



# Biomonitoring Equivalents and Interpretation: Current Activities

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# Overview

- US agency activities
- Health Canada activities
- Recent Case Studies and Publications
- Urinary flow data from NHANES – application to biomonitoring evaluation and interpretation



# US Agency Activities

- USEPA

- Engagement of scientists in the Computational Toxicology group, Office of Research and Development, and Office of Water
- Participation on manuscripts
  - NHANES data review
  - Speciated urinary arsenic evaluation

- CDC

- Urinary flow data evaluation and modeling analysis and manuscript



# US Agency Activities (cont'd)

- ATSDR Health Consultation/Exposure Investigation
  - Concern over potential exposure to 2,4-D in a rural area
  - Urinary biomonitoring in 64 volunteers from 38 households
- Comparison of results to NHANES:

“Based on this comparison, the fraction of the... participants above the NHANES 75<sup>th</sup> percentile was higher than expected. **This suggests an increased exposure relative to the rest of the United States.**”





# ATSDR Conclusions

- BE values used to assess potential risks:

“The maximum concentration of 2,4-D... was about 7-fold less than the BE, and the average concentration was 175-fold less than the BE.”

“Despite an apparent greater exposure than the US population, these data indicate that, at the time of testing, the participants were not exposed to 2,4-D at levels that are expected to cause adverse health effects.”



# Health Canada Activities

- Sponsored several new BE values over the past two years
  - Selenium
  - 3-PBA
  - Fluoride
  - Diisobutyl phthalate (DiBP)
  - Dicyclohexyl phthalate (DCHP)
  - Diisodecylphthalate (DiDP)
  - Cobalt
- Used analogies for data-poor chemicals
- Health Canada plans to address at least 6 more chemicals over the next 2 years
- CHMS data review (multiple analytes with BEs) manuscript near submission



# Case Study: US NHANES Data Review

# Current Publication

- Review of NHANES data in the context of BE values – *Environmental Health Perspectives*, March 2013, 121:287-294.

Review

## **Evaluation of Biomonitoring Data from the CDC National Exposure Report in a Risk Assessment Context: Perspectives across Chemicals**

*Lesa L. Aylward,<sup>1</sup> Christopher R. Kirman,<sup>2</sup> Rita Schoeny,<sup>3</sup> Christopher J. Portier,<sup>4</sup> and Sean M. Hays<sup>5</sup>*

<sup>1</sup>Summit Toxicology LLP, Falls Church, Virginia, USA; <sup>2</sup>Summit Toxicology LLP, Orange Village, Ohio, USA; <sup>3</sup>Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC, USA; <sup>4</sup>National Center for Environmental Health/Agency for Toxic Substances and Disease Registry, Atlanta, Georgia, USA; <sup>5</sup>Summit Toxicology LLP, Lyons, Colorado, USA

- Covers approximately 130 NHANES analytes
- Coauthors from USEPA, CDC/ATSDR

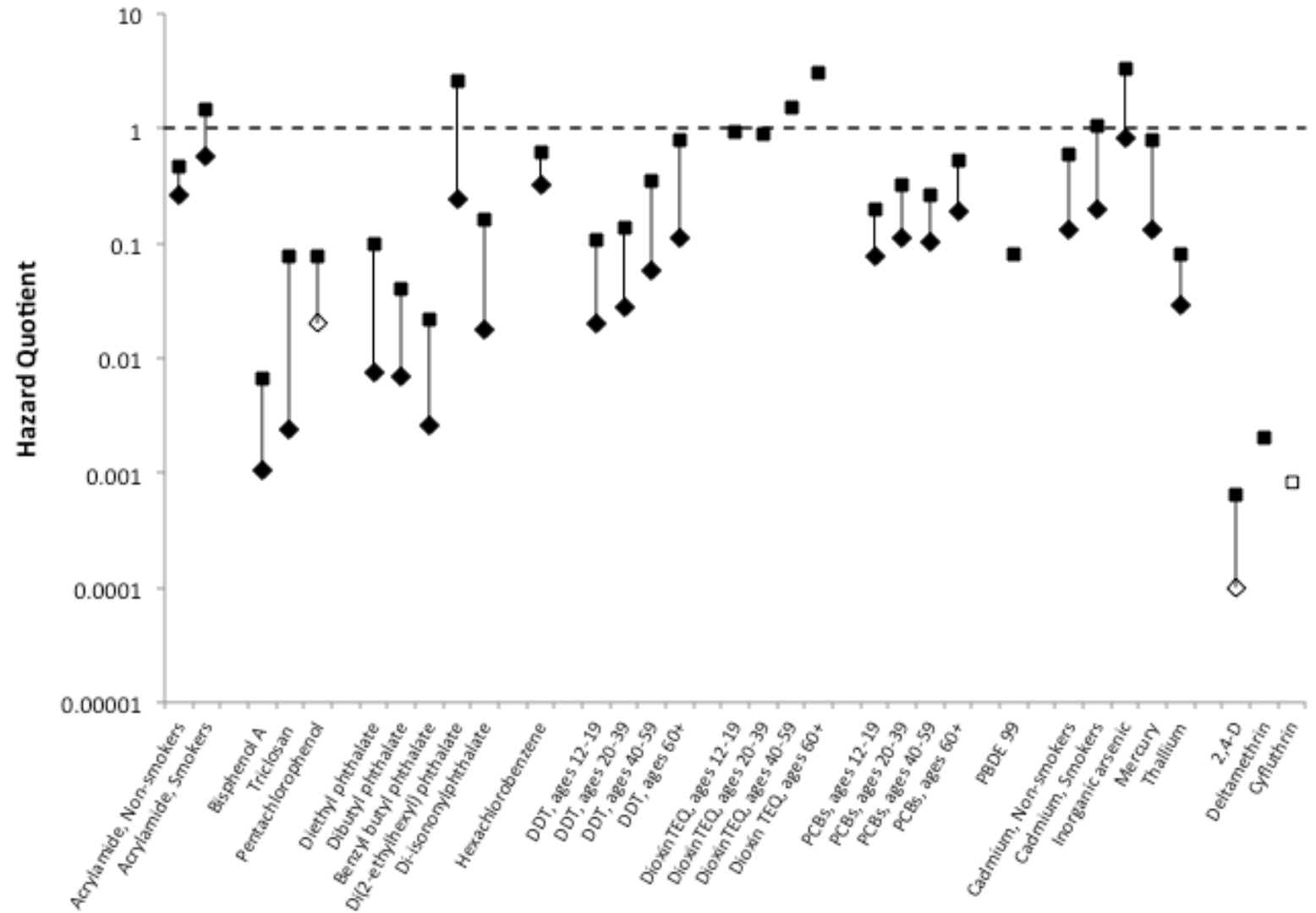
# BE Review Paper

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

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

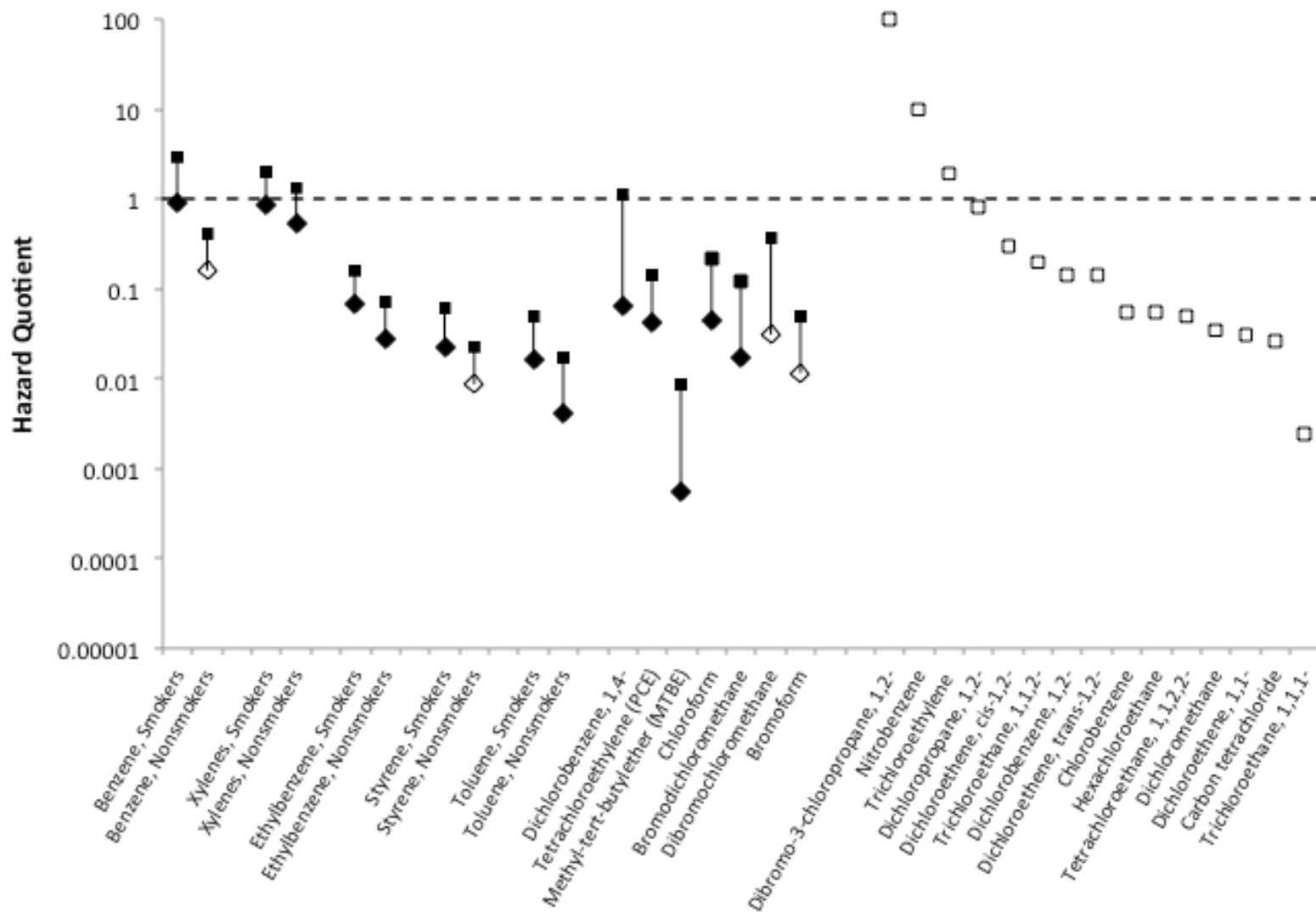
- Allows evaluation of both detected and non-detected analytes, and evaluation of both blood and urinary biomarkers

# Non-VOCs, GM to 95<sup>th</sup> %ile





# VOCs





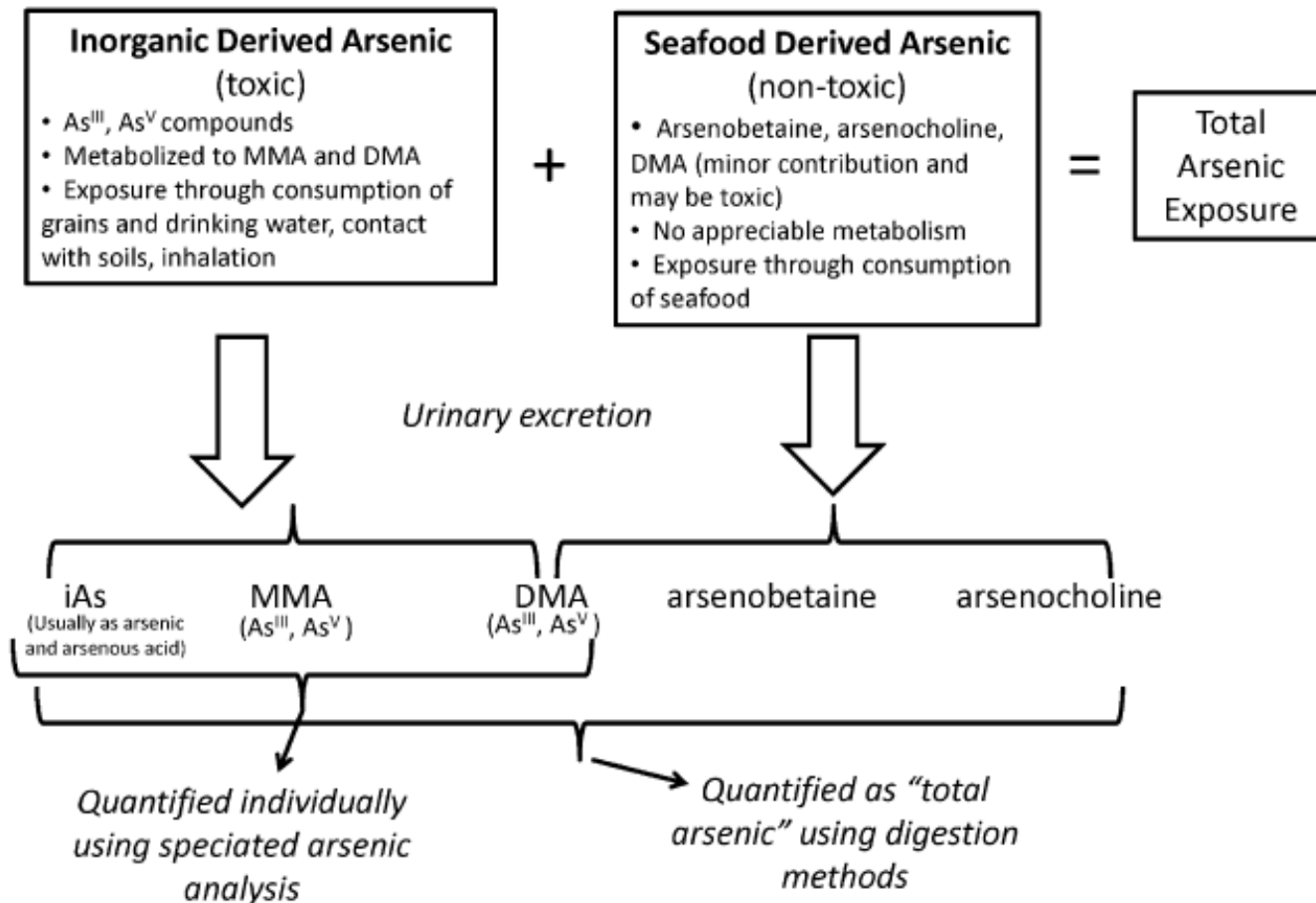
# Case Study: Speciated Urinary Arsenic



# Evaluation of Speciated Urinary Arsenic

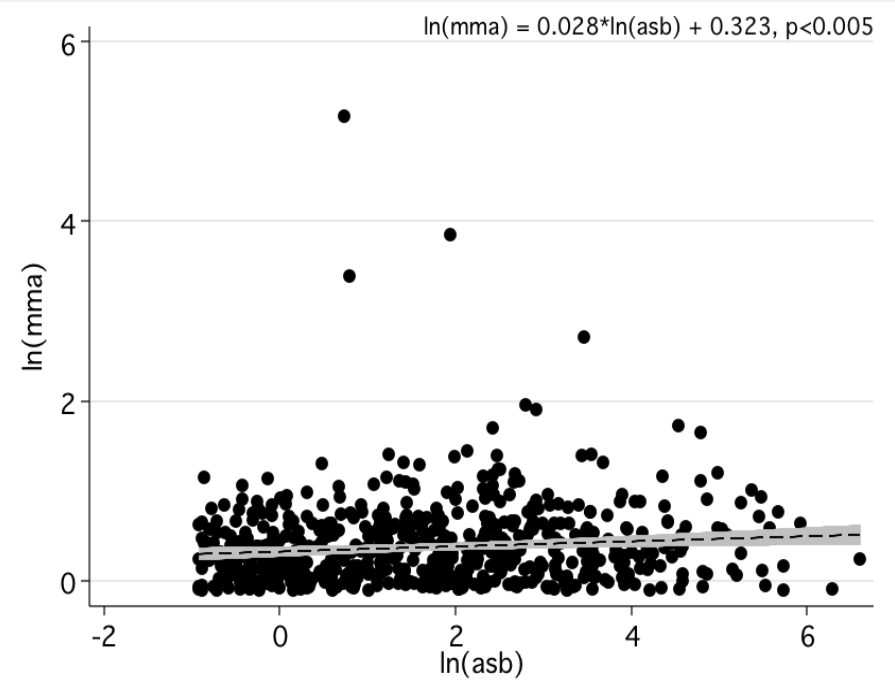
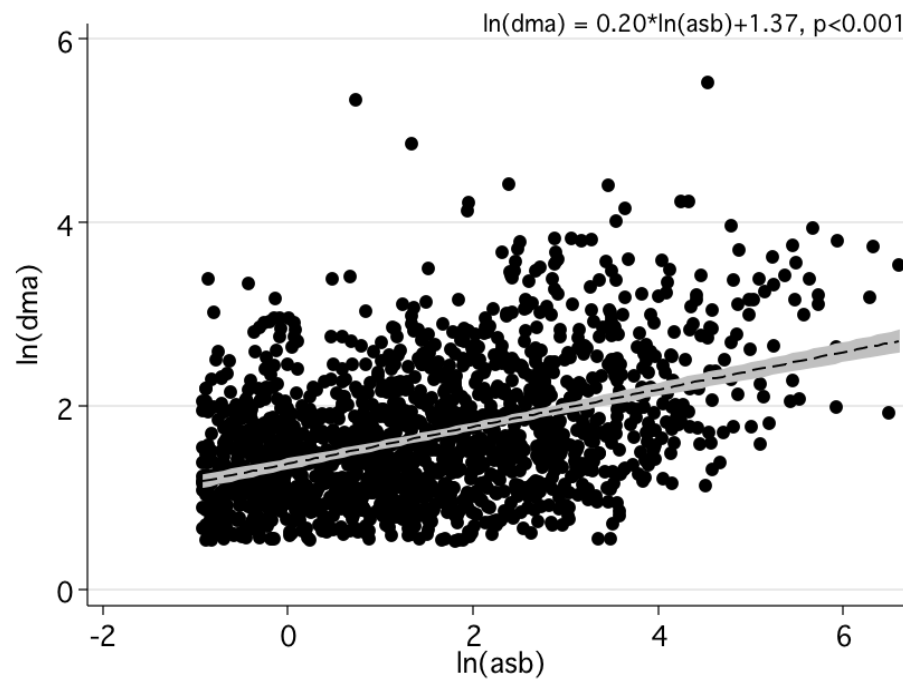
- Manuscript coauthored with USEPA Office of Water and Office of Research and Development scientists
- Examines NHANES speciated urinary arsenic data in risk assessment context
  - Patterns among iAs, DMA, MMA
  - Comparison to BE values

# Arsenic Biomarkers

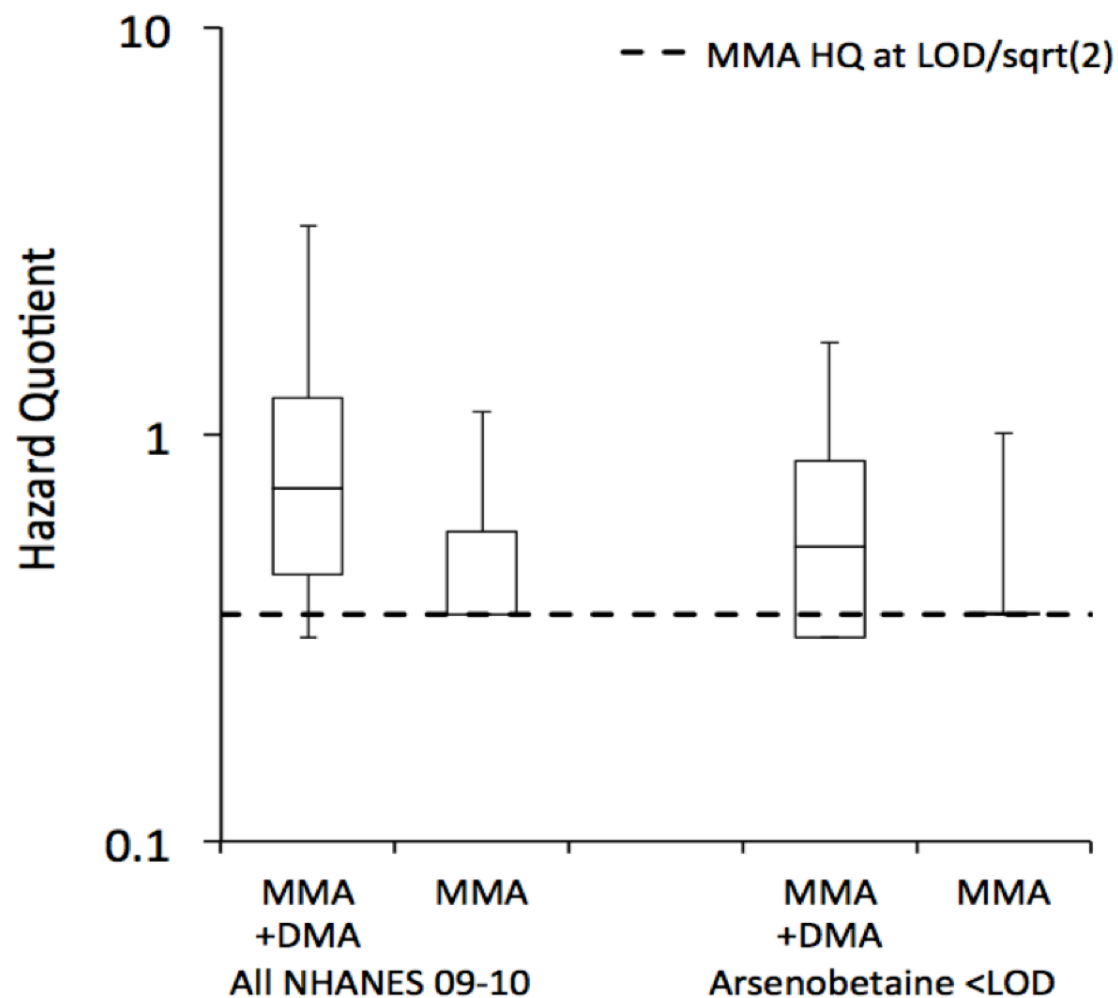


From Hays et al. 2010, *Regulatory Toxicology Pharmacology*, 58:1-9.

# DMA and MMA vs. Arsenobetaine



# Hazard Quotients, NHANES 2009-2010







# Case Study: Selenium



# Selenium

- Essential micronutrient
  - Recommended Dietary Allowances (RDAs) have been set
- Toxic (selenosis) at high exposures
  - RfD, MRL
  - Upper Limits (ULs) on RDAs
- Most guidelines based on studies in China of both low and high selenium exposure regions
  - Detailed data correlating selenium in blood & urine with average daily dietary intake of selenium

# Selenium

Yang et al. 1989 a & b; Basis for RfD, MRL, UL

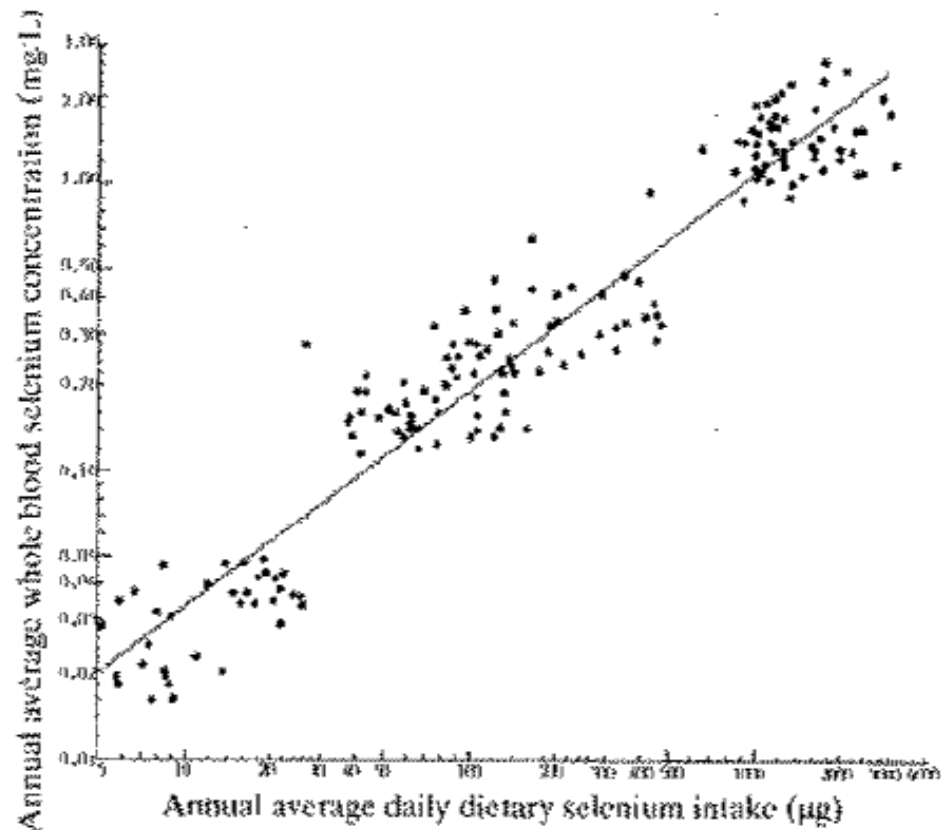


Figure 1. Correlation between dietary Se-intake and blood Se concentration of 167 male adults.

( $\text{Log } Y = 0.767 \text{ Log } X - 2.248$ ,  $r = 0.962$ ,  $p < 0.001$ )

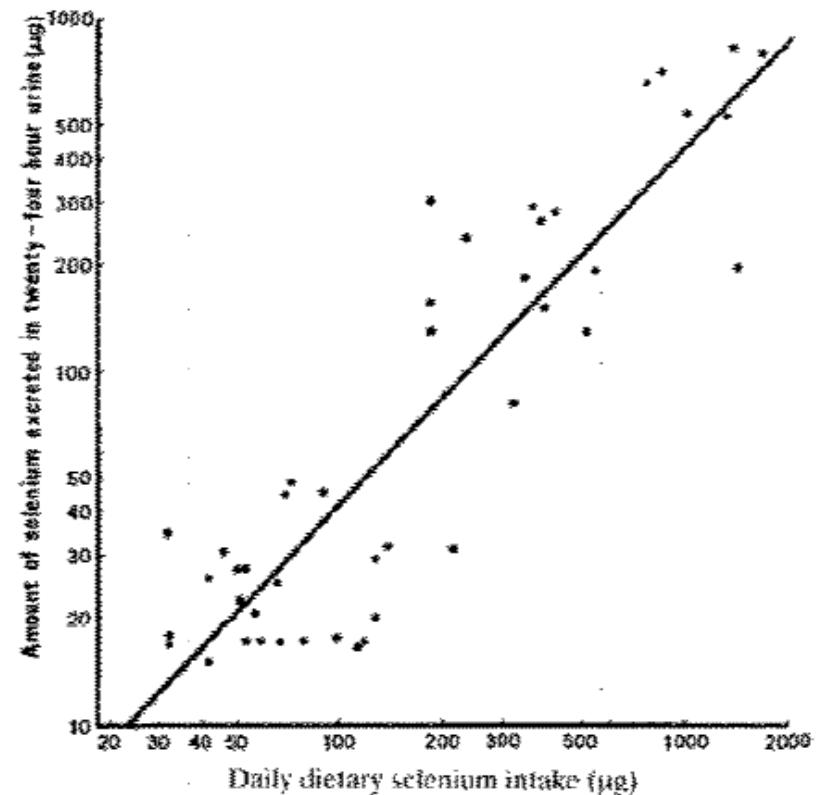


Figure 2. Correlation between daily selenium intake and amount of selenium excreted in twenty-four hour urine of adult inhabitants.

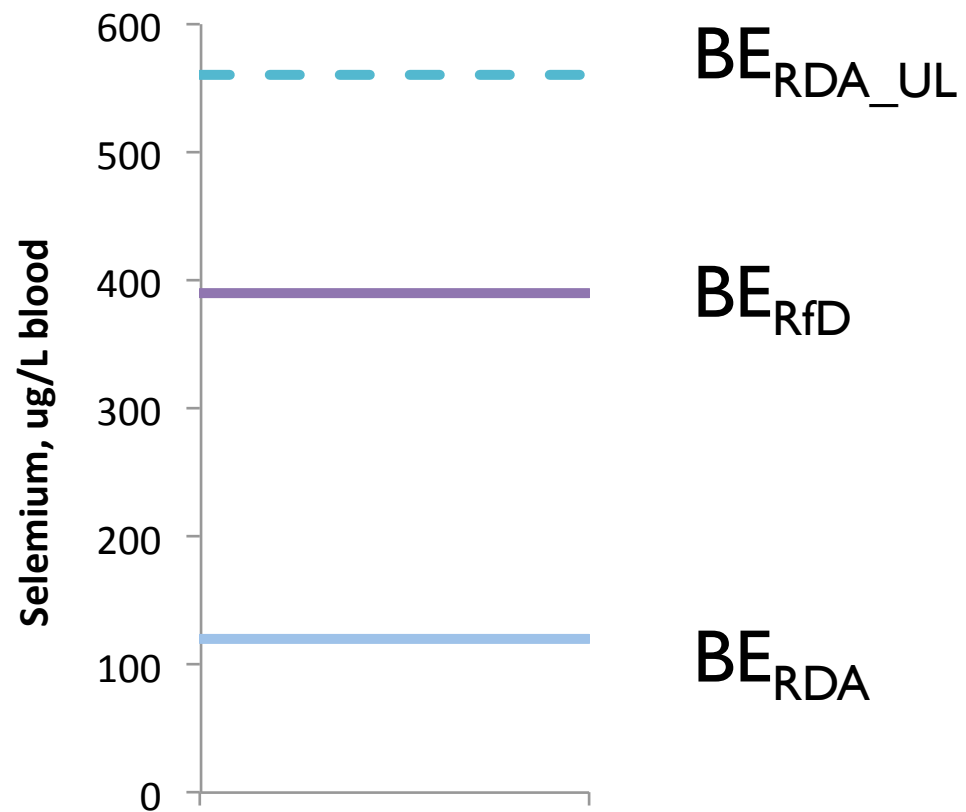
( $\text{Log } Y = 1.021 \text{ Log } X - 0.418$ ,  $r = 0.886$ ,  $p < 0.001$ ,  $n = 44$ )



# Selenium Guidelines & BEs

<b>Guideline</b>	<b>Daily Dose (<math>\mu\text{g}/\text{kg-d}</math>)</b>	<b>BE (<math>\mu\text{g}/\text{L}</math> blood)</b>
RDA (NAS, 2000)	0.8	120
RfD (US EPA, 1991)	5.0	390
MRL (ATSDR, 2003)	5.0	390
UL (NAS, 2000)	5.7	560

# CHMS Cycle I





# Provisional BE Values for 3-PBA





# Urinary 3-Phenoxy Benzoic Acid

- Evaluation contracted for by Health Canada
- Non-specific metabolite arising from multiple pyrethroids
- Cannot be interpreted directly in terms of toxicity
- Structural similarities across contributing pyrethroids may allow assumption of pharmacokinetic similarity
- Screening approaches can be applied for a tiered assessment

# Pyrethroids with 3-PBA Moiety

Cyhalothrin

Permethrin

Cypermethrin

Deltamethrin

Tralomethrin

Fenpropathrin

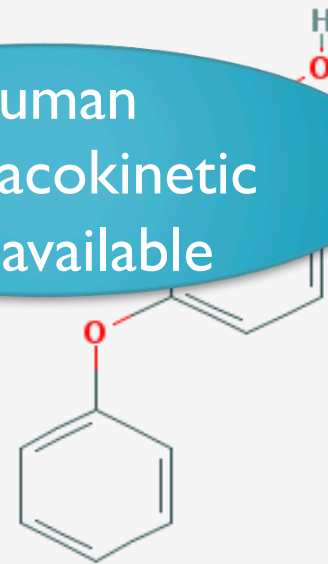
Cyphenothrin

Esfenvalerate

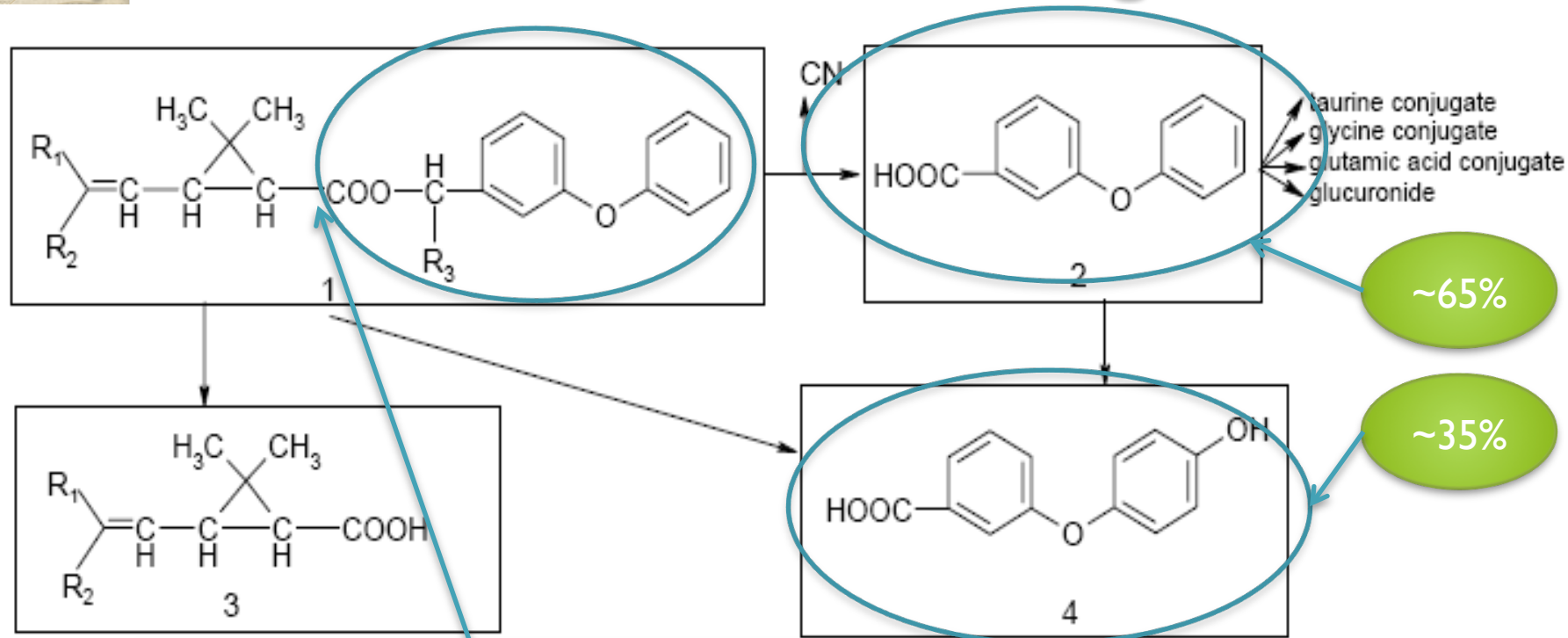
Flucythrinate

Phenothrin

Human  
pharmacokinetic  
data available



# Pyrethroid Structures Leading to 3-PBA



Cleavage of the ester linkage leads to a split in the molecule into a 3-PBA portion and a portion that is specific to the pyrethroid

- $R_3 = \text{CN}$   
 $R_3 = \text{H}$   
 $R_3 = \text{CN}$   
 (PBA)
- 3 { 3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane carboxylic acid (DCCA)  
 3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane carboxylic acid (DBCA)
- 4 { 3-(4-hydroxy)-phenoxybenzoic acid (4-OHPBA)



## Estimation of Urinary 3-PBA for Each Pyrethroid

- Identify all pyrethroids leading to 3-PBA
- Identify TDIs/ADIs for each pyrethroid
- Apply available pk data to estimate unit urinary 3-PBA concentrations (ug/L per mg/kg-d) for each pyrethroid
- Calculate Provisional BE values corresponding to available RfD or TDIs for each pyrethroid



# Tiered Evaluation Approach

- Tier I: Compare biomonitoring data to most stringent pyrethroid-specific Provisional BE value
  - Effectively attributes all 3-PBA to exposure to the most potent compound
  - Ignores within-person, within- and across-day variability
- If available biomonitoring data below Tier I Provisional BE, suggests low cumulative exposure and risk
  - If data exceed Tier I, proceed to more detailed assessments



# Provisional BE Values ( $\mu\text{g/L}$ )

Compound	USEPA BE <sub>RfD</sub>	JMPR BE <sub>ADI</sub>
Cyhalothrin	6	117
Permethrin	1875	375
Cypermethrin	425	142
Deltamethrin	6	58
Fenpropathrin	208	250
Cyphenothrin	79	
Esfenvalerate <sup>b</sup>	14	142
Tau-fluvalinate	29	
d-Phenothrin	58	583

Tier I  
Provisional BE  
Value





# A Look At CHMS Cycle I Data

## 3-PBA, $\mu\text{g/L}$ Urine

Age Group	Geometric Mean	95 <sup>th</sup> %ile	Pass Tier I (< 6 $\mu\text{g/L}$ )?
All	0.25	2.96	✓
6-11	0.21	1.78	✓
12-19	0.28	3.26	✓
20-39	0.25	2.54	✓
40-59	0.27	3.54	✓
60-79	0.24	2.22	✓



# Urinary Flow Rate Data From NHANES



# NHANES 2009-2010 Dataset

- *Spot sample* urinary flow rate data (n~8,000 ages 6 to 85):
  - “Participants will be asked to record their time of last void before coming to the MEC.”
    - Volume of void at MEC measured (ml)
    - Flow rate= Volume/(Time since last void) (ml/min)
- Collaboration with US CDC researchers to analyze and model flow rate data
- Results can inform biomonitoring study design and data interpretation

# Challenge

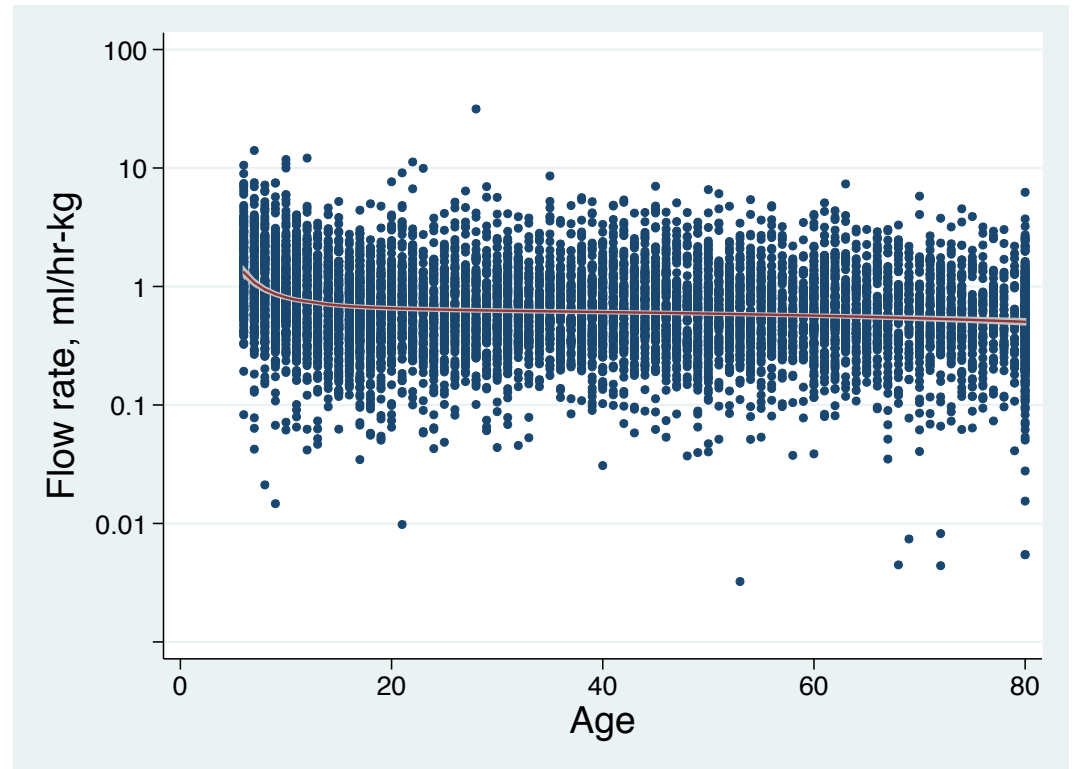
- Hydration status (urinary flow rate) affects the urinary concentration independent of the excretion rate of the analyte
  - Concentration is usually equated with exposure level
- Methods for adjusting for hydration status are imperfect
- Urinary flow rates (ml/hr) allow calculation of analyte excretion rate, ER, expected to be directly related to daily dose by the urinary excretion fraction:

$$ER(ug / hr - kg) = \frac{Void\ volume, ml}{Time, hr * BW, kg} * C_{analyte}$$

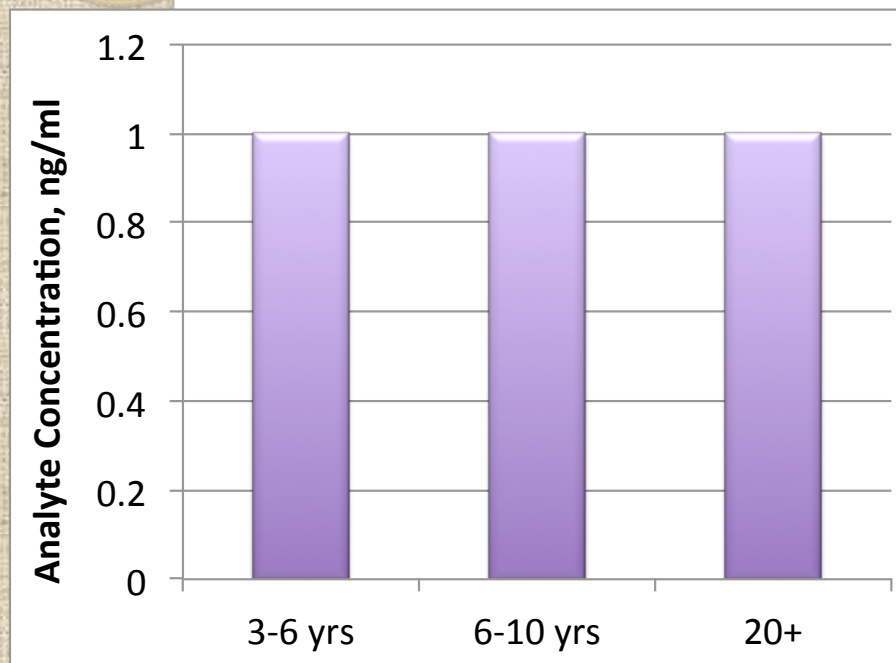
$$Dose(ug / d - kg) = F_{UE} * ER(ug / d - kg)$$

# Factors Influencing Flow Rate: Age

***At the same urinary concentration of an analyte, children excrete more analyte per unit time and kg bodyweight than adults***



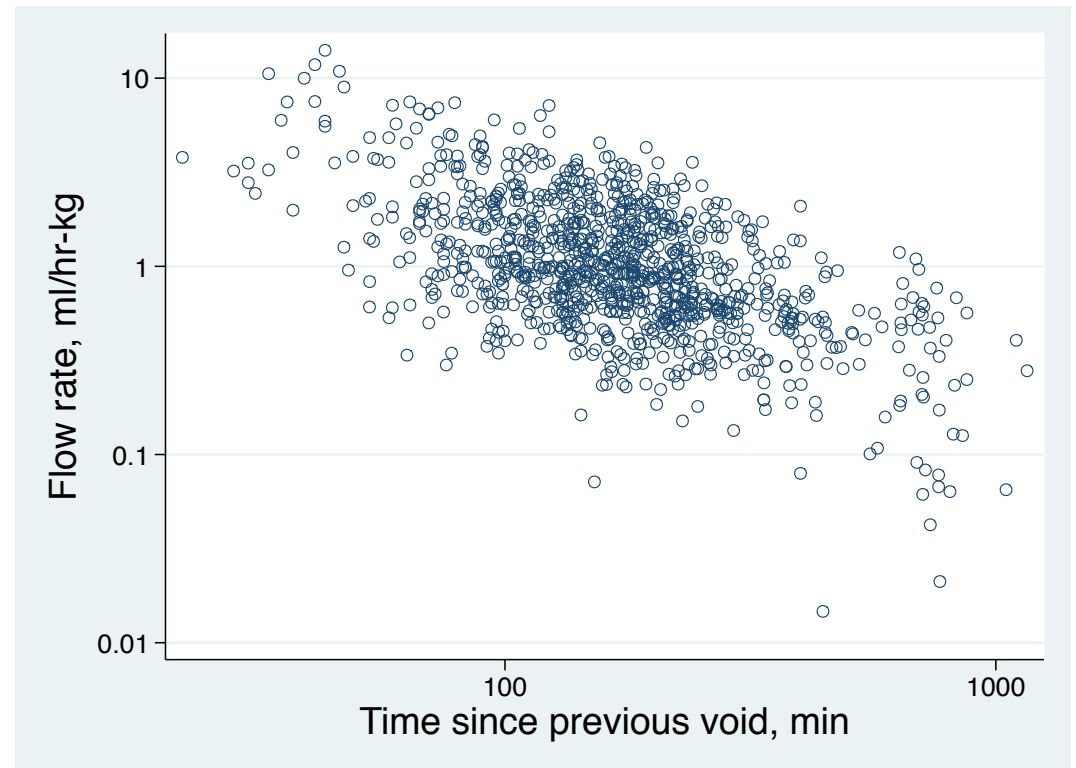
# Why It Matters





# Time Since Previous Void

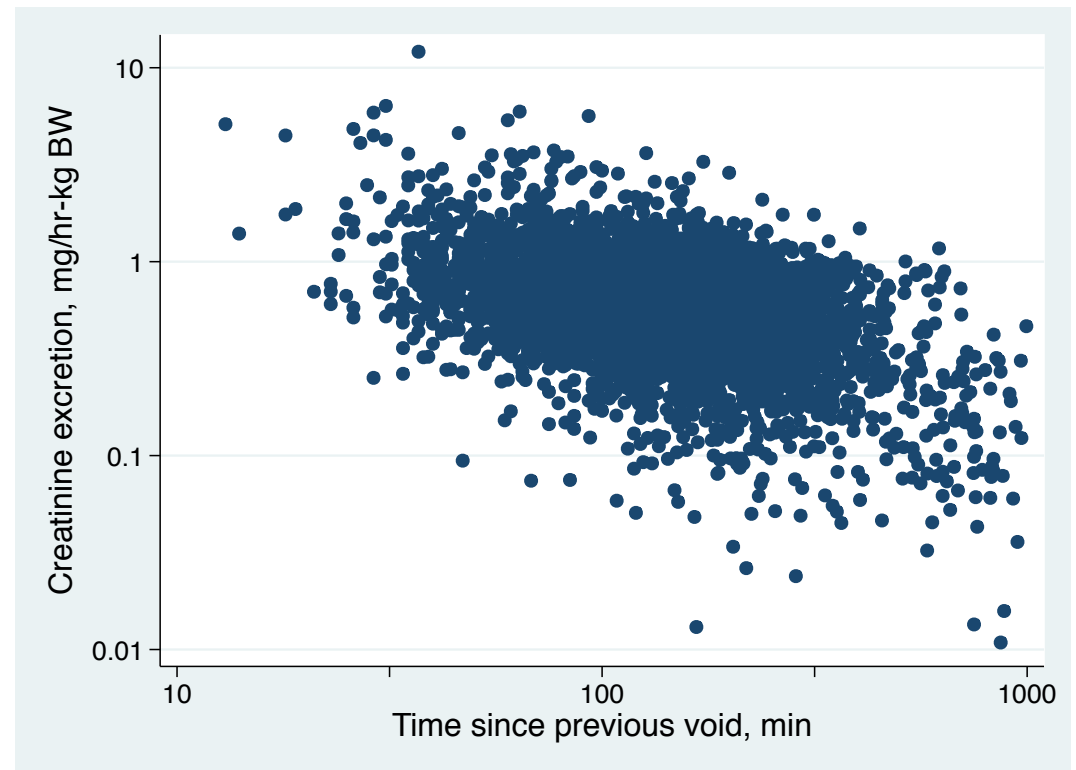
***At the same urinary concentration of an analyte, participants with a shorter time since last void excrete more analyte per unit time than participants with longer time since last urinary void.***





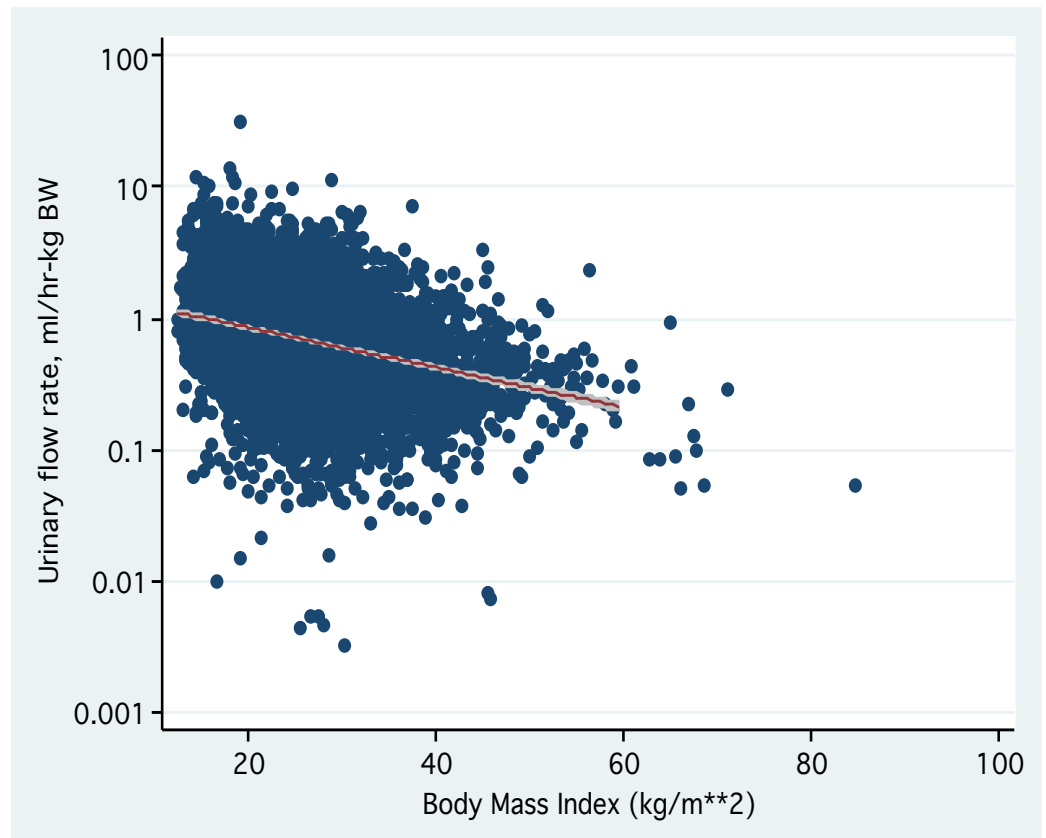
# Time Since Previous Void (cont'd)

***Also influences  
creatinine excretion  
rate***

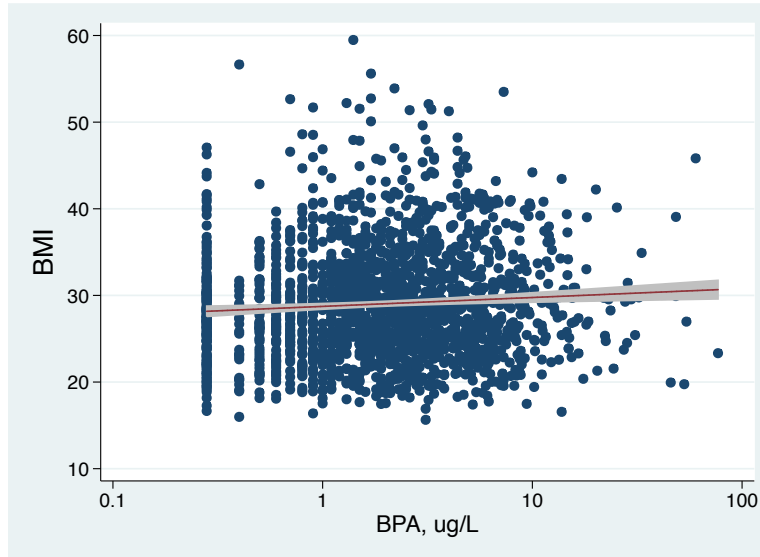


# Body Mass Index

***At the same urinary concentration of an analyte, participants with a lower body mass index excrete more analyte per unit time and kg bodyweight than participants with higher body mass indices.***



# Example: BMI and Urinary BPA





# Flow Rate Analyses - Status

- Descriptive statistics complete
- Completing modeling for prediction of flow rate and creatinine excretion rate in spot samples
- Manuscript in preparation. Goals:
  - Familiarize researchers with database
  - Identify variables predicting flow rate and creatinine excretion rate under spot sample conditions
  - Discuss applications in study design and data interpretation