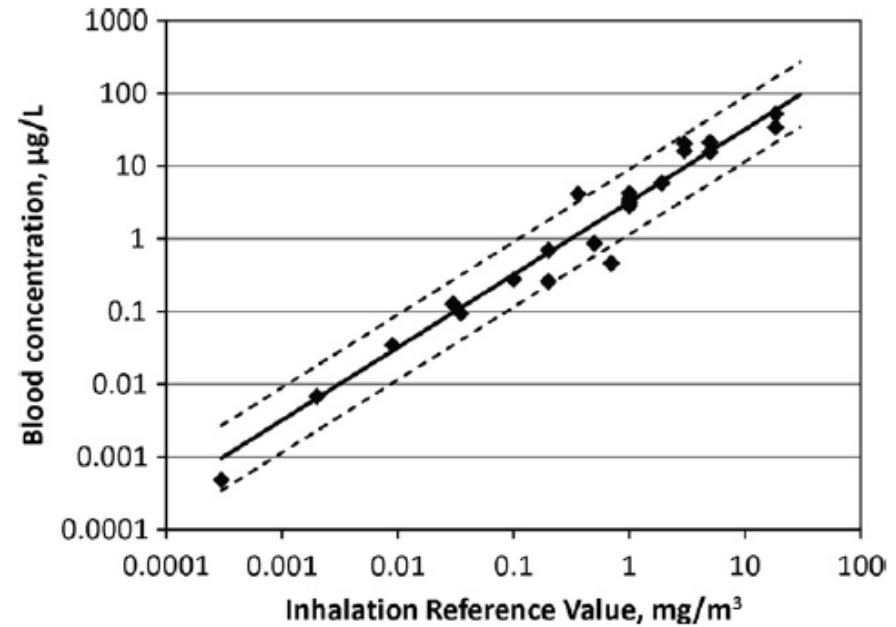
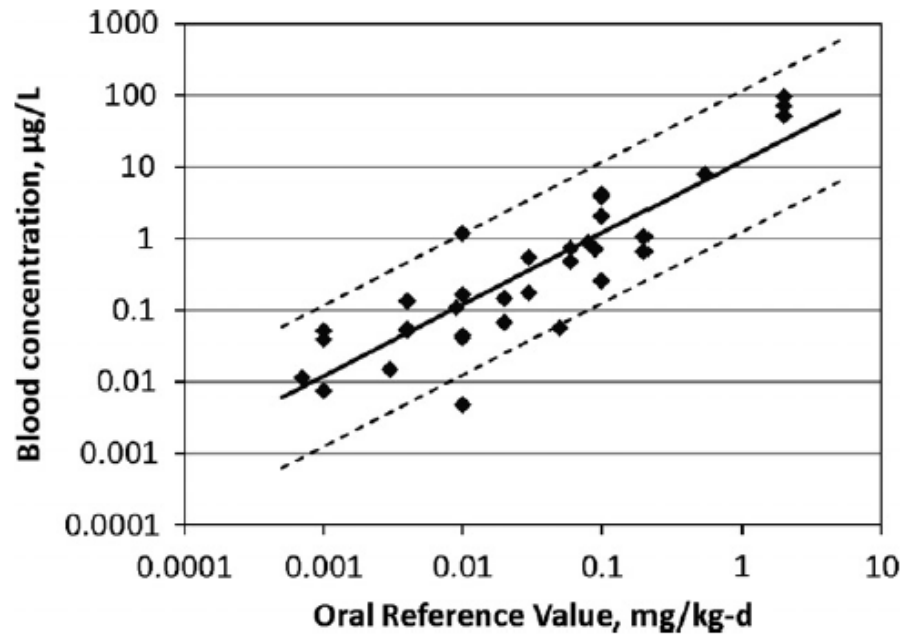


Cross-VOC Results: Oral and Inhalation Slopes, 37 VOCs



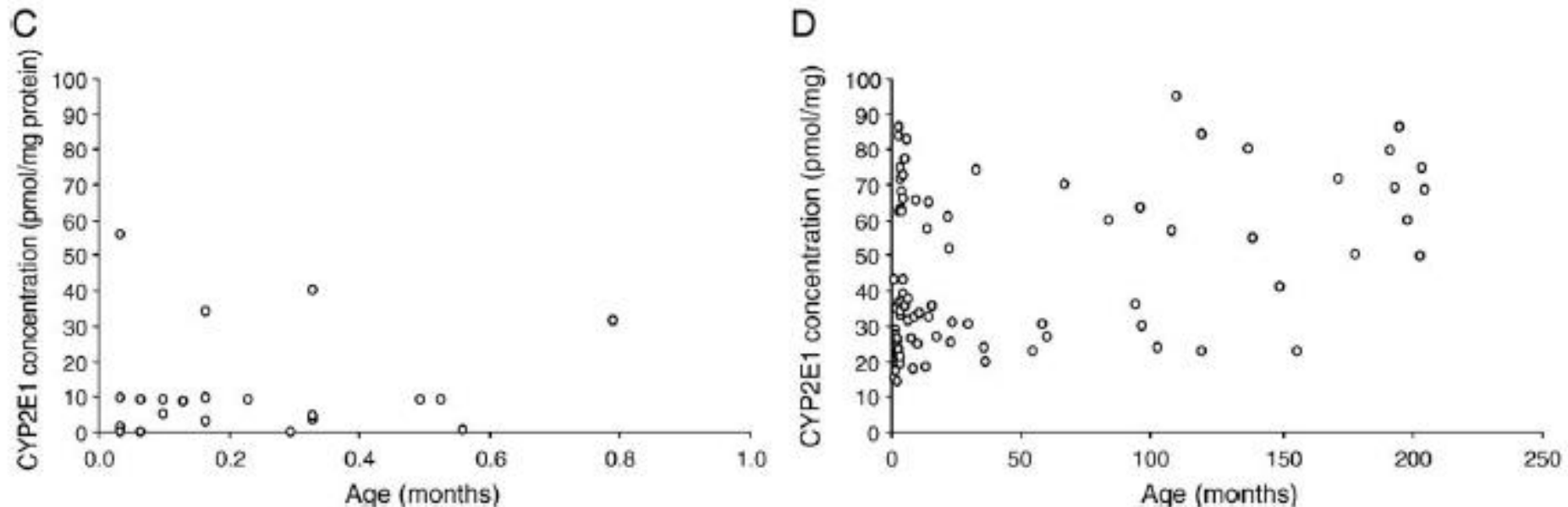
● Toluene

Overall VOC Results – Extrapolation Possibilities



TK Variation, Children to Adults: Toluene

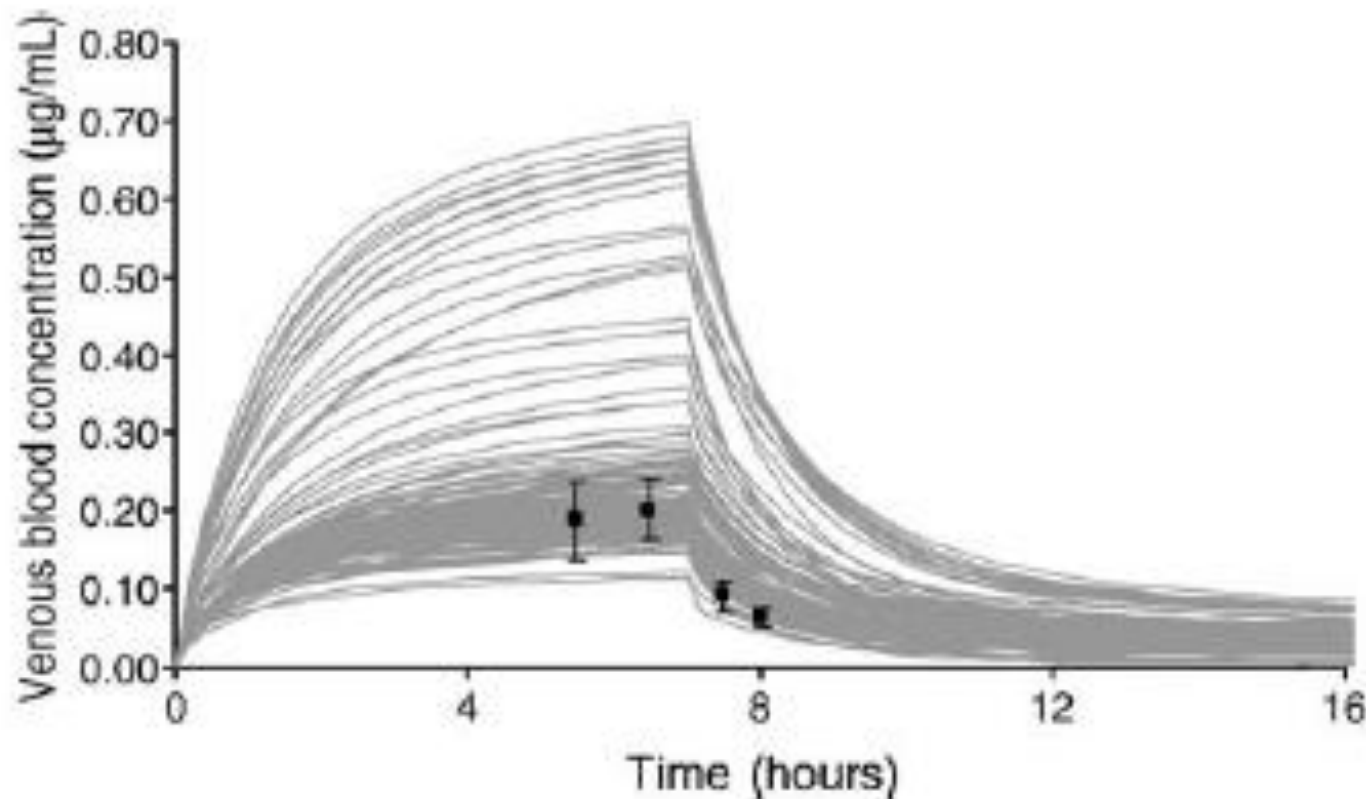
- Nong et al. 2006 incorporated data on the development of CYP2E1 capability and physiological parameters in neonates, infants and children into the PBTK model for toluene



Nong et al. 2006, Toxicol Appl Pharmacol, 214:78

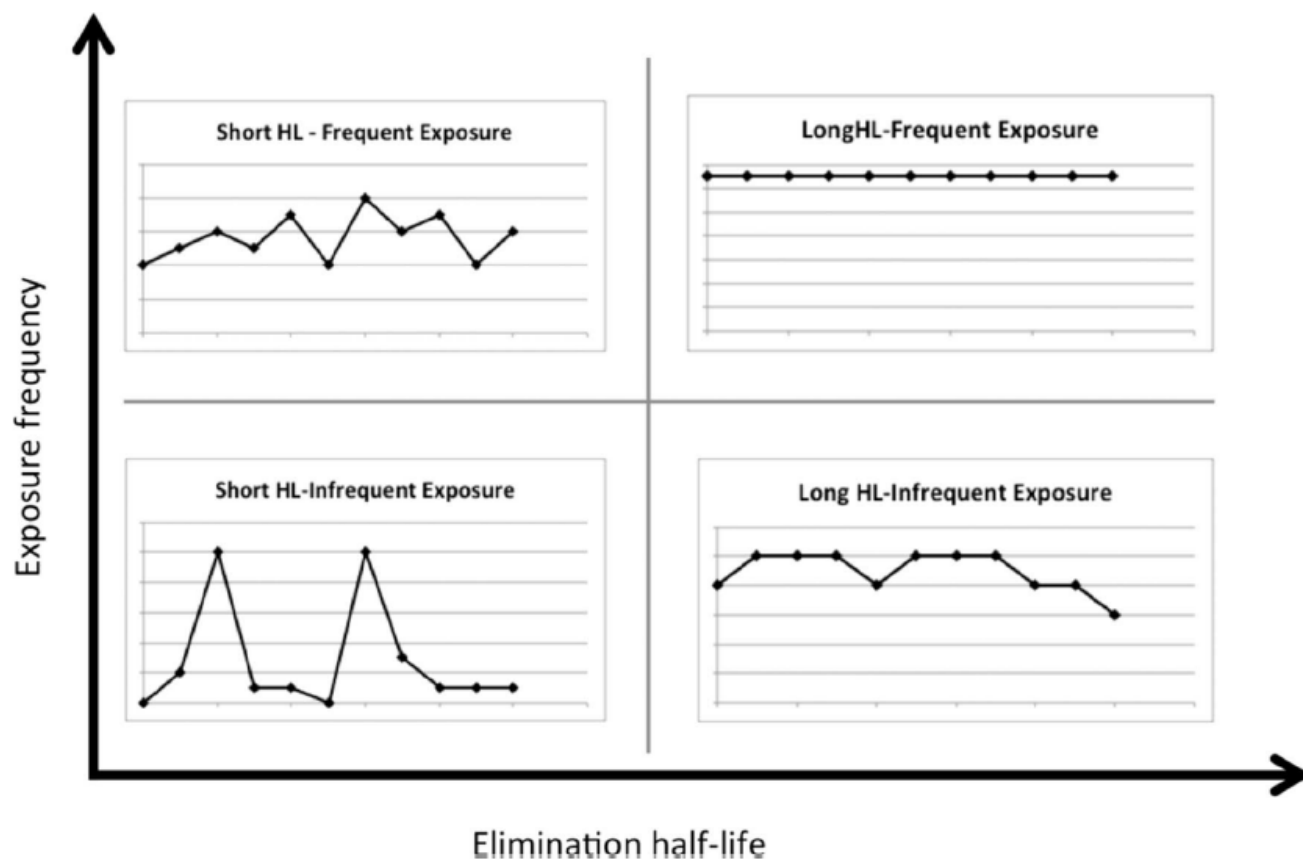
Results

- Predicted blood concentrations generally bracketed measured adult concentrations and were within ~3x of adult values



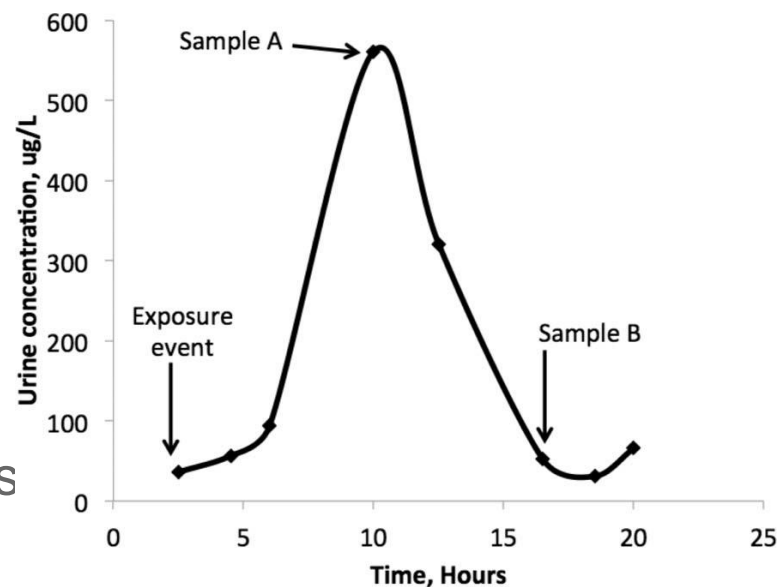
Considerations- Temporal Variability

- Variation in biomarker concentration in an individual depends on the relationship between the HL of elimination and the intervals between exposure



Temporal Variability- Cont'd

- Modeling typically estimates steady-state average concentration
- For short-lived compounds, sampling at a particular time point may over- or under-estimate actual average biomarker concentration in the individual
- Issue is relevant for
 - VOCs in blood
 - Parabens in urine
- Not relevant for persistent compounds



Considerations - Uncertainty

- Models are uncertain
- Guidance values are also uncertain!
- Is having estimated HBM values, with their attendant uncertainties, more valuable and useful than not having them?

Considerations – HBM Values vs. BE Values

- BEs have always been envisioned as a risk assessment tool
 - Underlying guidance values are risk assessment values, not diagnostic criteria
 - Interpretation of individual results difficult, but BE values can help public health and environmental regulators to identify population-level exposures of concern
 - *Uncertainties attendant to modeling and derivation of guidance values acceptable*
- HBM values seem to be targeted more towards interpretation of individual biomonitoring data with feedback to the individual
 - *Uncertainties may be less acceptable?*