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 75th 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."

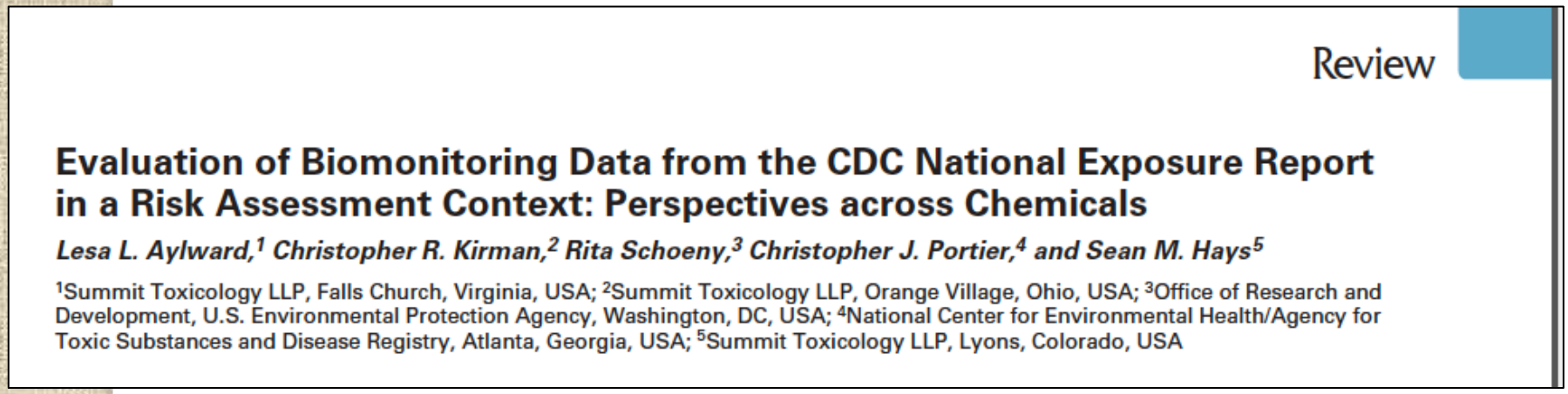
Health Canada Activities

- 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

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

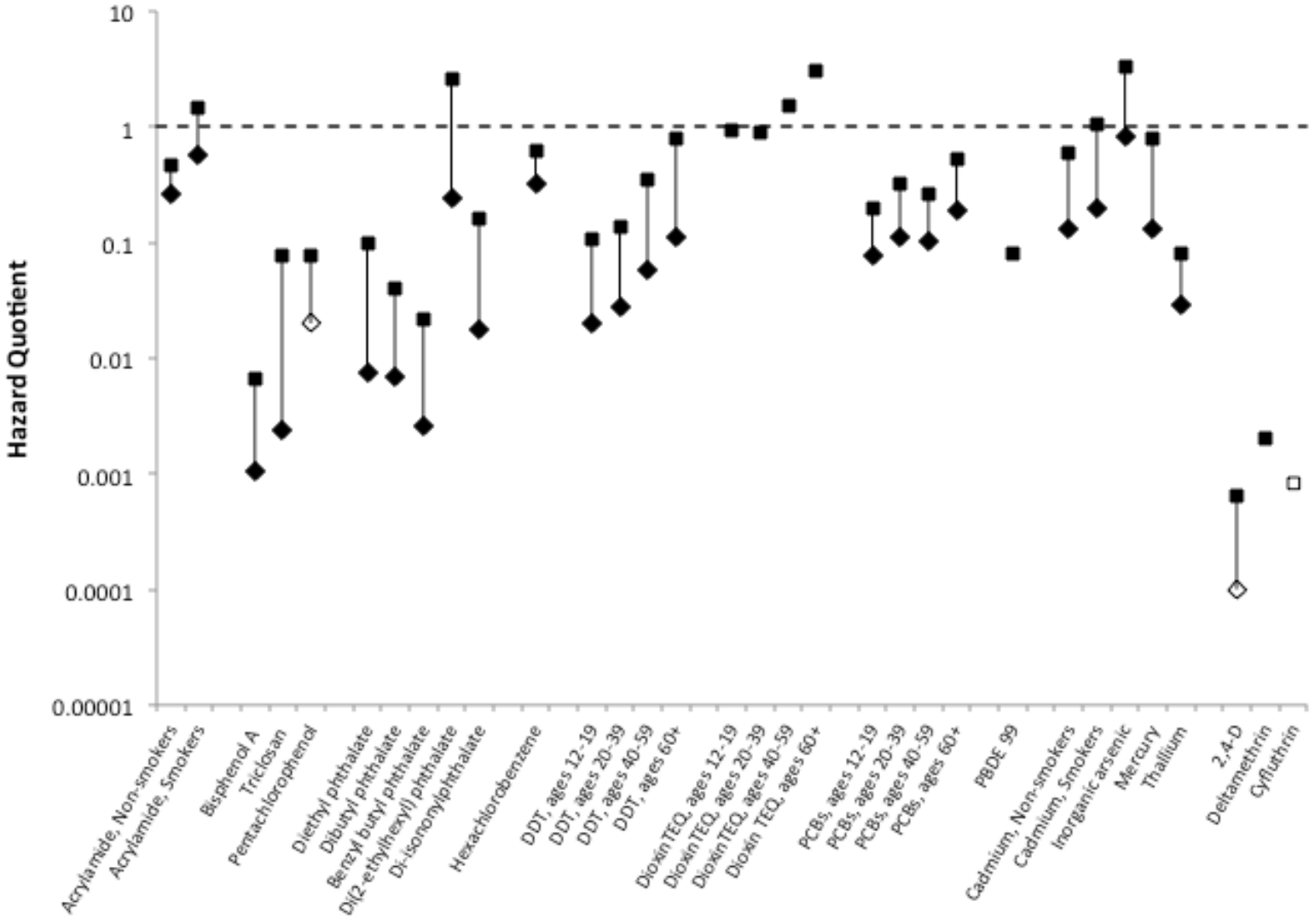
BE Review Paper

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

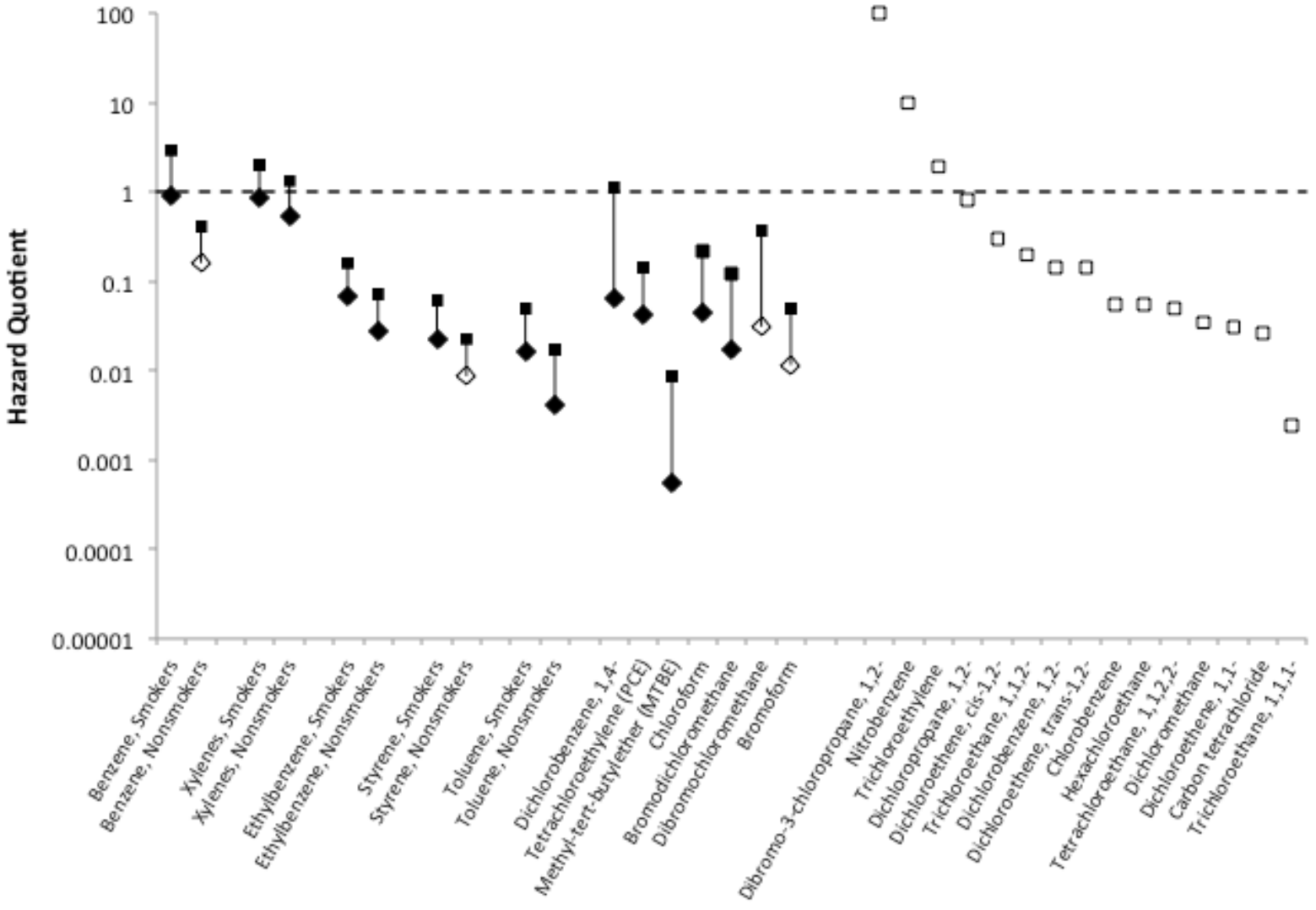
$$HQ = \frac{[Biomarker]}{BE_{RfD}}$$

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

Non-VOCs, GM to 95th %ile



VOCs

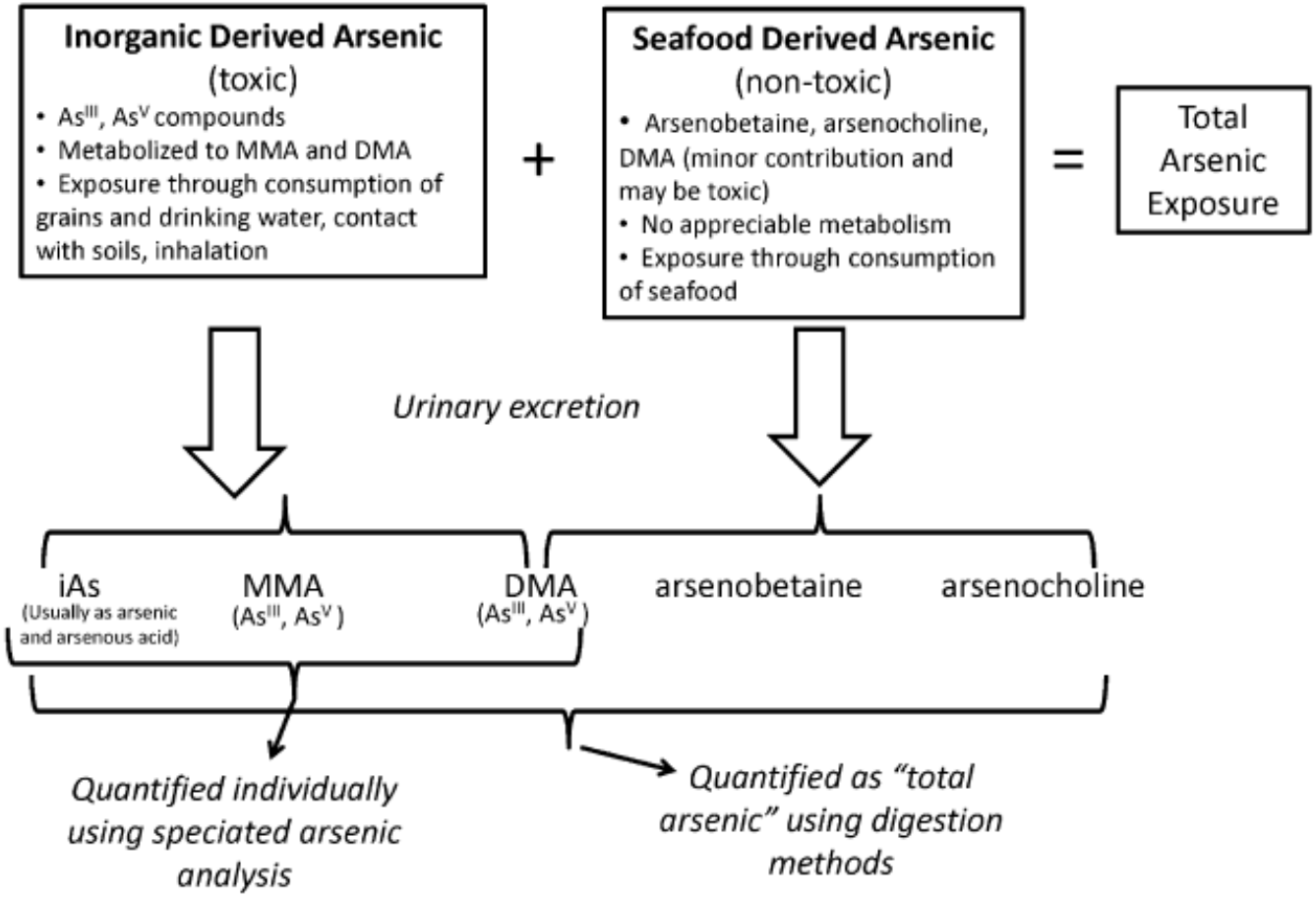

Hazard Quotient
100
10
1
0.1
0.01
0.001
0.0001
0.00001
Benzene, Smokers
Benzene, Nonsmokers
Xylenes, Smokers
Xylenes, Nonsmokers
Ethylbenzene, Smokers
Ethylbenzene, Nonsmokers
Styrene, Smokers
Styrene, Nonsmokers
Toluene, Smokers
Toluene, Nonsmokers
Dichlorobenzene, 1,4-
Tetrachloroethylene (PCE)
Methyl-tert-butylether (MTBE)
Chloroform
Bromodichloromethane
Dibromochloromethane
Bromoform
Dibromo-3-chloropropane, 1,2-
Nitrobenzene
Trichloroethylene
Dichloropropane, 1,2-
Dichloroethene, cis-1,2-
Trichloroethane, 1,1,2-
Dichlorobenzene, 1,2-
Dichloroethene, trans-1,2-
Chlorobenzene
Hexachloroethane
Tetrachloroethane, 1,1,2,2-
Dichloromethane
Dichloroethene, 1,1-
Carbon tetrachloride
Trichloroethane, 1,1,1-

Case Study: Speciated Urinary Arsenic

Evaluation of Speciated Urinary Arsenic

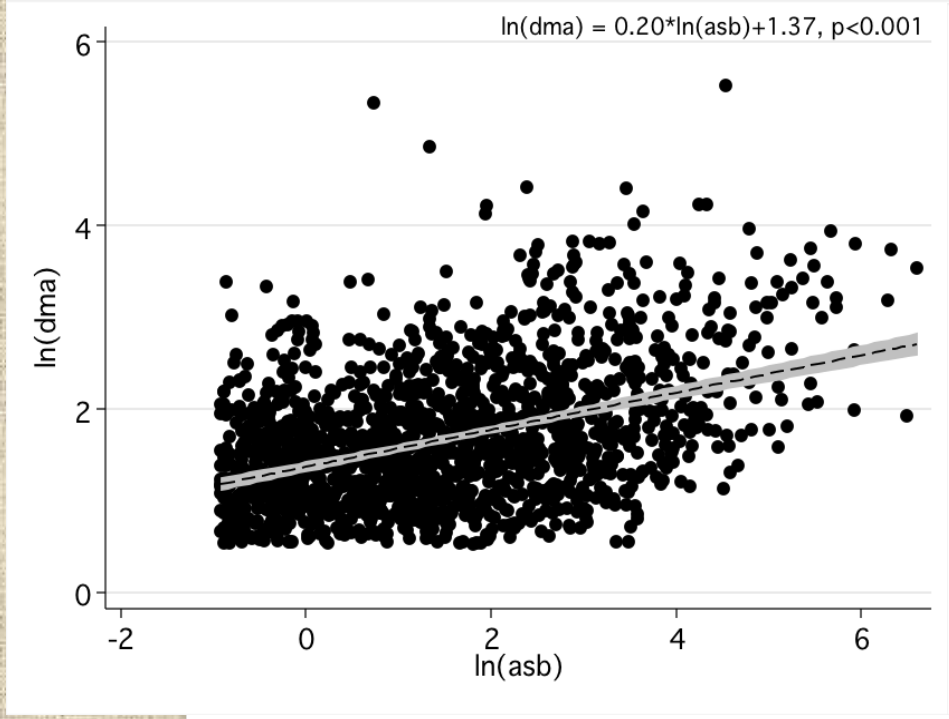
- Manuscript coauthored with USEPA Office of Water and Office of Research and Development scientists
- Examines NHANES speciated urinary arsenic data in risk assessment context
  - Patterns among iAs, DMA, MMA
  - Comparison to BE values

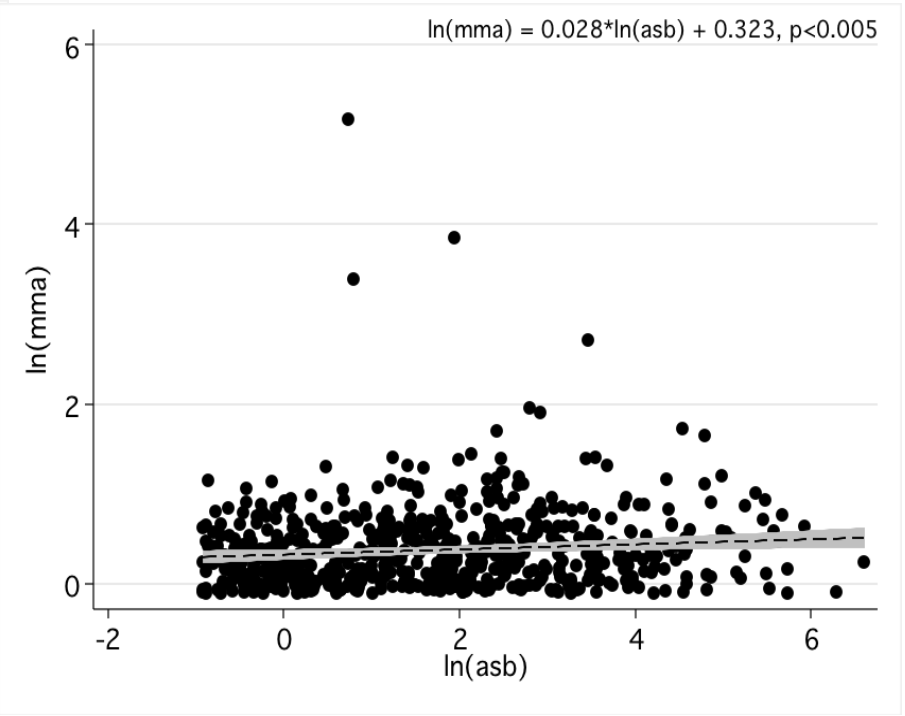
Arsenic Biomarkers



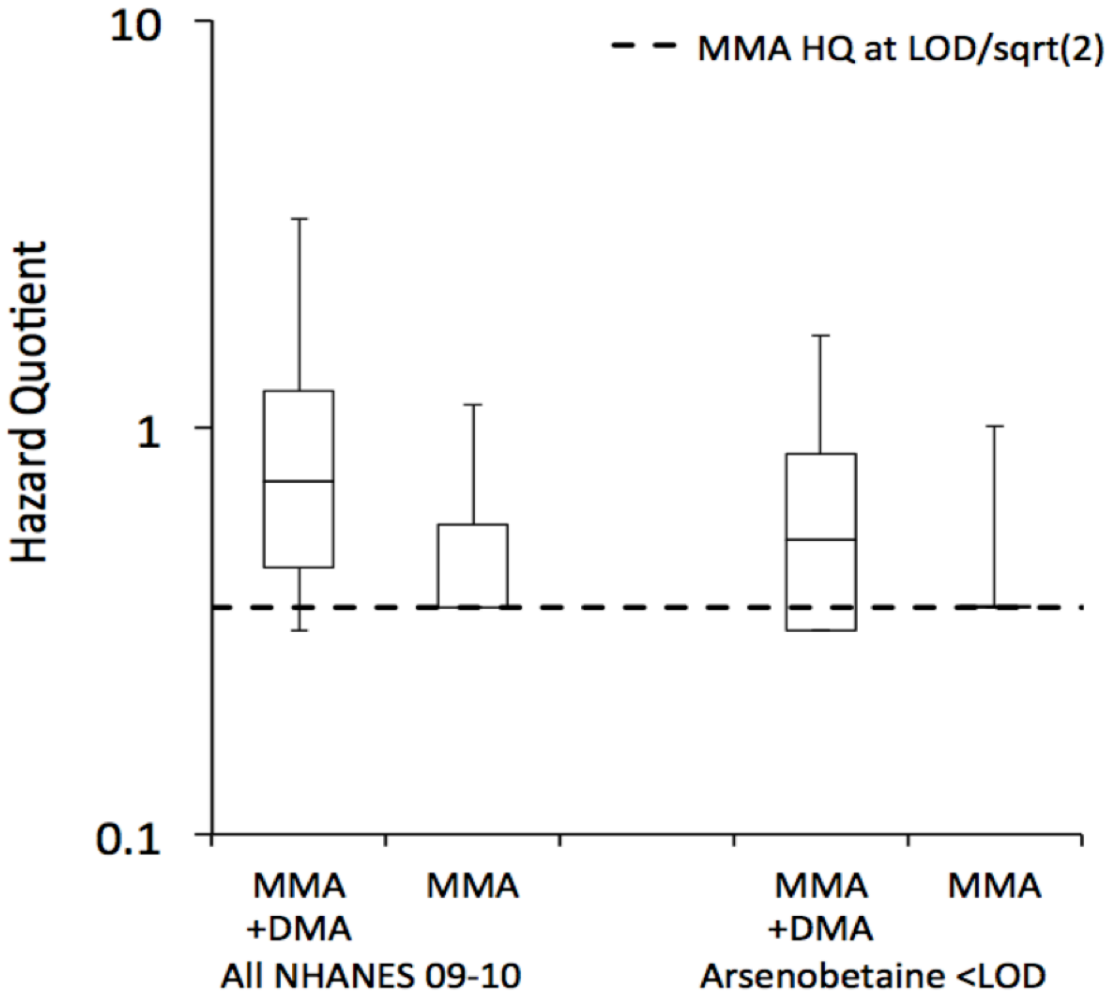
From Hays et al. 2010, Regulatory Toxicology Pharmacology, 58:1-9.

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

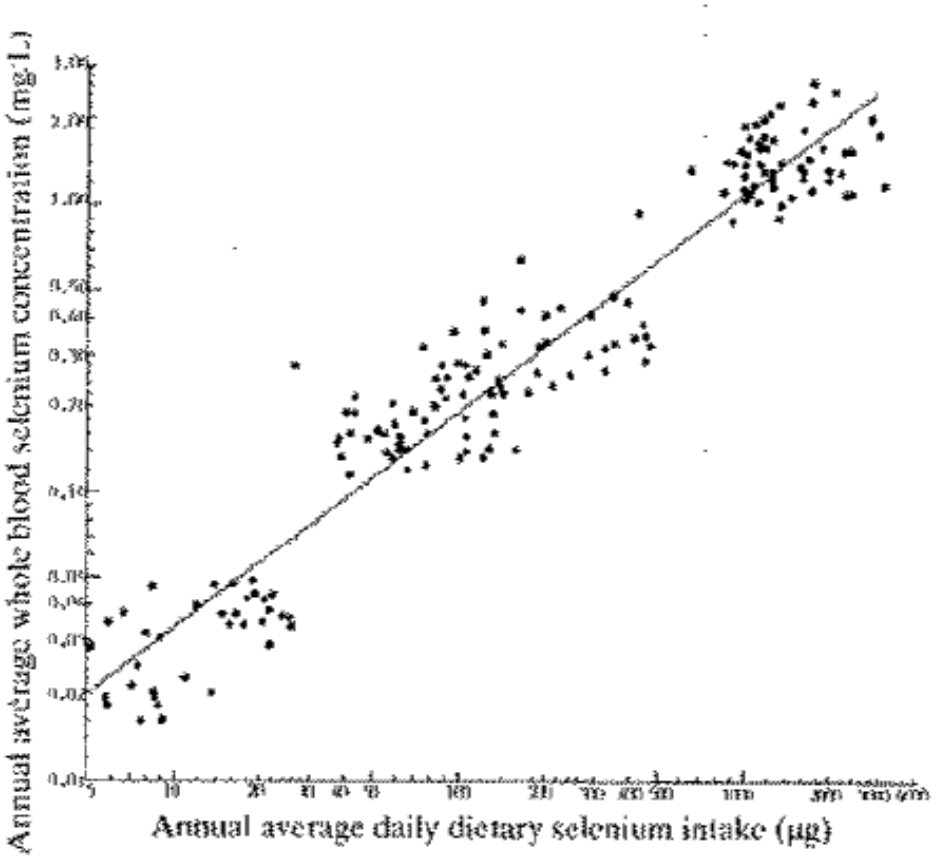


Figure 1. Correlation between dietary Se-intake and blood Se concentration of 167 male adults.
(Log Y = 0.767 Log X − 2.248, r = 0.962, p < 0.001)

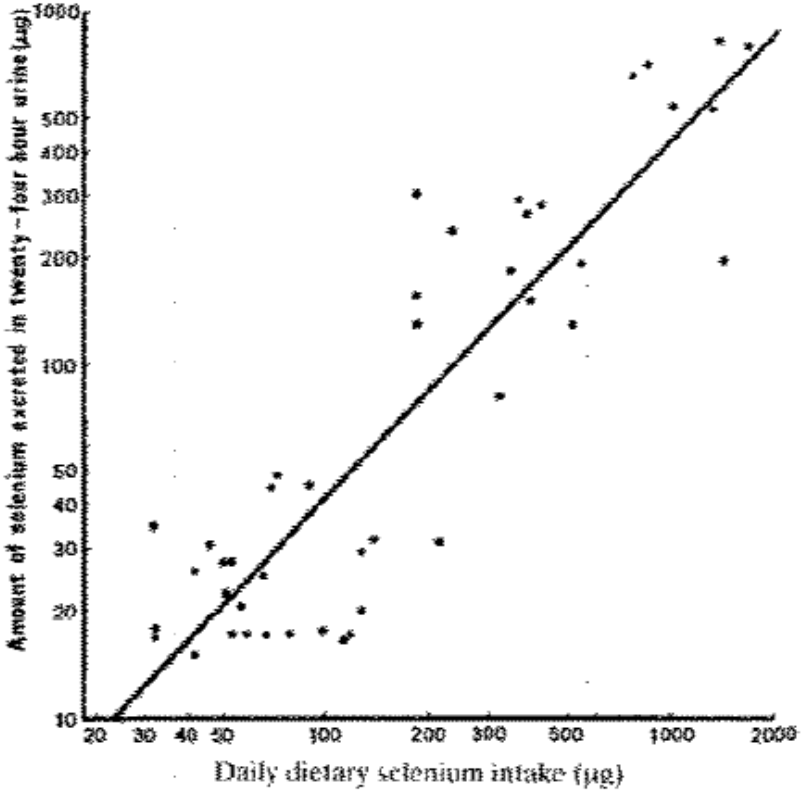
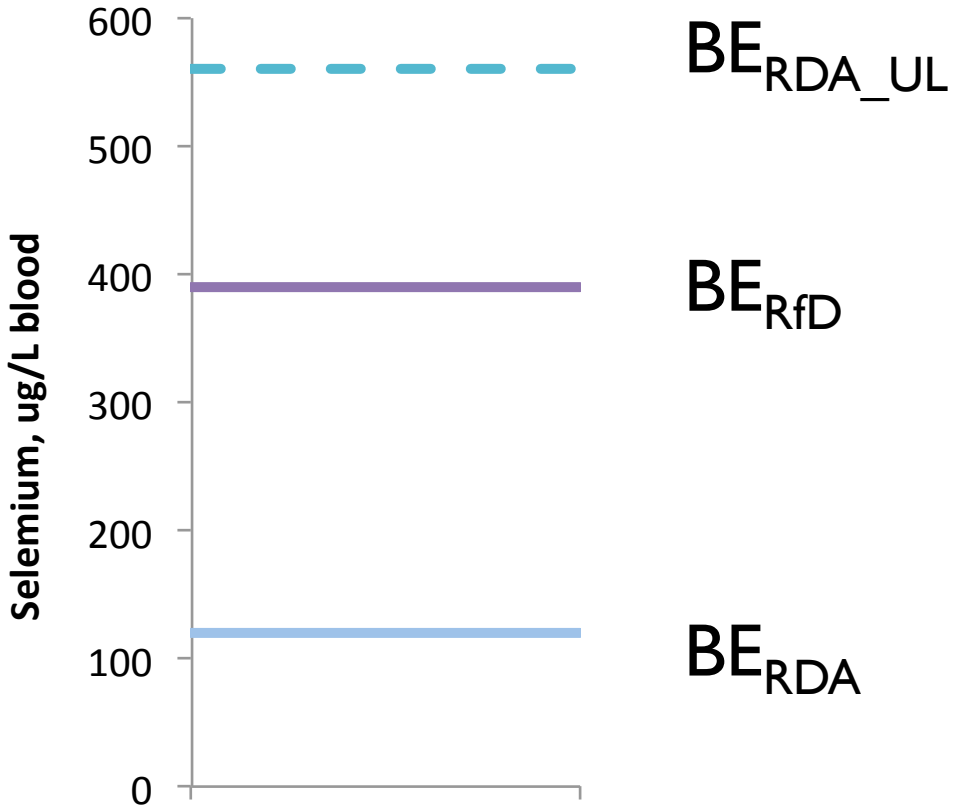


Figure 2. Correlation between daily selenium intake and amount of selenium excreted in twenty-four hour urine of adult inhabitants.
(Log Y = 1.021 Log X − 0.438, r = 0.886, p < 0.001, n = 44)

Selenium Guidelines & BEs

Guideline	Daily Dose (µg/kg-d)	BE (µg/L blood)
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 1


600
500
400
300
200
100
0
Selemium, ug/L blood
BE RDA_UL
BE RfD
BE RDA

Provisional BE Values for 3-PBA

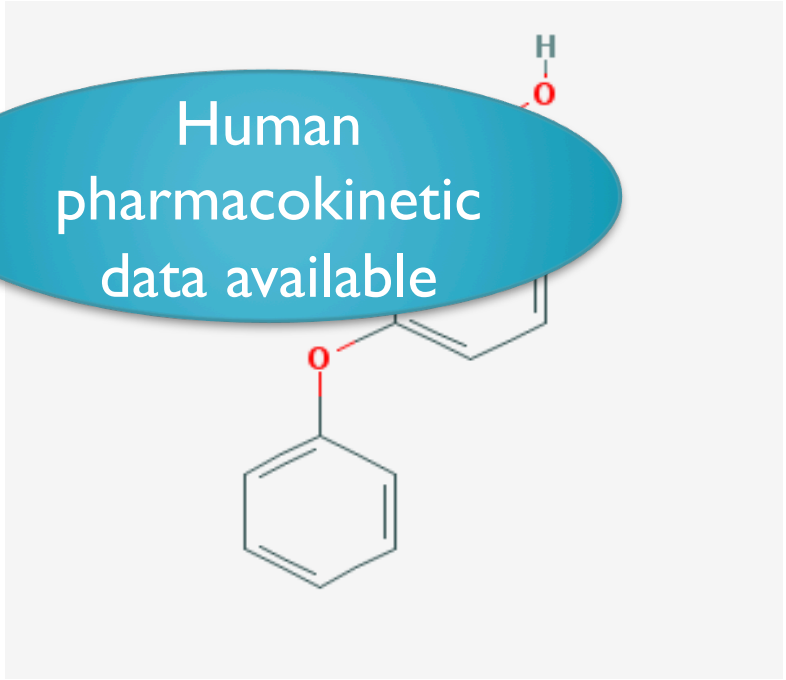
Urinary 3-Phenoxy Benzoic Acid

- 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

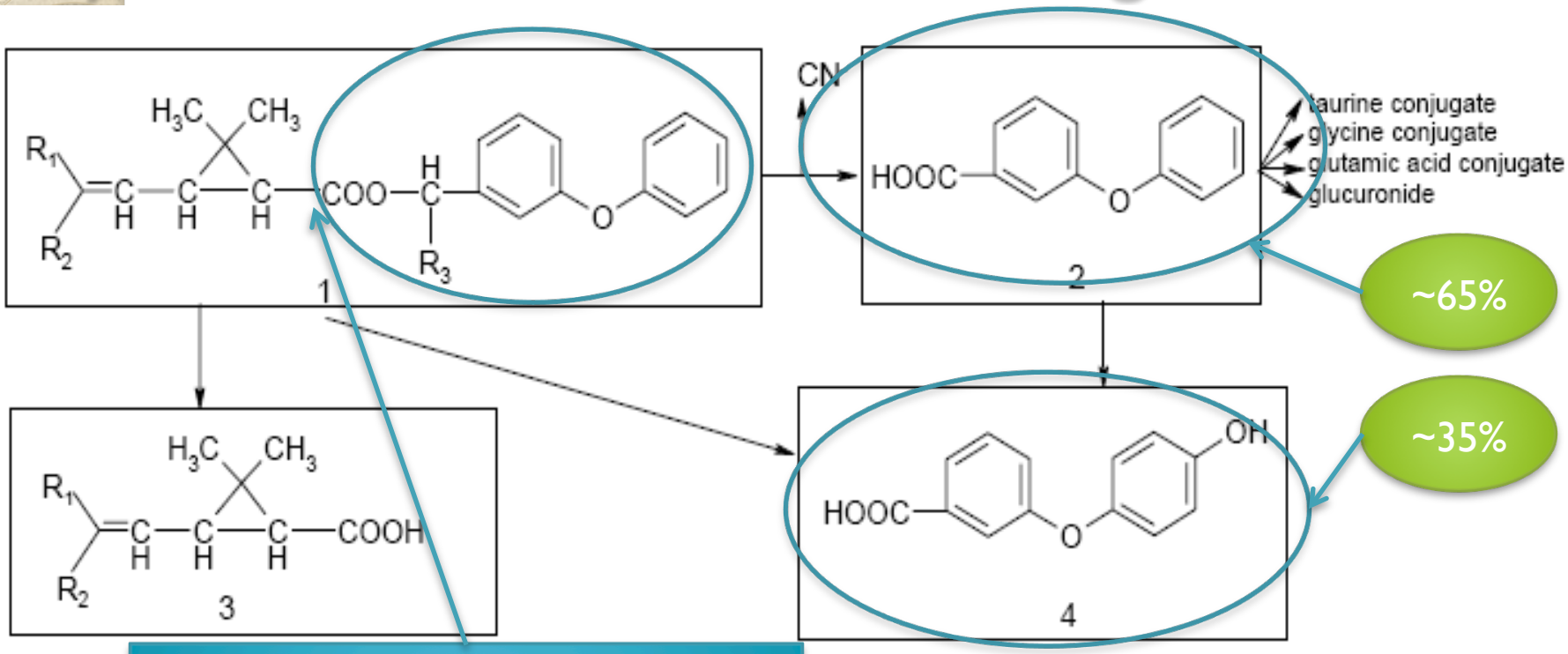
Pyrethroids with 3-PBA Moiety

- 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 R_3 = CN
R_3 = H
Cl R_3 = CN

PBA)

3 { 3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane carboxylic acid (DCCA)
3-(2,2-dibromovinyl)-2,2-dimethy-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 1: 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 1 Provisional BE, suggests low cumulative exposure and risk
  - If data exceed Tier 1, proceed to more detailed assessments

Provisional BE Values (μ g/L)

Compound	USEPA BE_{RfD}	JMPR BE_{ADI}
Cyhalothrin	6	117
Permethrin	1875	375
Cypermethrin	425	142
Deltamethrin	6	58
Fenpropathrin	208	250
Cyphenothrin	79	
Esfenvalerate[b]	14	142
Tau-fluvalinate	29	
d-Phenothrin	58	583

Tier 1 Provisional BE Value

A Look At CHMS Cycle 1 Data
3-PBA, µg/L Urine

Age Group	Geometric Mean	95th %ile	Pass Tier 1 (< 6 µg/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

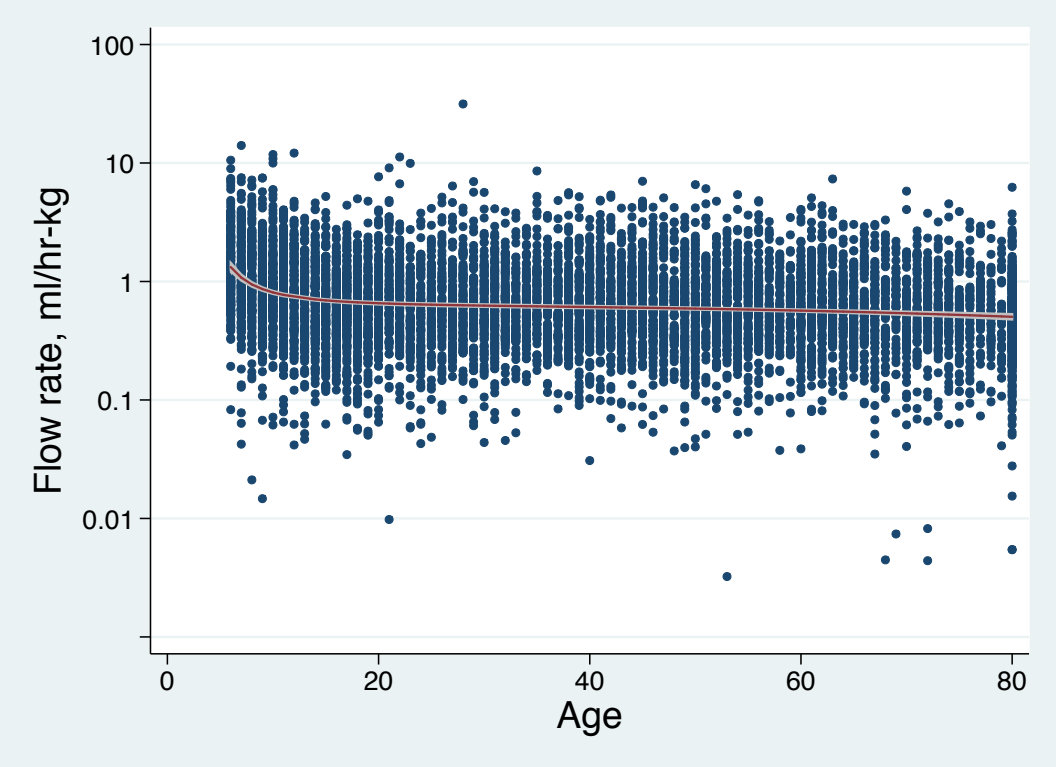
Challenge

- 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:

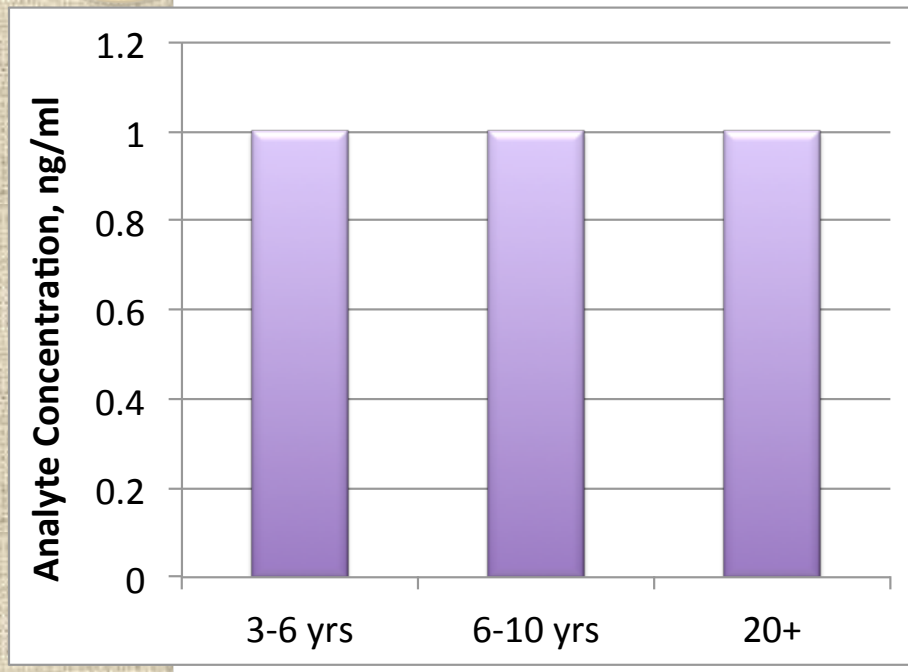
$$ER(ug/hr-kg) = \frac{Void\ volume, ml}{Time, hr * BW, kg} * C_{analyte} \qquad Dose(ug/d-kg) = F_{UE} * ER(ug/d-kg)$$

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

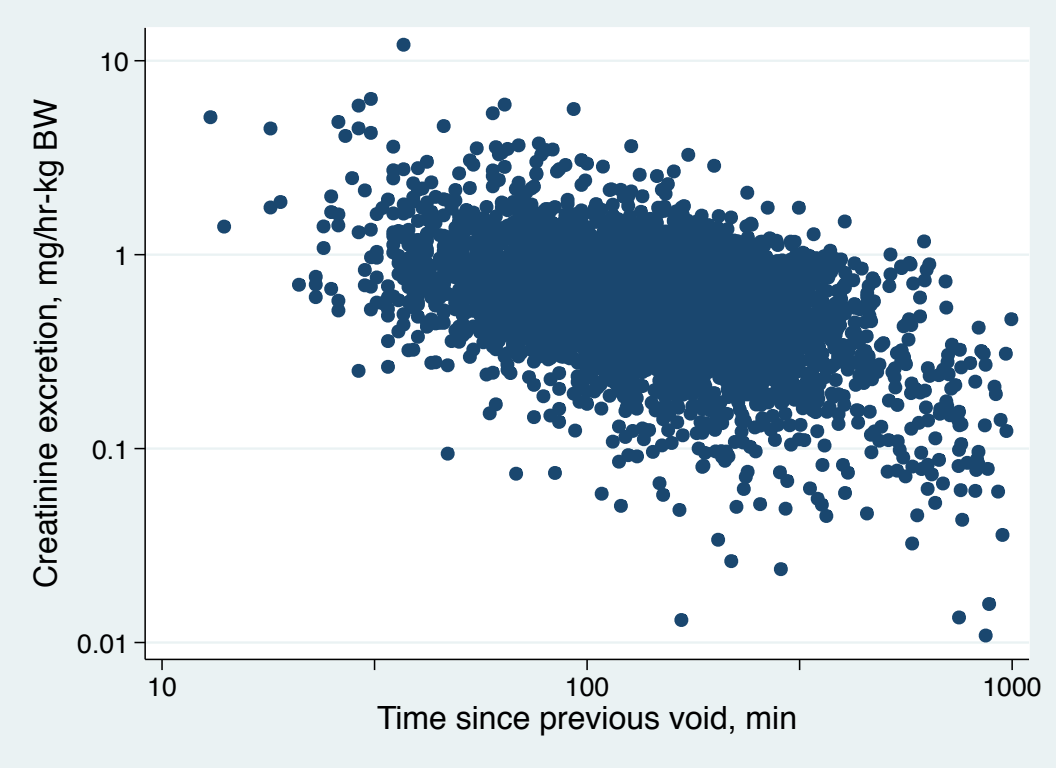


Time Since Previous Void

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.

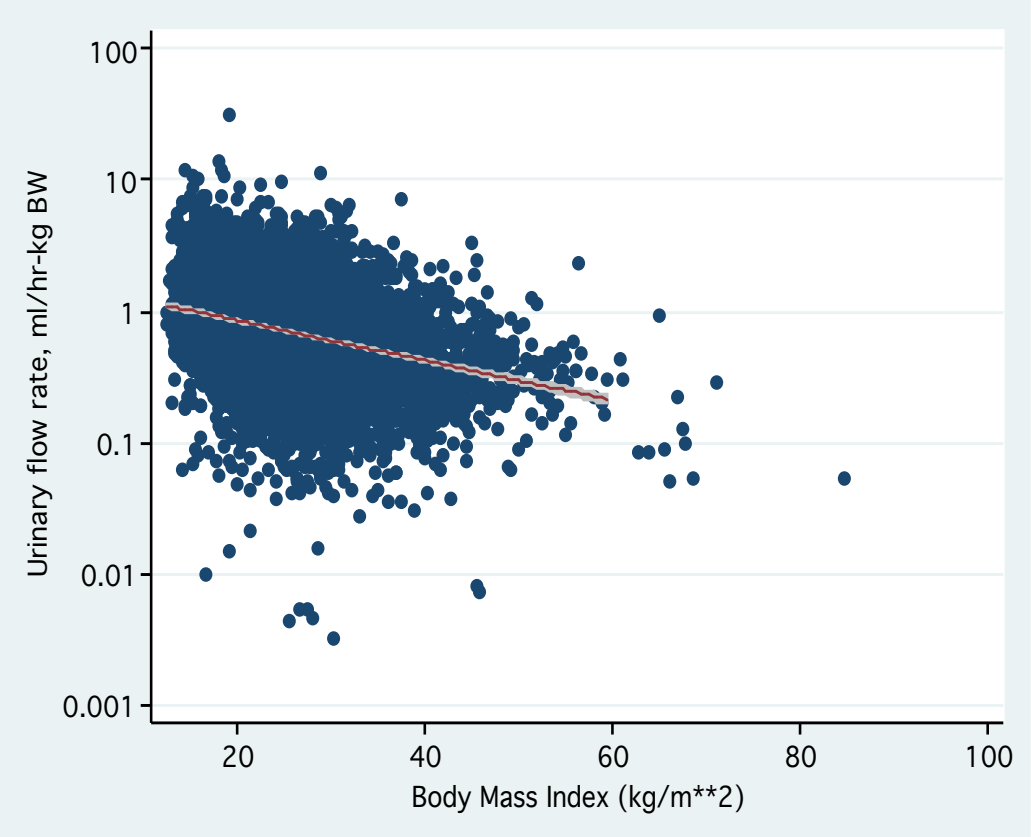
Time Since Previous Void (cont'd)

Also influences creatinine excretion rate

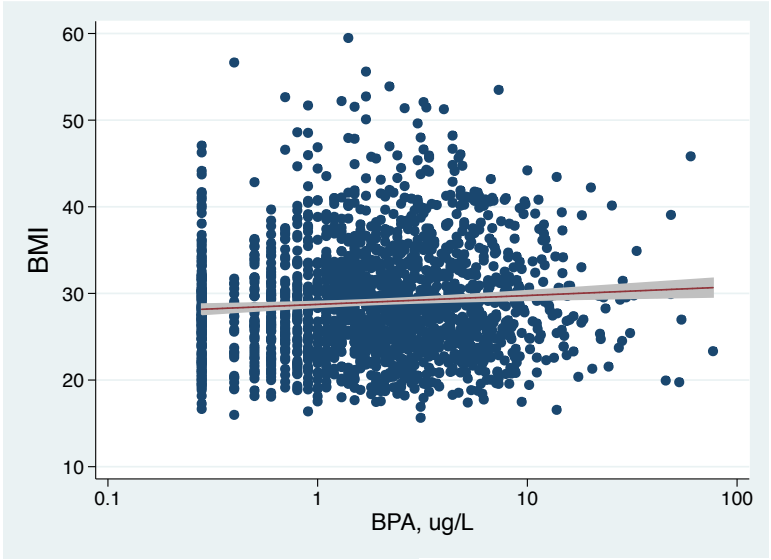


Body Mass Index

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