Physiologically Based Pharmacokinetic (PBPK) Modeling Contaminants of Concern in Drinking Water

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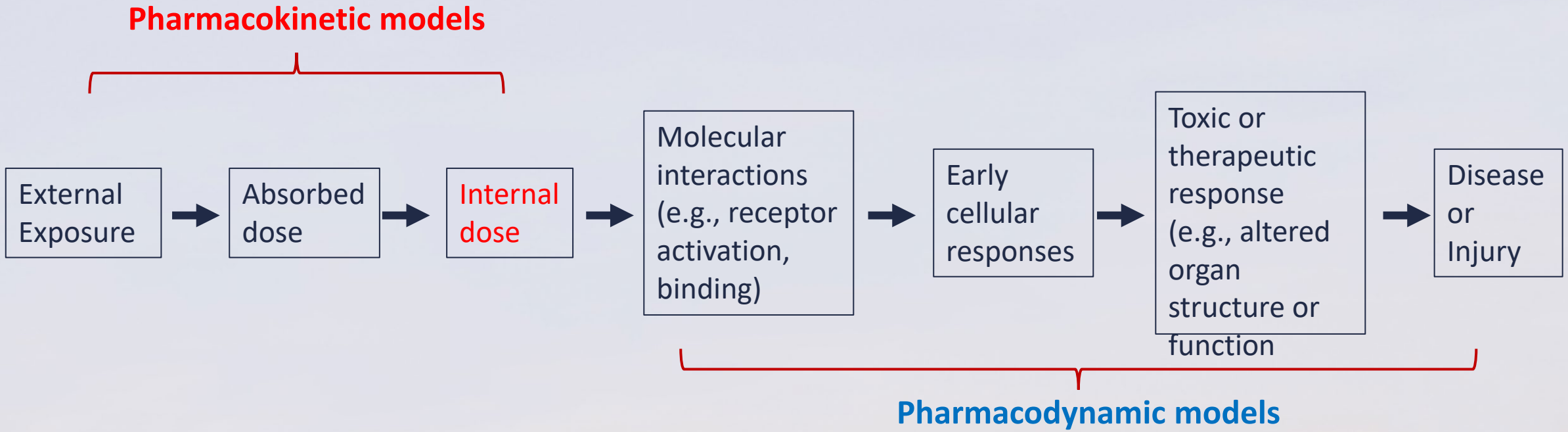
Outline

- PBPK Modeling in Context
- What, Why and When of PBPK Models
- Bromodichloromethane (BDCM) Case Study
  - Toxicological Importance of BDCM
  - Significance of Exposure Route
  - Model Development
  - Internal Dose Measures & Exposure Route
  - Model Applications
    - Drinking Water Equivalency Analysis (aggregate exposure)
    - Impact of Variability (IVIVE)

Exposure to Adverse Effect Pathway



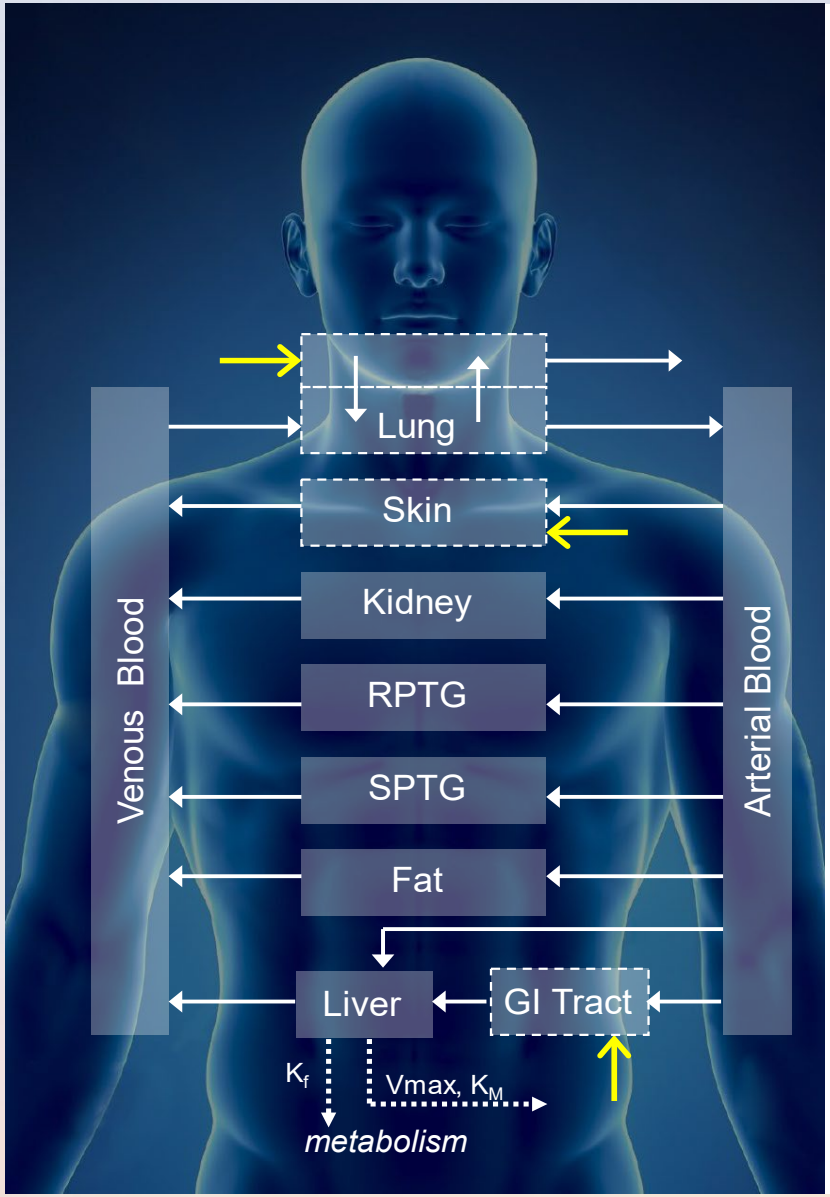
- Both beneficial and adverse responses to chemicals are related to the concentration of active form of chemical reaching the target site, rather than simply exposure or applied dose
- Need a tool that can relate internal concentration of active compounds at their target sites with the applied or exposure dose in an animal model or human subject.

Types of Pharmacokinetic Models

- Non-compartmental Pharmacokinetic Models
  - Simplest, model-independent
- Compartmental Pharmacokinetic Models
  - interconnected, well-mixed, and kinetically homogeneous compartments
- Physiologically-Based Pharmacokinetic Models
  - a series of physiologically realistic body compartments connected by blood flow

Why a PBPK Model?

- ***Physiologically realistic*** mathematical description of the processes of absorption, distribution, metabolism and excretion (ADME) in a biological organism
- Scientifically accepted and used for many types of ***extrapolation*** to support risk analysis
- Use to estimate ***biologically effective internal dose*** in humans resulting from actual exposures (multi-media, multi-pathway)
- Quantitative estimation of the ***impact of variability*** in key model parameters

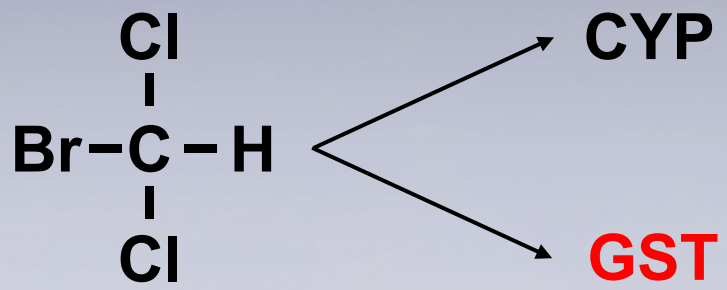


Model Elements

- Basic Decisions
  - exposure routes
  - compartments/organs
  - tissue transport
  - sites of metabolism
  - metabolic pathways
- Physiological Parameters
  - cardiac output
  - alveolar ventilation
  - blood flows
  - organ volumes
- Chemical-Specific Parameters
  - partitioning & transport
  - biotransformation
  - absorption

Toxicological Significance of BDCM (& Brominated THMs)

- Biotransformation by two competing pathways – cytochrome P450s (CYP) and Glutathione S-transferases (GST)



- **Liver**
- **Kidney**
- **Intestine**
- **Bladder**

- GST theta (GSTT1) activates BDCM to mutagenic intermediates and is functional in the urinary tract
- Biotransformation in target tissues may be responsible for target organ toxicity
- GSTT1(+/+ and +/-) people exposed to higher levels of THMs in drinking water are at greater risk for developing bladder cancer than GSTT1(-/-) people

Trihalomethane Exposure and Dosimetry

- THM exposure is universal
  - chloroform, BDCM, dibromochloromethane, bromoform
- Multi-route exposure (drinking, showering, bathing & other household uses) is an important issue due to volatility and skin permeability for all THMs
- Exposure via inhalation and/or dermal routes results in higher concentrations of THMs reaching the systemic circulation compared to oral exposure
- THMs reaching the systemic circulation are available for metabolism in target tissues

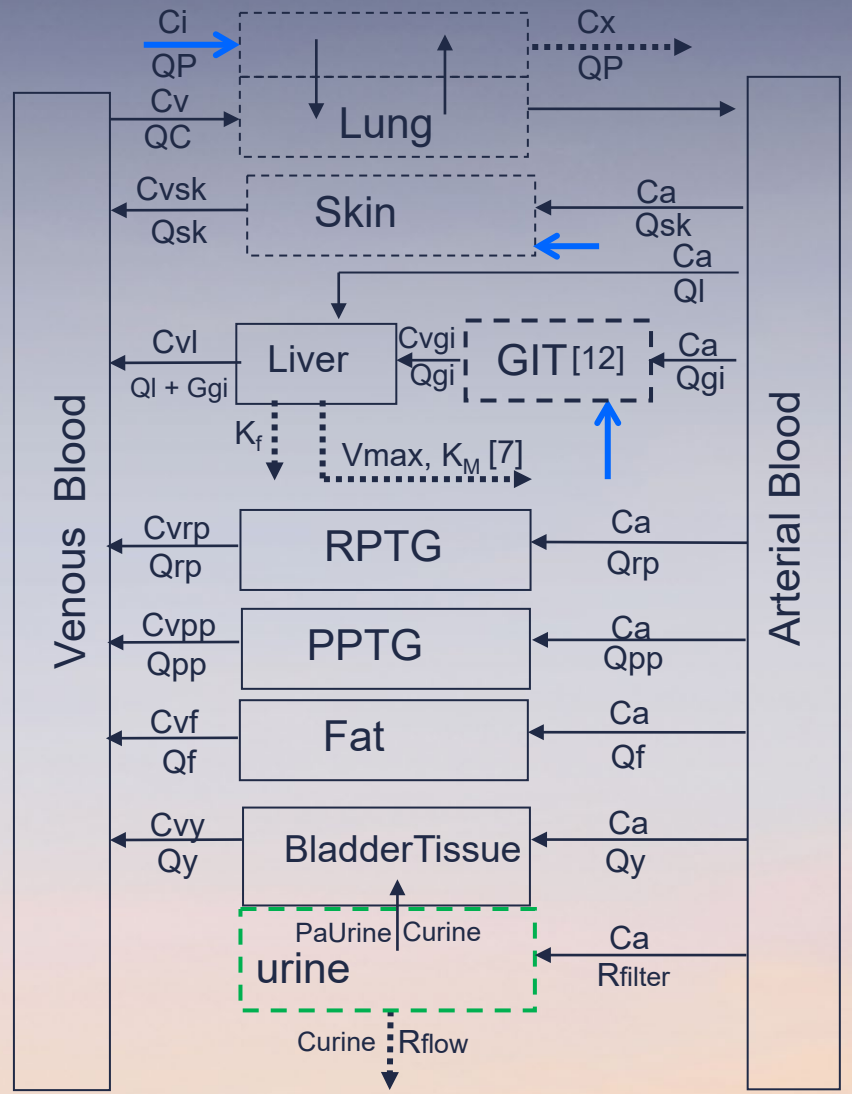
Significance of Exposure Route (Backer et al., 2000*)

Activity	Shower	Bath	Drink
Tap H_2O	6.27 ppb	6.22 ppb	5.52 ppb
Time	Median Blood BDCM (ppt)		
Background pre-exposure	3.3	2.3	2.6
10 min post	19.4	17.0	3.8
30 min post	10.3	9.9	---
60 min post	---	---	2.8

*10 minute shower or bath, drink 1 liter of water in 10 minutes (n=10-11/activity). --- = not measured.

General THM Model Structure

- Routes of exposure
  - oral, dermal, inhalation
- Excretion
  - exhaled breath, urine
- Bladder as target tissue
- Biotransformation
  - liver, *bladder*
- Blood flow-limited transport



Distinctive Feature of BDCM PBPK Model

Chemical-specific model parameters independently estimated using human data & human-derived tissues

- male & female human blood/air partition coefficients from individual subjects (US EPA/ORD)
- oral absorption coefficient estimated from human in vivo data from controlled exposures (Leavens *et al*., 2007)
- dermal permeation coefficient based on *in vitro* studies using human skin (Xu *et al*., 2002)
- metabolism parameters for cytochrome P450 and glutathione *S*-transferase pathways derived from studies with pooled human subcellular (microsomes & cytosol) fractions (Ross & Pegram, 2003; US EPA/ORD)

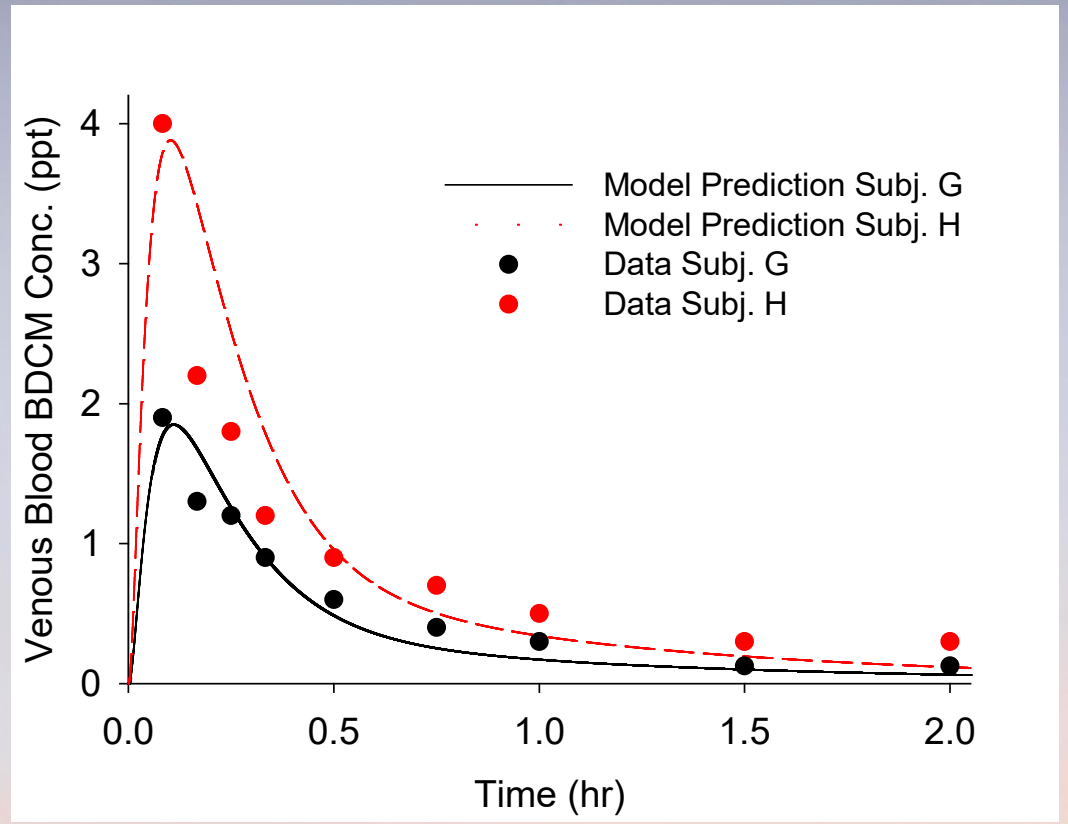
*Kenyon, E.M., Eklund, C., Leavens, T.L., and Pegram, R.A. 2016. Development and Application of a Human PBPK Model for Bromodichloromethane (BDCM) to Investigate Impacts of Multi-Route Exposures. *J. Appl. Toxicol.* 36: 1095–1111.

Model Evaluation

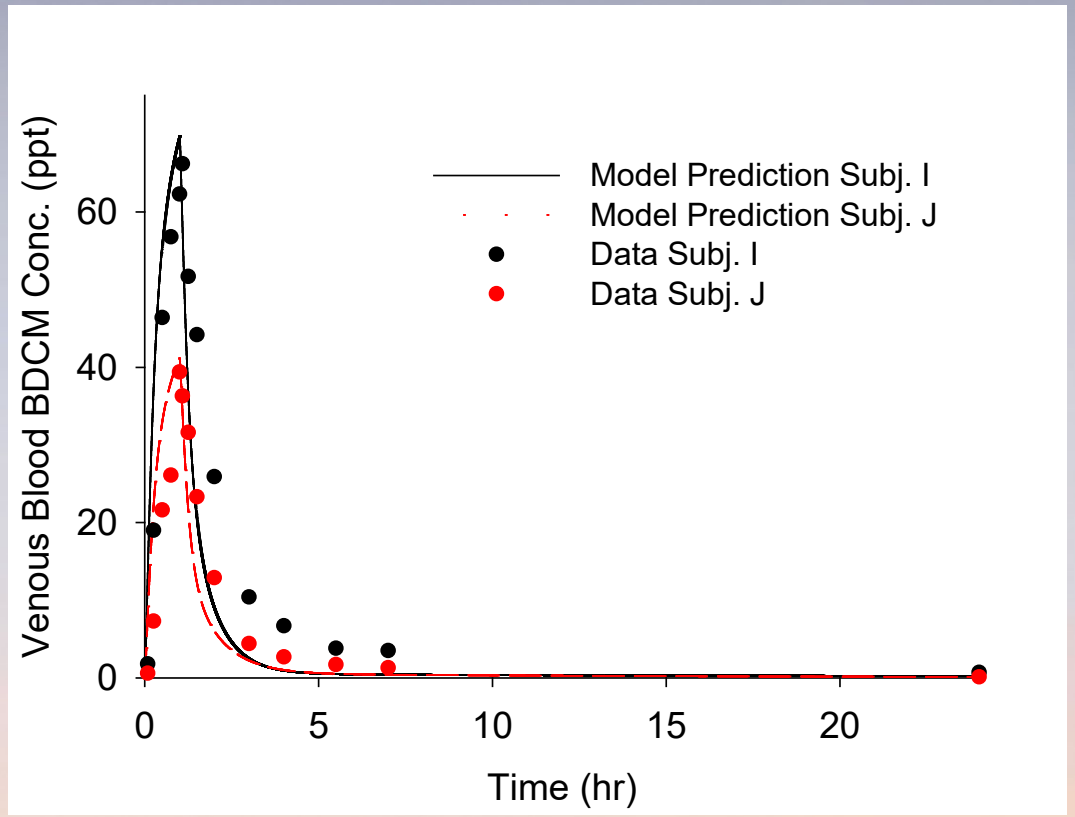
- Evaluate model predictive performance using data not used to estimate physiological and chemical-specific parameters
- Human data generally very limited or lacking for water contaminants
  - Water use studies (drinking, bathing, showering)
    - Venous blood, exhaled breath, urine
    - Requires sufficient experimental detail (subject-specific data, sampling times)
  - Swimming studies
    - Necessitates modeling physiological effects of exercise
    - Physiological changes due to water immersion, temperature, and activity
- Use of *in vitro* human-tissue derived estimates for chemical-specific parameters eliminates animal extrapolation, but necessitates *in vitro* to *in vivo* extrapolation (IVIVE)

Model Evaluation: BDCM Individual Subject Data

Oral Exposure

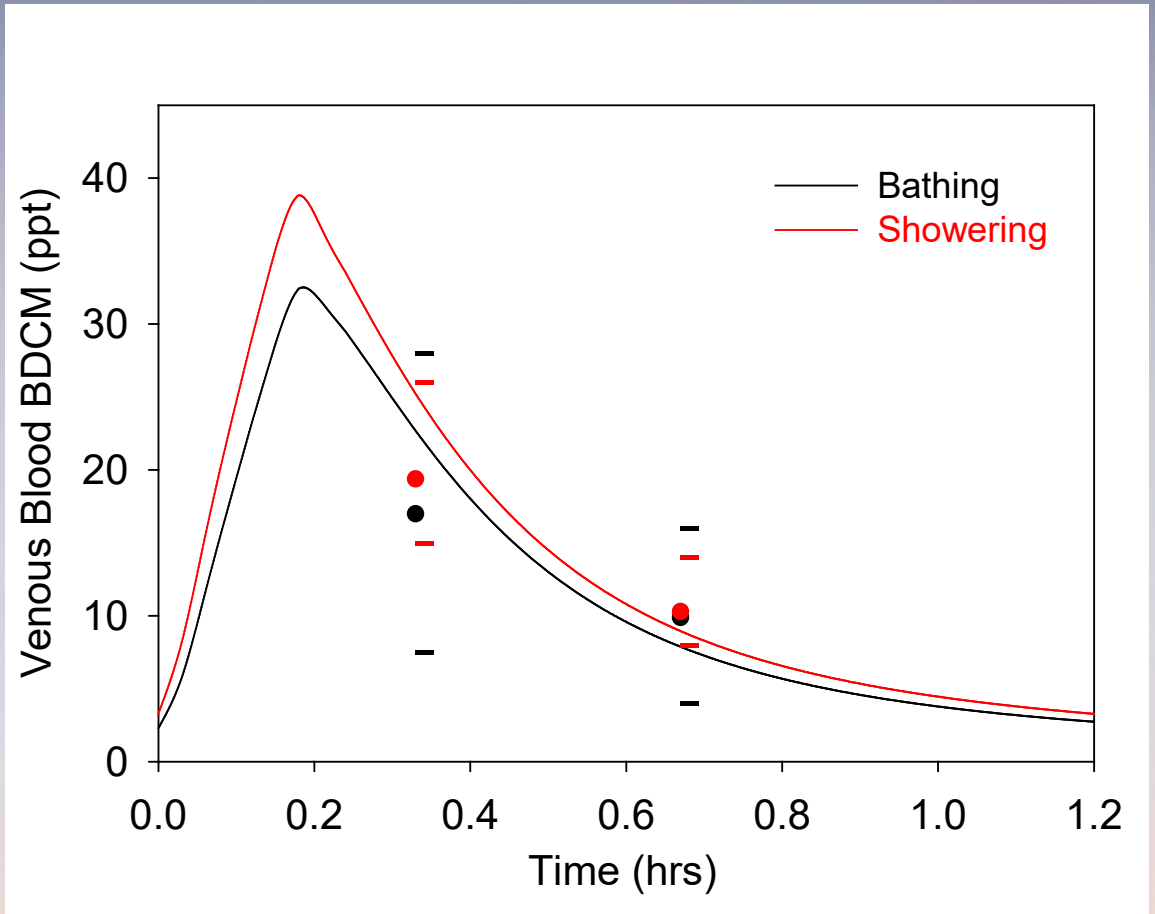


Dermal Exposure



Data: Leavens et al., 2007

Model Evaluation: Water Use Activity



Data: Backer et al., 2000

Model Evaluation: Trihalomethanes in Blood

Scenario	Chemical	Predicted (ng/l)	Observed (ng/l)
Drinking[1]	Chloroform	10	30-98
	Dibromochloromethane	1.5	0.57-2.8
Showering[1]	Chloroform	132	89-187
	Dibromochloromethane	4.9	3.0-6.3
Bathing[1]	Chloroform	165	53-199
	DBCM	6.2	1.5-6.6
Showering[2]	Chloroform	232	150-240
	BDCM	81	54-88
	Dibromochloromethane	37	21-46
	Bromoform	4.2	2.2-6.2

[1]Backer et al., 2000
[2]Backer et al., 2008

Model Evaluation: BDCM in Exhaled Breath

Study	Group	Predicted (ug/m^3)	Observed (ug/m^3)
Font-Ribera et al., 2010[a]	Swimmers	2.3	1.8 (0.7 – 3.2)
Marco et al., 2015[b]	Swimmers, Cl pool	2.31	1.55 (0.5 – 2.8)
	Swimmers, Br pool	0.23	0.14 (0.07 – 0.25)
	Bathers, Cl pool	8.2	0.84 (0.59 – 1.2)
Salas et al., 2017[c]	Group 1 Non-swim	8.22	1.26 [1.04, 1.45]
	Group 2 Swim	1.58	1.61 [1.38, 1.82]
	Group 3 Non-swim	8.27	1.08 [1.04, 1.11]
	Group 3 Swim	2.22	2.09 [1.61, 2.65]

[a] Data reported are mean and range of exhaled breath at end of swimming for 40 minutes.
[b] Swimmers were actively swimming at capacity the entire 40 minutes; bathers were immersed but not actively moving.
[c] Data reported are median, P25 and P75 at end of swimming for 40 minutes. IQR is interquartile range. Non-swimming groups were immersed, but not actively moving.

Potential Model Applications

- Multi-route (aggregate) exposure assessment
- Predicting toxicity based on total dose of active metabolites to target tissue (e.g. bladder)
- Population-based risk analysis for potentially susceptible sub-populations (GSTT1(+))
- Predicting the effect(s) of changes in disinfection scenarios or source water characteristics (e.g. increased bromine) on tissue dosimetry

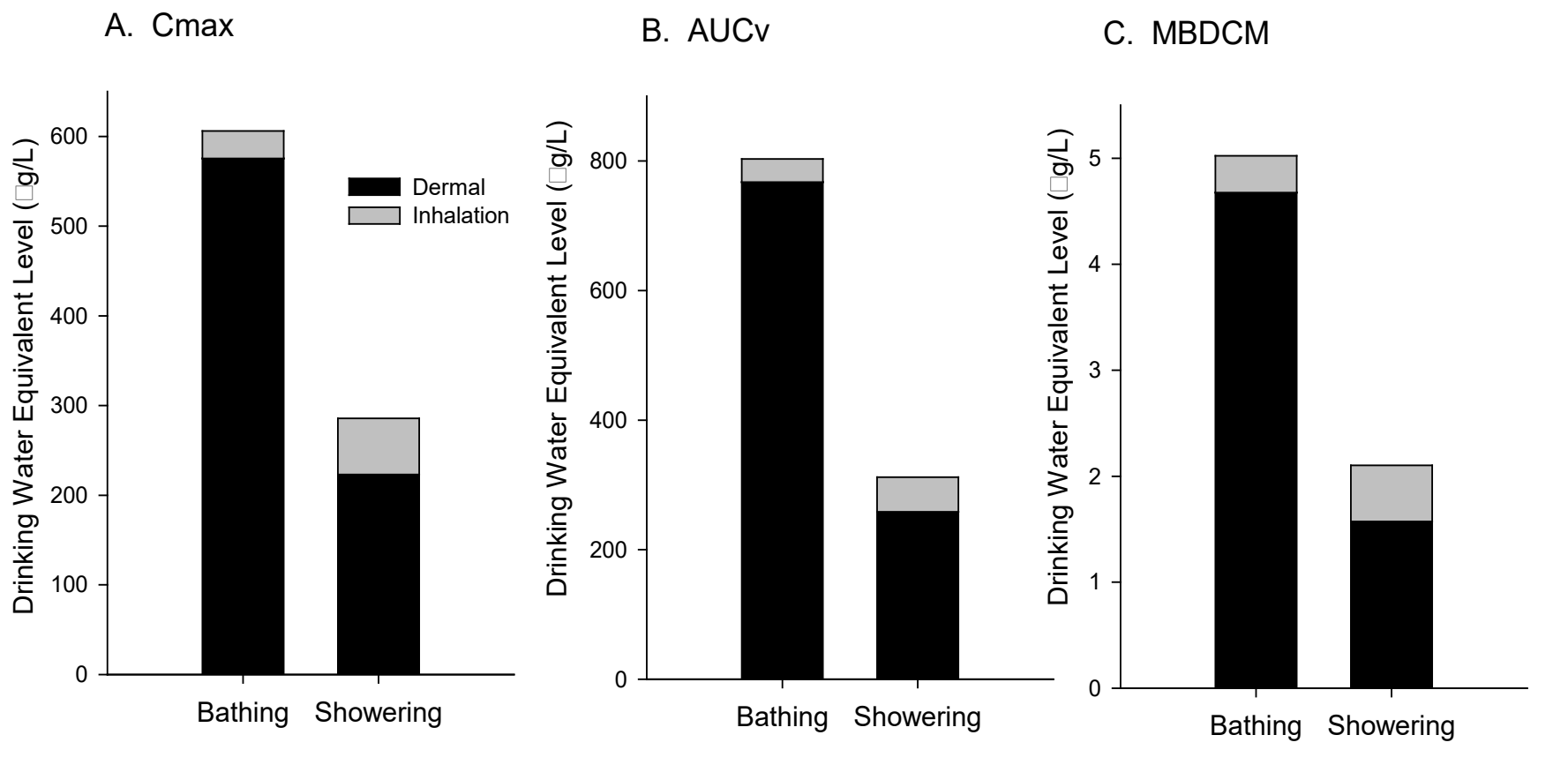
Drinking Water Equivalency Analysis

Drinking Water Equivalent Level is the ingested water concentration required to produce the same value for a given measure of internal dose resulting from a specific exposure scenario or activity

- Use PBPK model to simulate a water use activity and obtain resultant measure of internal dose
  - 20 min bath with 10 µg/L BDCM water
  - 10 min shower with 10 µg/L BDCM water

- Use PBPK model to determine concentration of chemical in water needed to obtain the same value for the internal dose metric after drinking a liter of water

Drinking Water Equivalent Analysis



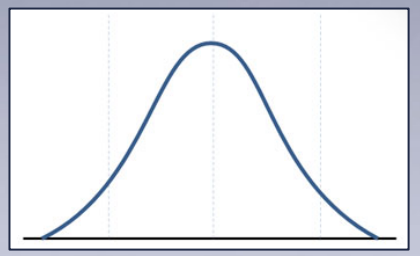
Drinking Water Equivalent Analysis - ingested water concentration (assuming 1 liter of water consumed) required to produce the same value for different dose metrics resulting from a 20 minute bathing or 10 minute showering event with 10 ppb (µg/L) BDCM in water.

Impact of Variability in Scaling Factors on IVIVE

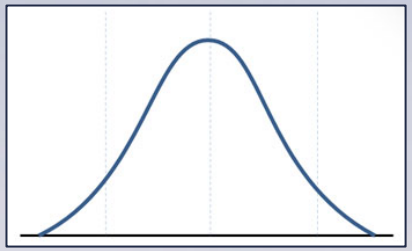
- *In vitro* derived biotransformation rates are frequently incorporated into PBPK models (*in vitro* to *in vivo* extrapolation)
- Variability in IVIVE scaling factors (e.g., liver volume, microsomal protein, enzyme expression) gives rise to variability in *in vivo* biotransformation rates
- Scaling factors can vary uniquely across lifestages, particularly in neonates
- PBPK modeling provides a useful framework to integrate lifestage-specific physiology and biochemistry with realistic exposure scenarios to investigate influence of variability on measures of internal dose and biomarkers of exposure

Incorporating Parameter Variability

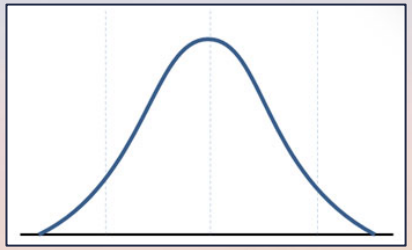
IVIVE Scaling Factors



pmol CYP2E1/mg MSP

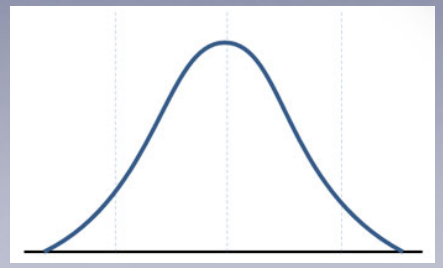


MPPGL



Liver Volume as Fraction BW

x



Distribution for Vmax

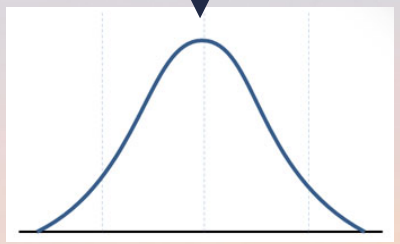
Monte Carlo

Chemical-Specific *In Vitro* Rate of Metabolism (Vmax)

Relevant Exposure Scenario

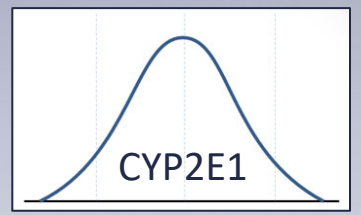
Age-Specific Physiological Parameters

PBPK Model

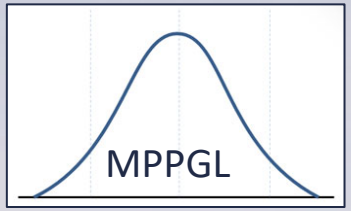


Distribution of PK Outcomes

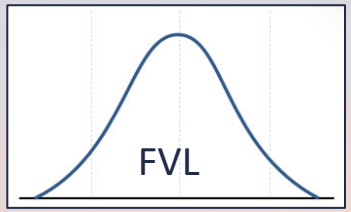
Scaling Factors Varied



CYP2E1/mg MSP



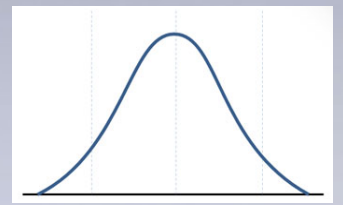
Log10 MPPGL



Liver Mass as Fraction BW

x

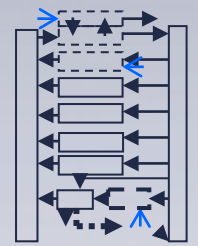
In Vitro Rate of Metabolism (Vmax)



Distribution for Vmax

IVIVE

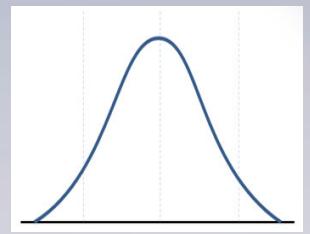
Age-Specific Physiological Parameters



PBPK Model

Monte Carlo

Distribution of PK Outcomes



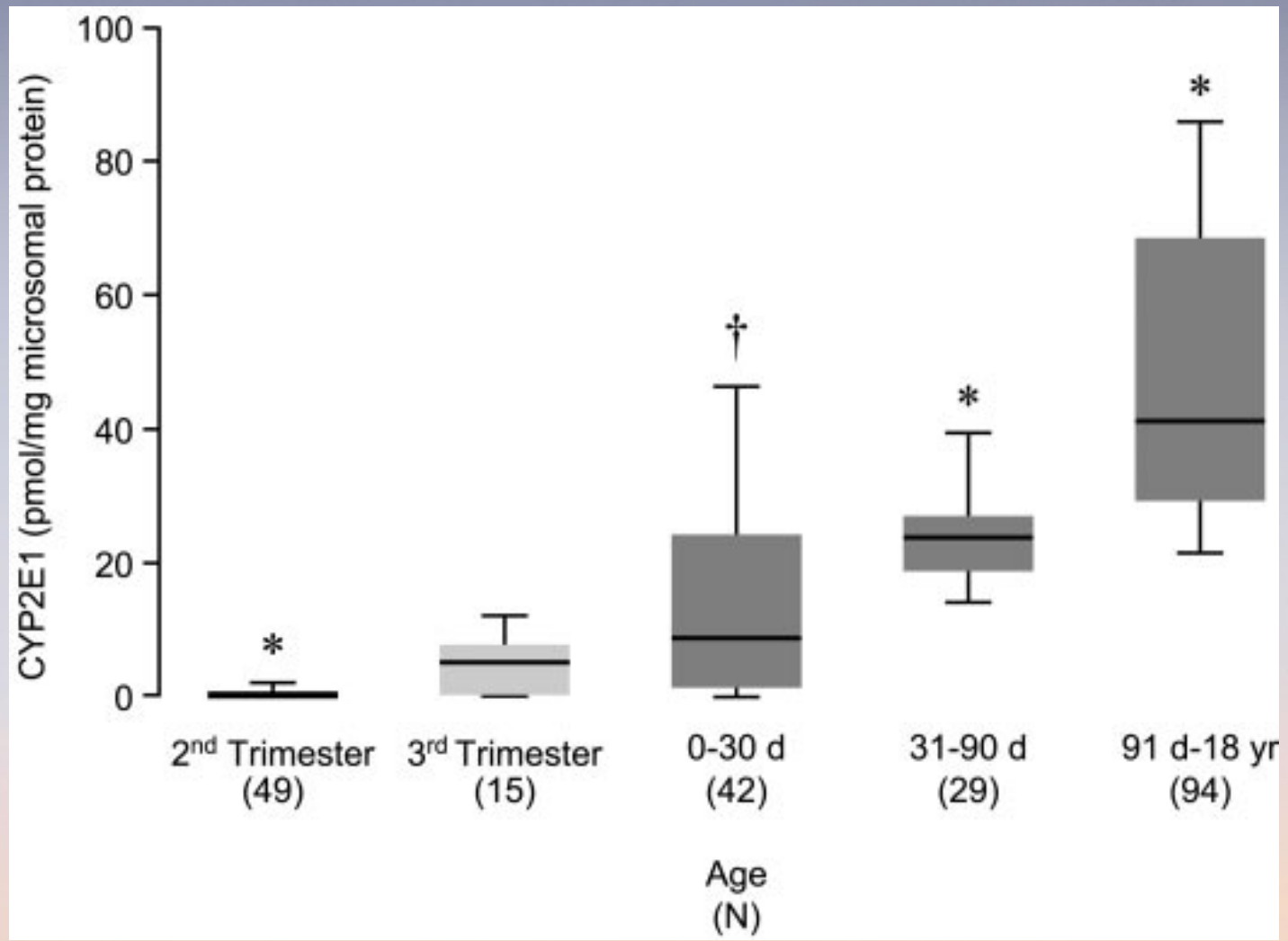
- Area under curve BDCM in venous blood (AUCv)
- Amount BDCM metabolized in liver (AML)

Exposure Scenarios
- Single 0.05 liter drink (5 µg/l)
- 20 minute bath (5 µg/l BDCM)

Input Parameter Data Sources

- CYP2E1 protein expression levels
  - Adult (Lipscomb et al. 1997, 2003a, b)
  - Pediatric (McCarver et al., 2017)
- MPPGL estimated based on subject age using equation published by Barter et al. (2008).
- Fractional Liver Volume (FVL)
  - Adult (Young et al., 2009)
  - Pediatric (McCarver et al., 2017)

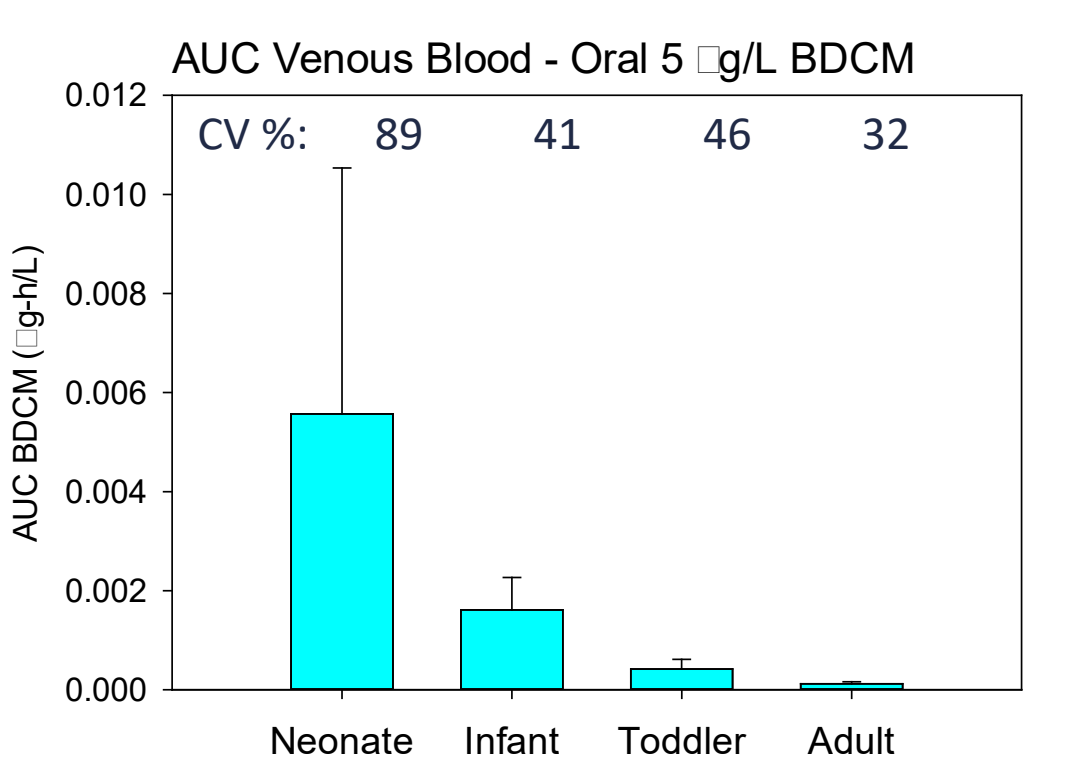
Input Parameter: Pediatric CYP2E1



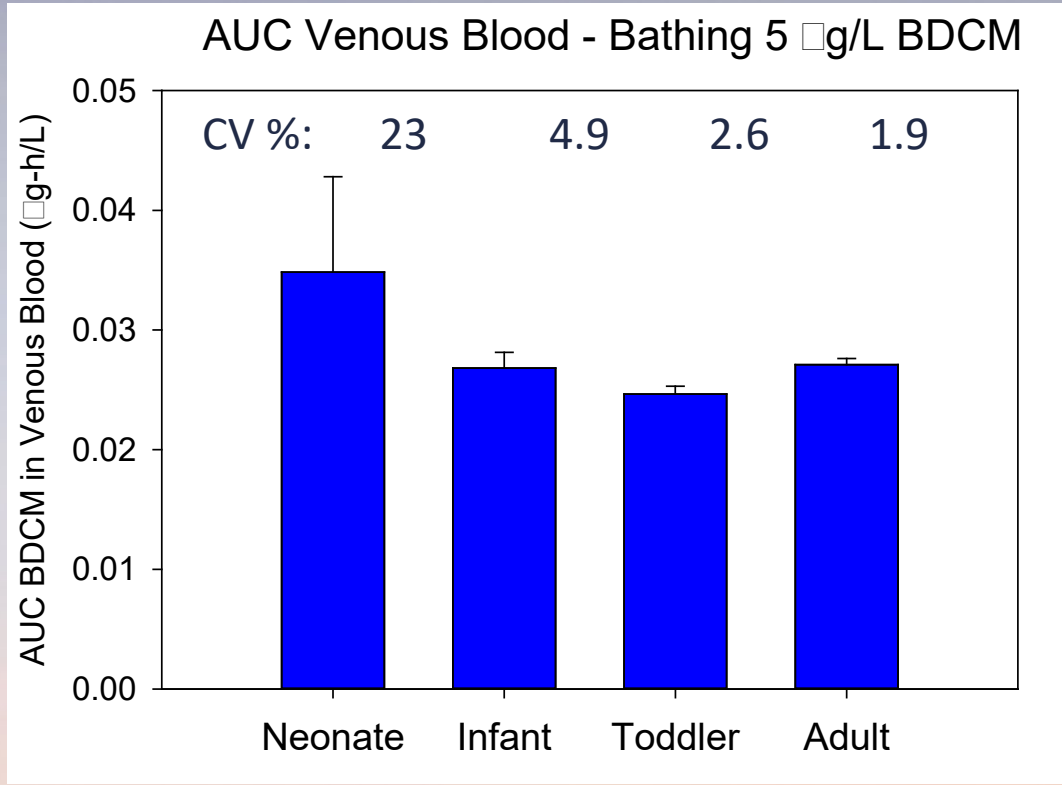
From: Johnsrud et al., 2003, Figure 4, p. 405

Metric: Area Under Curve BDCM in Venous Blood

Single 0.05 liter Drink



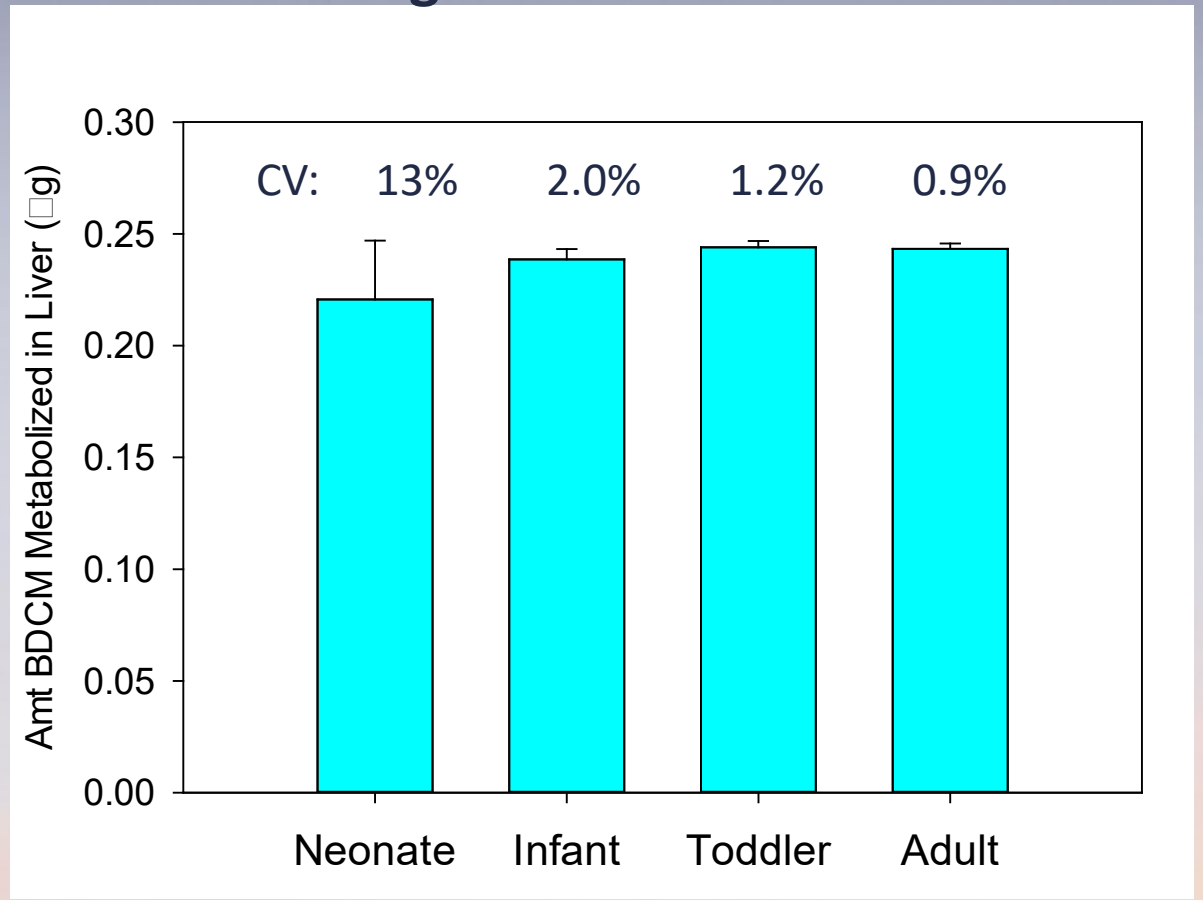
20 min Bath



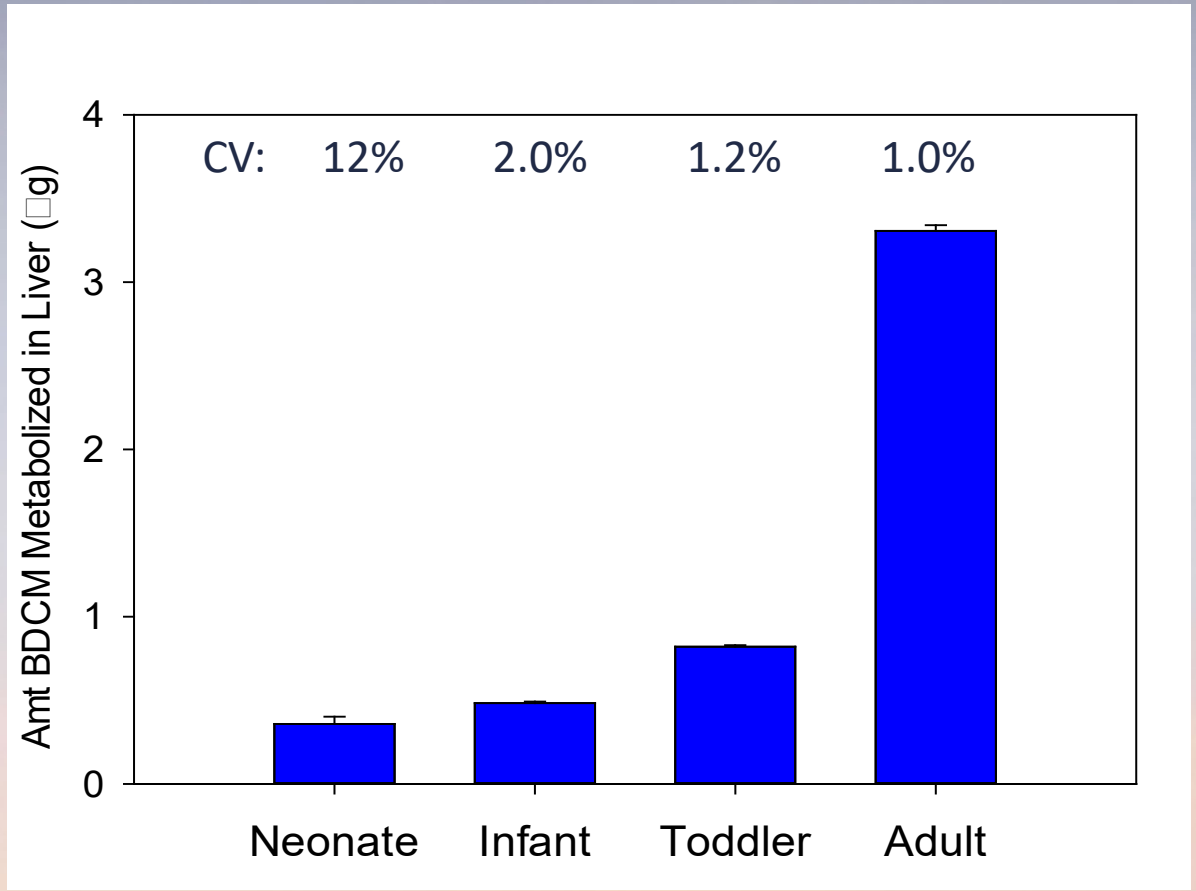
Water Concentration: 5 µg/liter BDCM

Metric: Amount Metabolized in Liver

Single 0.05 liter Drink



20 min Bath



Water Concentration: 5 µg/liter BDCM

Summary

- ***Physiologically realistic*** mathematical description of the processes of ADME in a biological organism
- Scientifically accepted and used for many types of ***extrapolation*** to support environmental risk assessment, veterinary and human drug development, and exposure reconstruction
- Quantitative estimation of the ***impact of variability*** in model parameters on toxicologically-relevant PK outcomes (probabilistic and population-based risk analysis)
- Exposure via inhalation and/or dermal routes (e.g. showering, bathing) results in higher concentrations of BDCM reaching the systemic circulation, resulting in more parent chemical reaching target organs for potential biotransformation to mutagenic metabolites
- Assessment of internal dose from multiple routes of exposure allows a more comprehensive analysis of potential human health risks

Acknowledgments

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- Christopher Eklund
- Jane Ellen Simmons
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- U.S. EPA, Office of Water Colleagues