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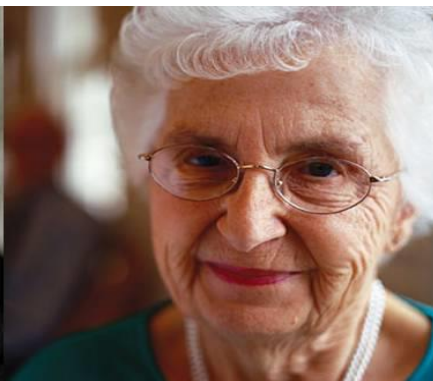
Pharmacokinetic modeling of health and exposure measures to support health risk interpretations

Andy Nong, PhD

Environmental Health Science And Research Bureau

Health Canada

April 19, 2016



Canada 

Research @ Health Canada

Reduce the negative impacts of environmental exposures on the health of Canadians through research, surveillance, monitoring, epidemiological investigations, and emergency planning.

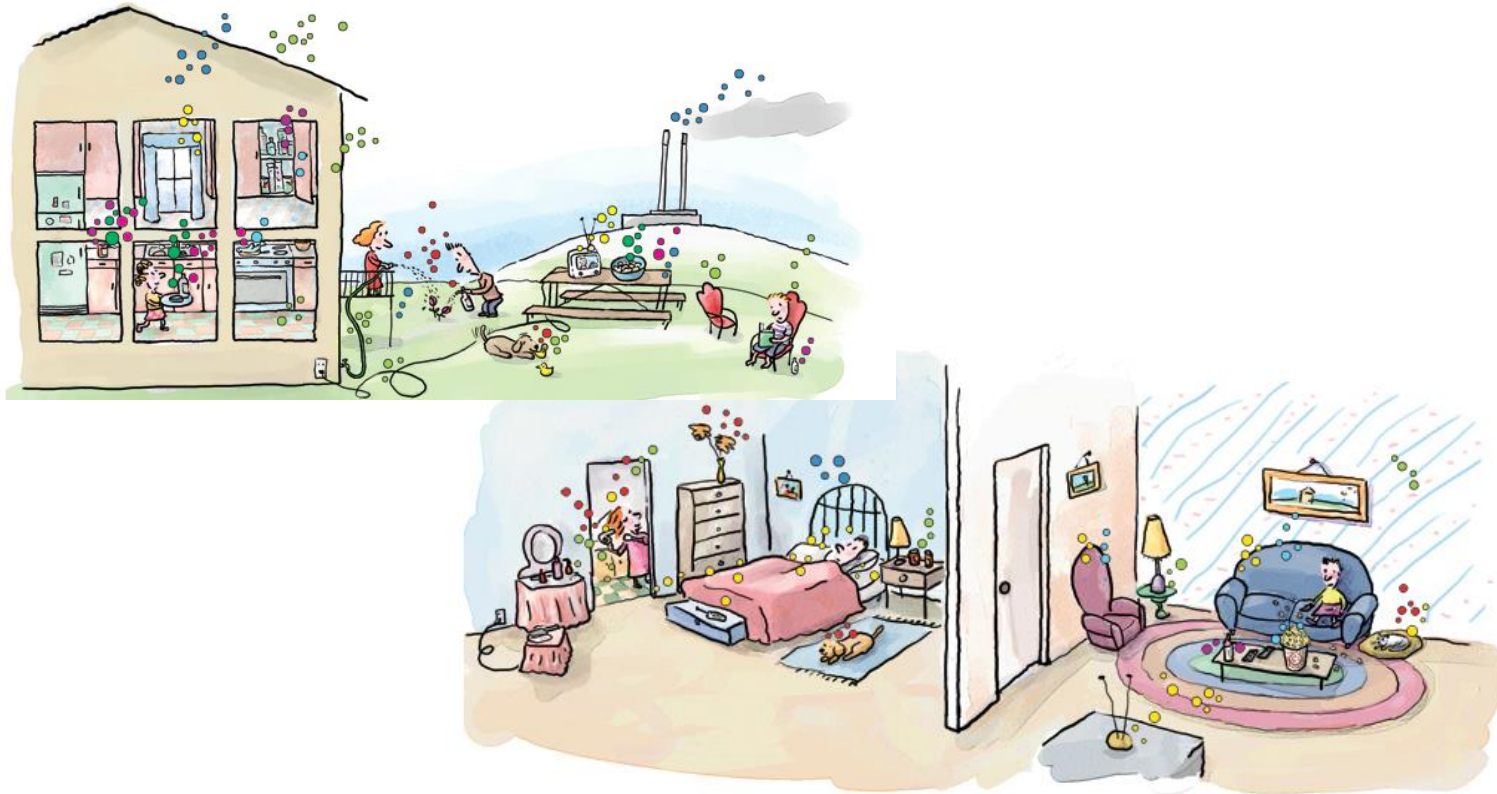
Chemicals Management Plan

In 2006, the Government of Canada launched the Chemicals Management Plan (CMP) to advance and improve the management of chemical substances and safeguard the health of Canadians.



Biomonitoring and Risk Assessment

How do we keep track of everyone exposure and related them to their health?



How to interpret biomonitoring data?


Biomonitoring equivalents (BE) translate reference values (e.g., RfD, TDI) established by regulatory agencies (e.g. HC, EPA, WHO) into tissue-level equivalent concentrations

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Guidelines for the derivation of Biomonitoring Equivalents: Report from the Biomonitoring Equivalents Expert Workshop


Sean M. Hays^{a,*}, Lesa L. Aylward^b, Judy S. LaKind^c, Michael J. Bartels^d, Hugh A. Barton^e, Peter J. Boogaard^f, Conrad Brunk^g, Stephen DiZio^h, Michael Doursonⁱ, Daniel A. Goldstein^j, John Lipscomb^k, Michael E. Kilpatrick^l, Daniel Krewski^m, Kannan Krishnanⁿ, Monica Nordberg^o, Miles Okino^p, Yu-Mei Tan^q, Claude Viau^r, Janice W. Yager^f

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Guidelines for the communication of Biomonitoring Equivalents: Report from the Biomonitoring Equivalents Expert Workshop

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How are Pharmacokinetics (PK) involved?

**PHARMACOKINETICS
RULES!**



4 lines = 40 km/h

Reverse dosimetry

20 km/h = 2 lines

Forward dosimetry

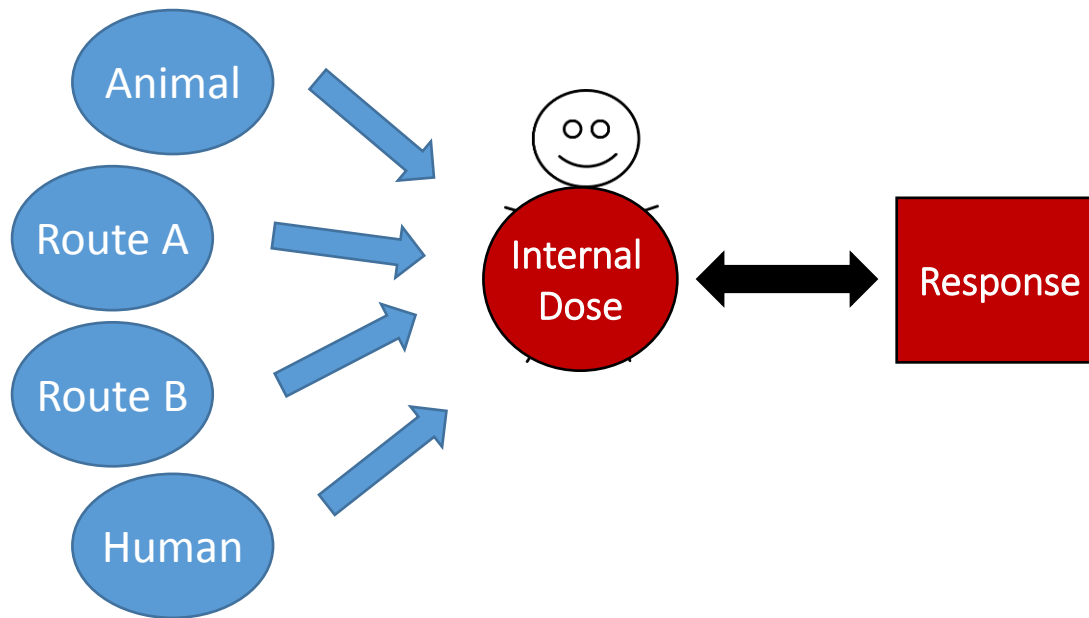


= 4 lines

**Biomonitoring
Equivalent**

PK Assumption: Tissue dose equivalence

For each equivalent dose, there is a specific tissue dose that is related to a specific response.



PK Assumption: Dose extrapolation

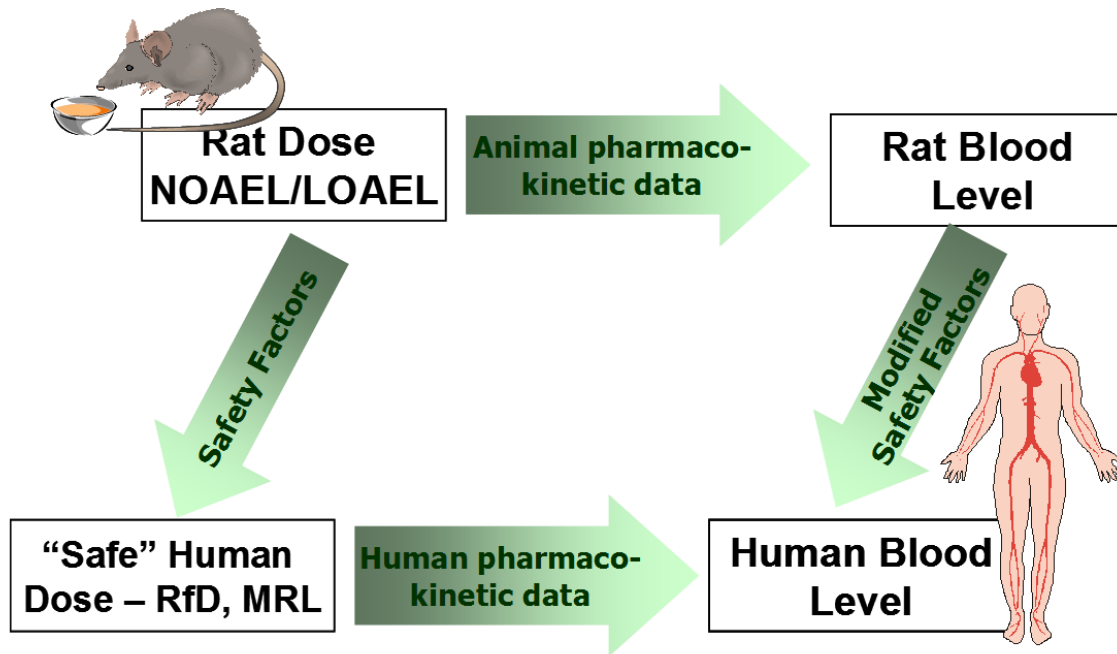


Fig. 1. Schematic diagram showing parallelism concept for calculating BEs and possible routes for deriving a BE.

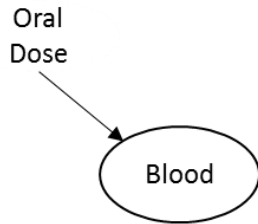
PK Assumption: Modeling

Simple

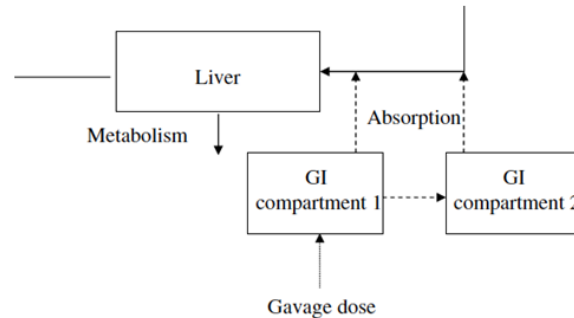


Complex

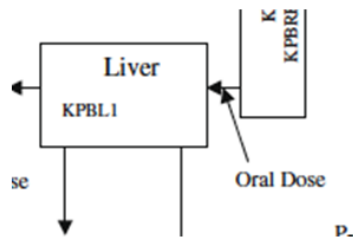
*Direct exposure estimate
(regression daily dose vs
blood concentration)*



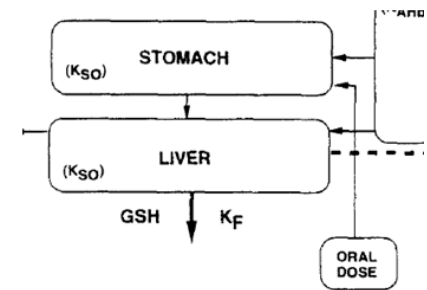
*Nonphysiologic GI Tract
(no blood flow or volume,
just a holding reservoir)*



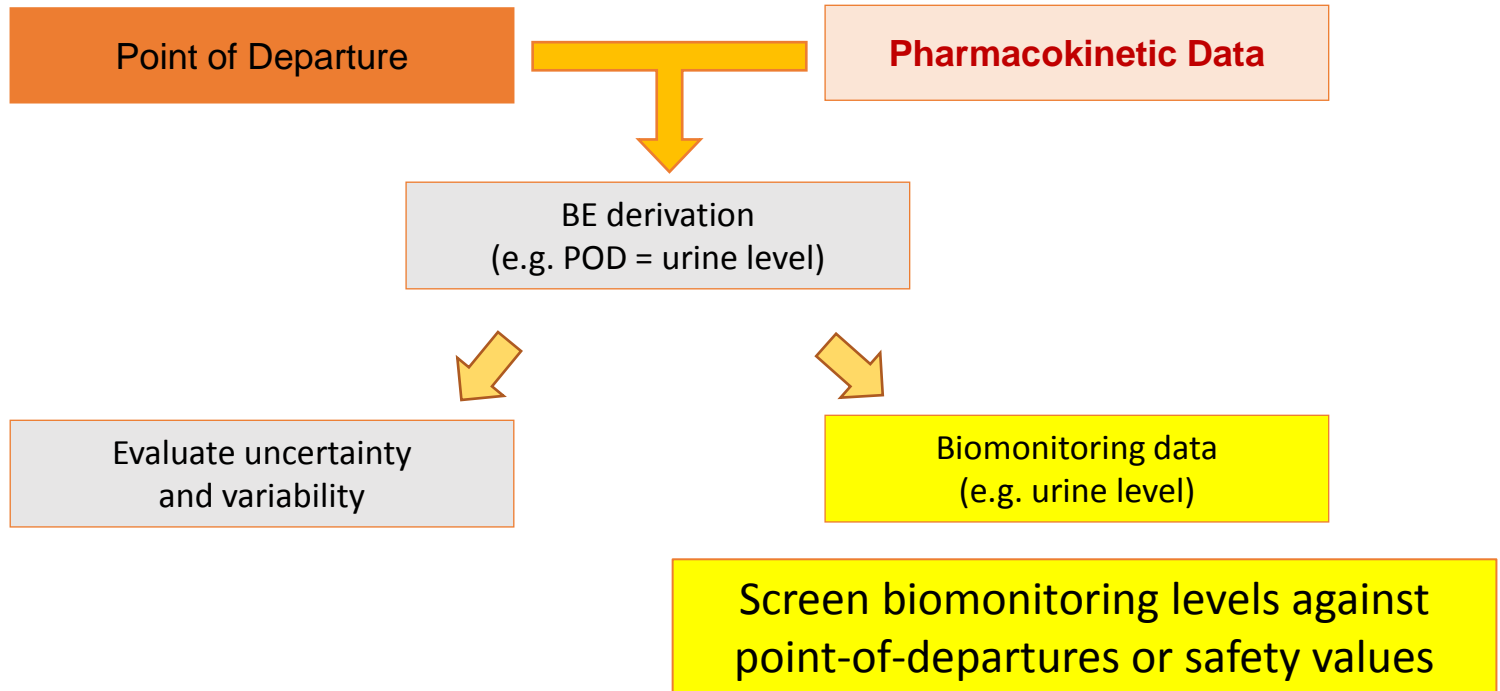
*No GI Tract
(direct uptake
To liver)*



*Physiologic GI Tract
(with volume &
blood flows)*



Biomonitoring Equivalents – revised 2016



Biomonitoring Equivalents for

Existing substances

- Metals
- Triclosan
- Phthalates

Drinking water

- Fluoride
- Metals

Pesticides

- Pyrethroids
- Organophosphates

Consumer products

- Phthalates

Foods

- POPs
- Metals

Contaminated Sites

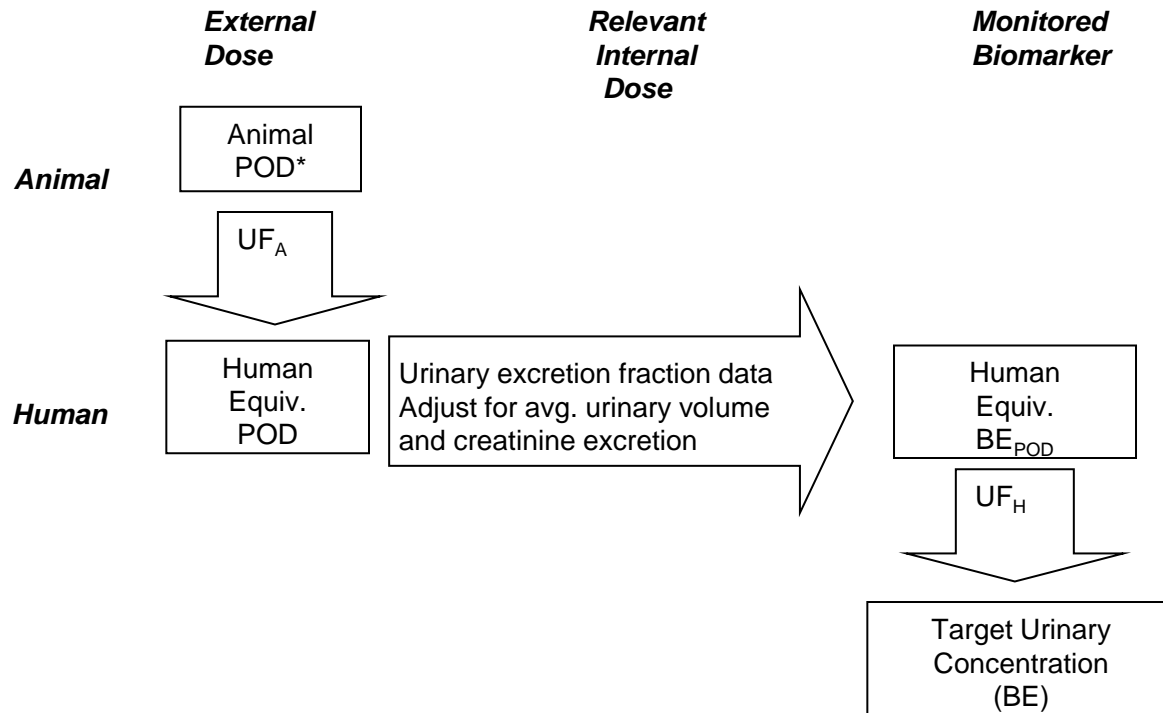
- Metals

BE for Phthalates



	Organization and exposure guidance value				
	Health Canada chronic TDI	USEPA chronic RfD	ATSDR chronic MRL	ATSDR Intermediate MRL	EFSA TDI
Critical endpoint, species	Developmental effects, mouse	Liver toxicity, guinea pig	Reduced spermatogenesis, rat	Reduced fertility, developmental effects on reproductive system, mouse	Effects on testicular development, rat

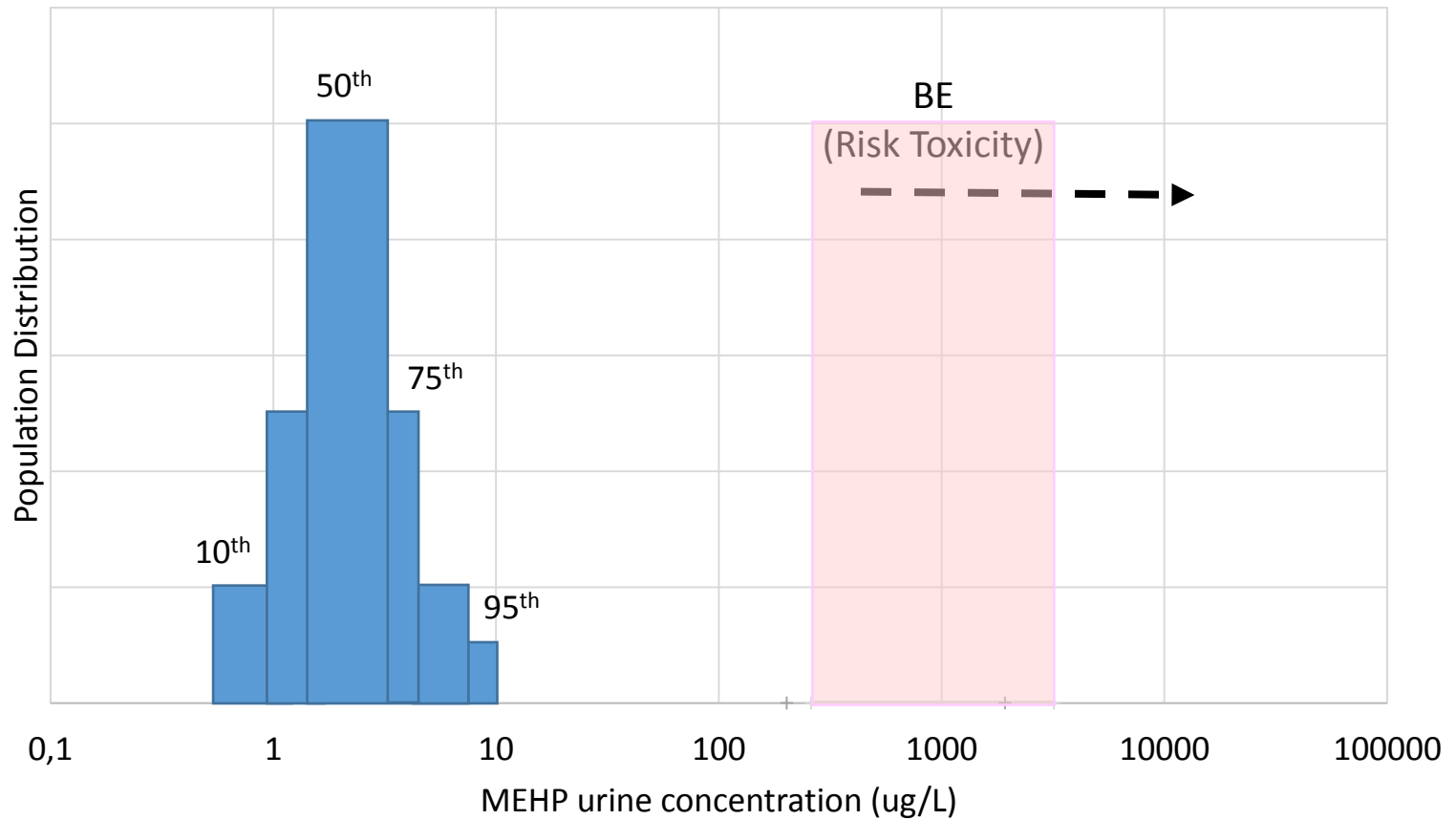
BE for Phthalates



BE for Phthalates



CHMS cycle 2 all ages (6-49 yrs)



BE for Selenium

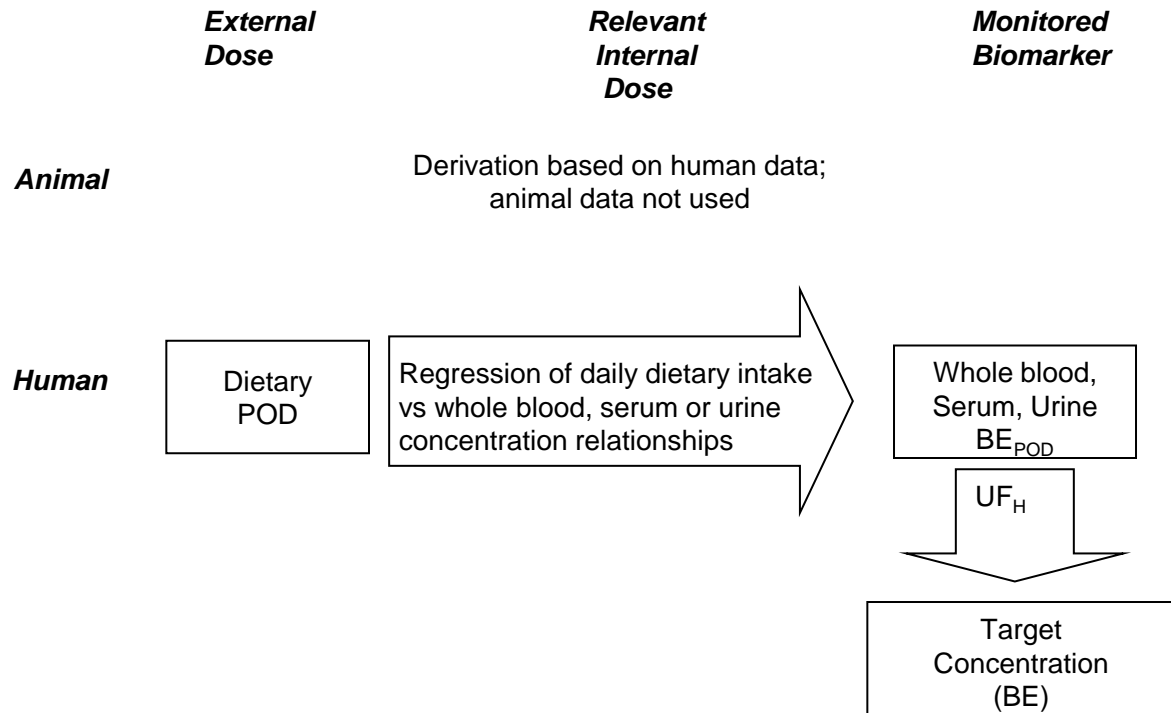


Essential micronutrient found in inorganic forms in soils and in organic forms of food.

Lower and Upper limits:

- Recommended Daily Allowances – Estimated Average Requirements
- High doses can lead to toxicity – selenosis

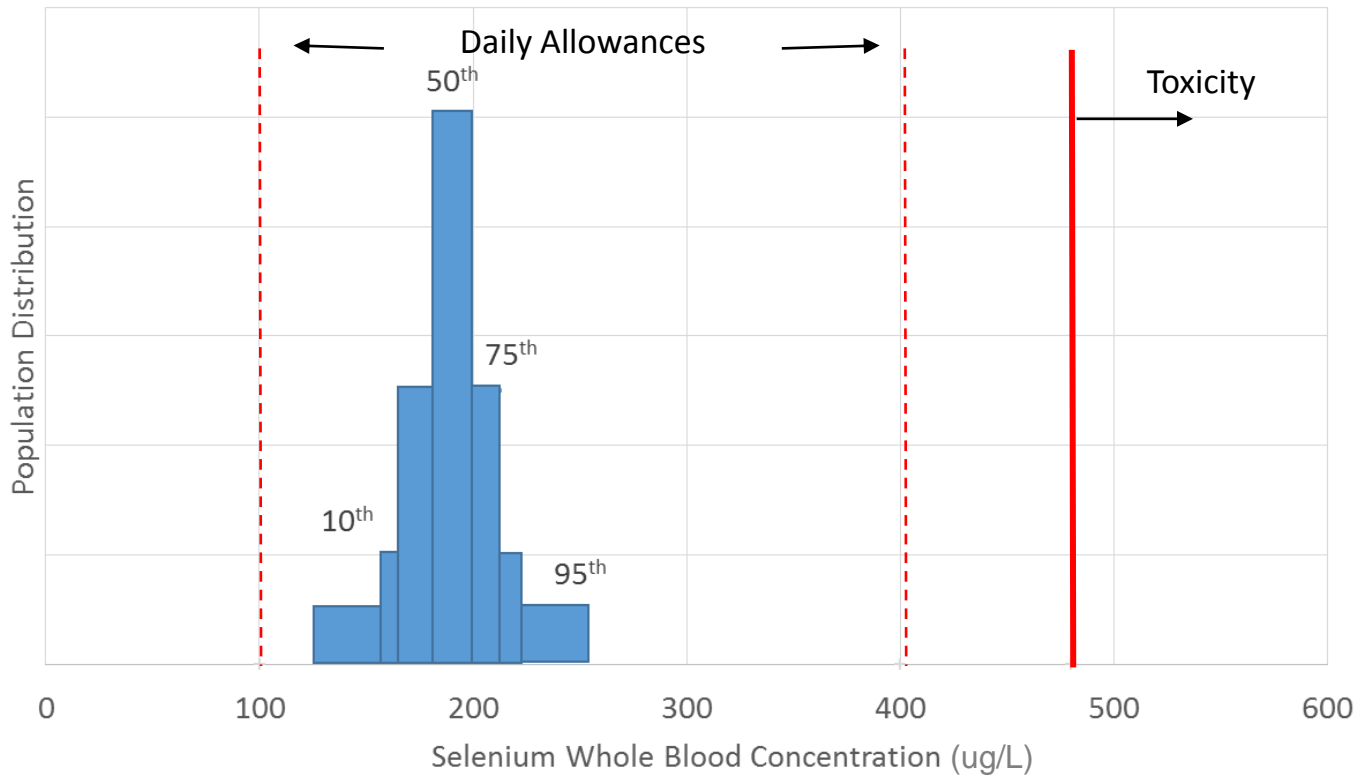
BE for Selenium



BE for Selenium



CHMS cycle 2 all ages (6-79 yrs)

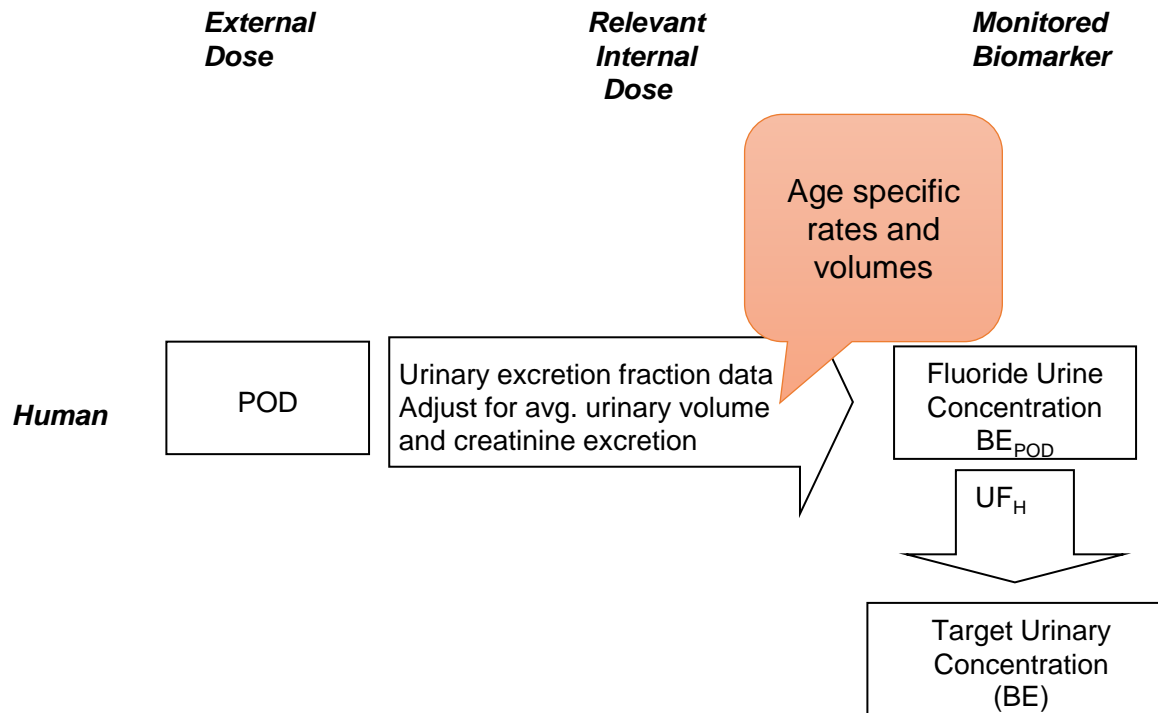


BE for Fluoride



- Fluoride is added to drinking water, toothpaste, and mouthwash, and occurs naturally in dietary source
- Excessive exposure can lead to cosmetic effects and affect skeletal integrity
- BE were derived for subpopulations of different ages and focus on their age-specific differences

BE for Fluoride



BE for Fluoride

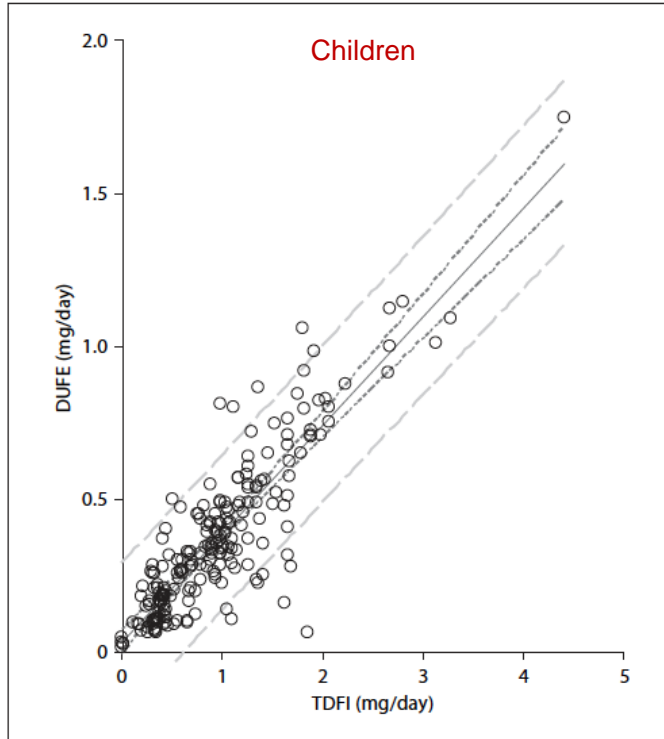


Fig. 1. Relationship between DUFE and TDFI for 212 young children (table 1) aged 0.15–7 years recorded in 9 studies in 6 countries. The full line is the best fit; the inner interrupted lines indicate the 95% CI of the regression, and the outer interrupted lines indicate the 95% PI.

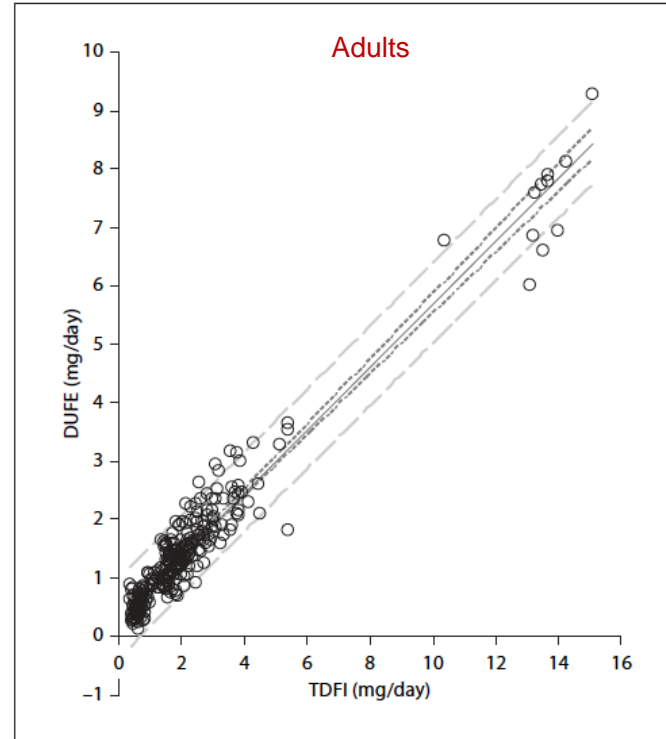


Fig. 2. Relationship between DUFE and TDFI for 269 data pairs from adults (table 2) aged 18–75 years recorded in 8 studies in 2 countries. The full line is the best fit; the inner interrupted lines indicate the 95% CI of the regression, and the outer interrupted lines indicate the 95% PI.

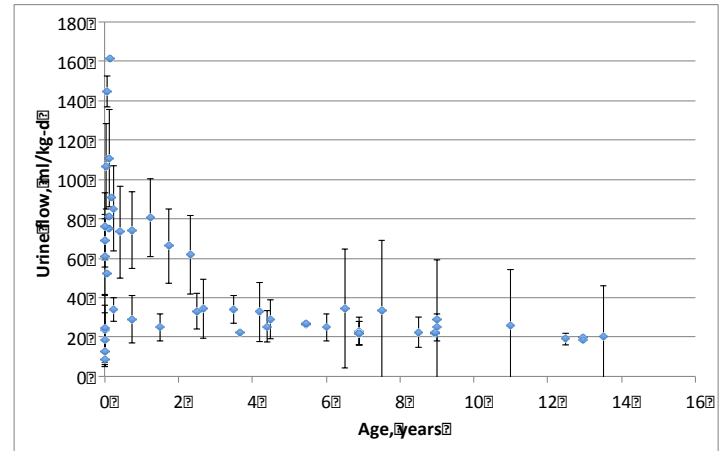
BE for Fluoride



Flow Rates

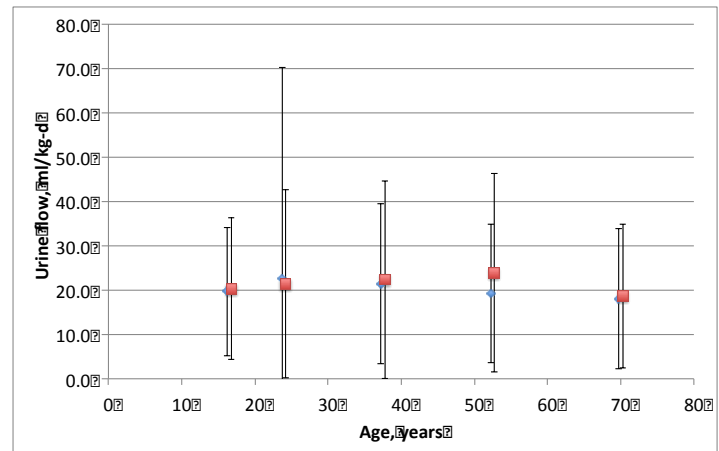
Children (top)

- Data for infants and toddlers inconsistent
- Data for ages 3+ coherent



Adults (bottom)

- Steady distribution for all ages



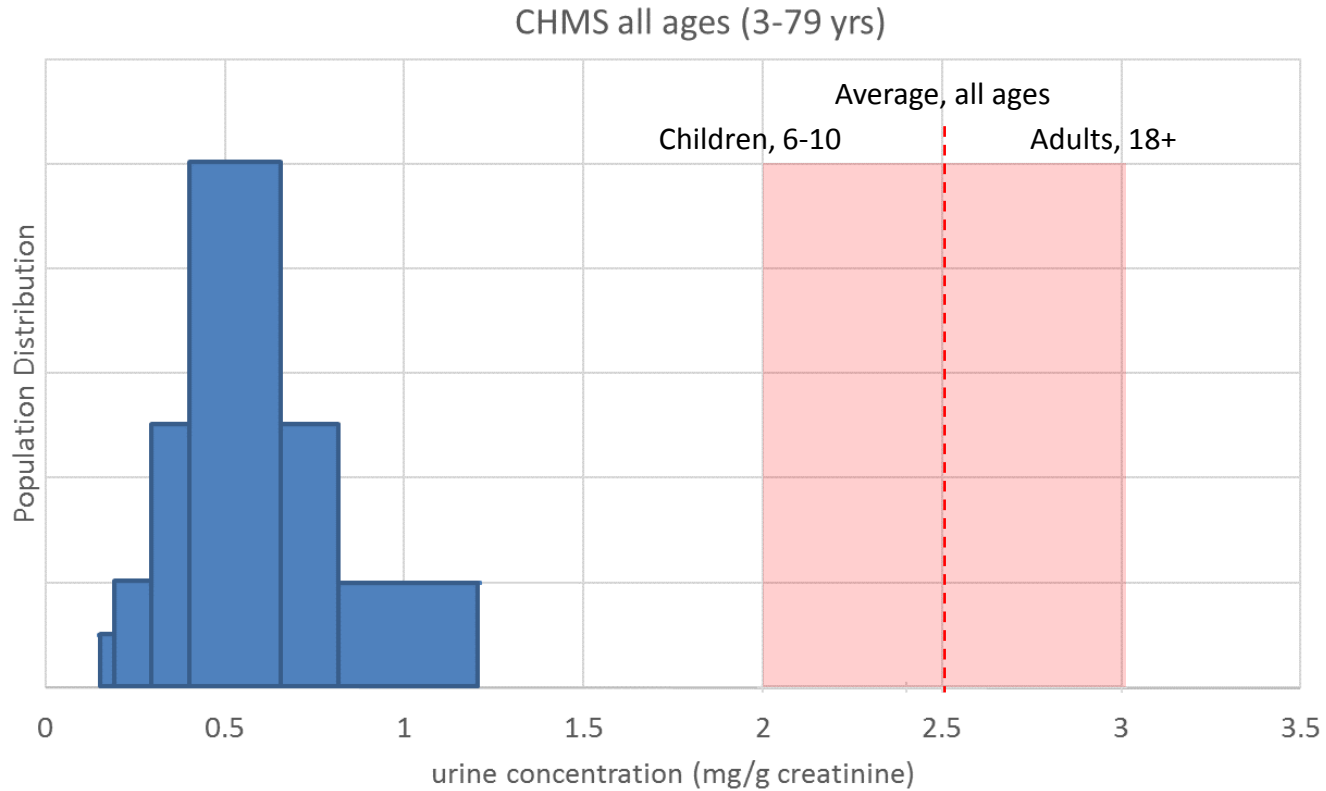
High variability independent of age-
CVs of 50 to 100%

BE for Fluoride



Age Group	Average Urinary Flow Rate ml/kg-d	Average Creatinine Excretion mg/kg-d
3 to <6	30	16
6 to <10	25	19
10 to <18	20	21
18+	20	20

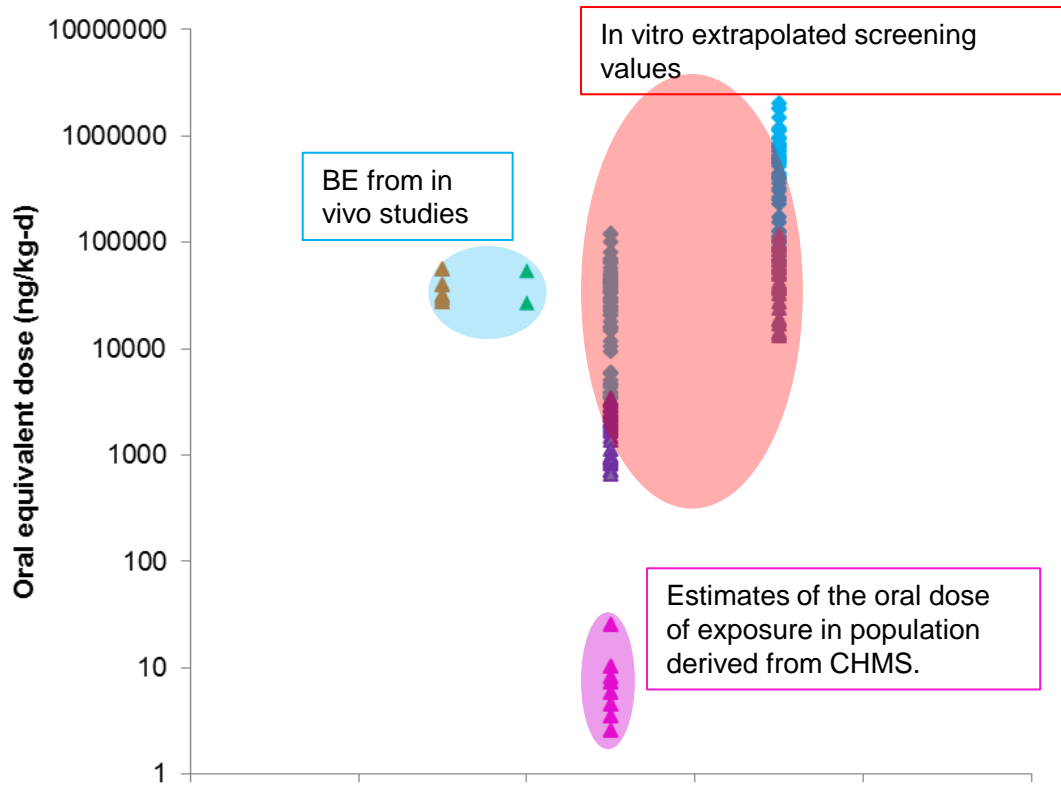
BE for Fluoride



BE & High Throughput Screening In Vitro Doses

- Biomonitoring data and BE are used to compare effects measured from in vitro endpoints
- System Biology – Pharmacokinetic models and reverse dosimetry are used to estimate equivalent exposure levels
- Biomonitoring data is applied to screen potential toxicity values from in vitro data

BE & High Throughput Screening In Vitro Doses



Summary

- Pharmacokinetic modeling enable to establish an external to internal dose relationship that can applied to any point-of-departure
- Since the PK is consistent for a specific chemical, different doses can be used to screen biomonitoring data
- Our extended research of Biomonitoring Equivalents have shown that number of chemicals from biomonitoring studies can be interpreted in a public health risk context

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