

US EPA ARCHIVE DOCUMENT

*Interpreting Human
Biomonitoring Data in a Public
Health Risk Context Using
Biomonitoring Equivalents*

ICCA/EPA Symposium:
Public Health Applications of Human Biomonitoring

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Reasons for Conducting Large Scale Population Based (Environmental) Biomonitoring Studies -- CDC

- Determine which chemicals get into members of the general population and at what concentrations
- Determine if exposure levels are higher in some groups than in others
- Track temporal trends in levels of exposure
- Assess the effectiveness of public health efforts to reduce exposure
- Establish reference ranges
- Determine the prevalence of people with levels above known toxicity levels
- Set priorities for research on human health effects

Source: (CDC, 2005)

Risk Assessment Based Methods Used to Interpret Biomonitoring Results

Increasing Utility for Health Risk Assessment

Increasing Difficulty of Development

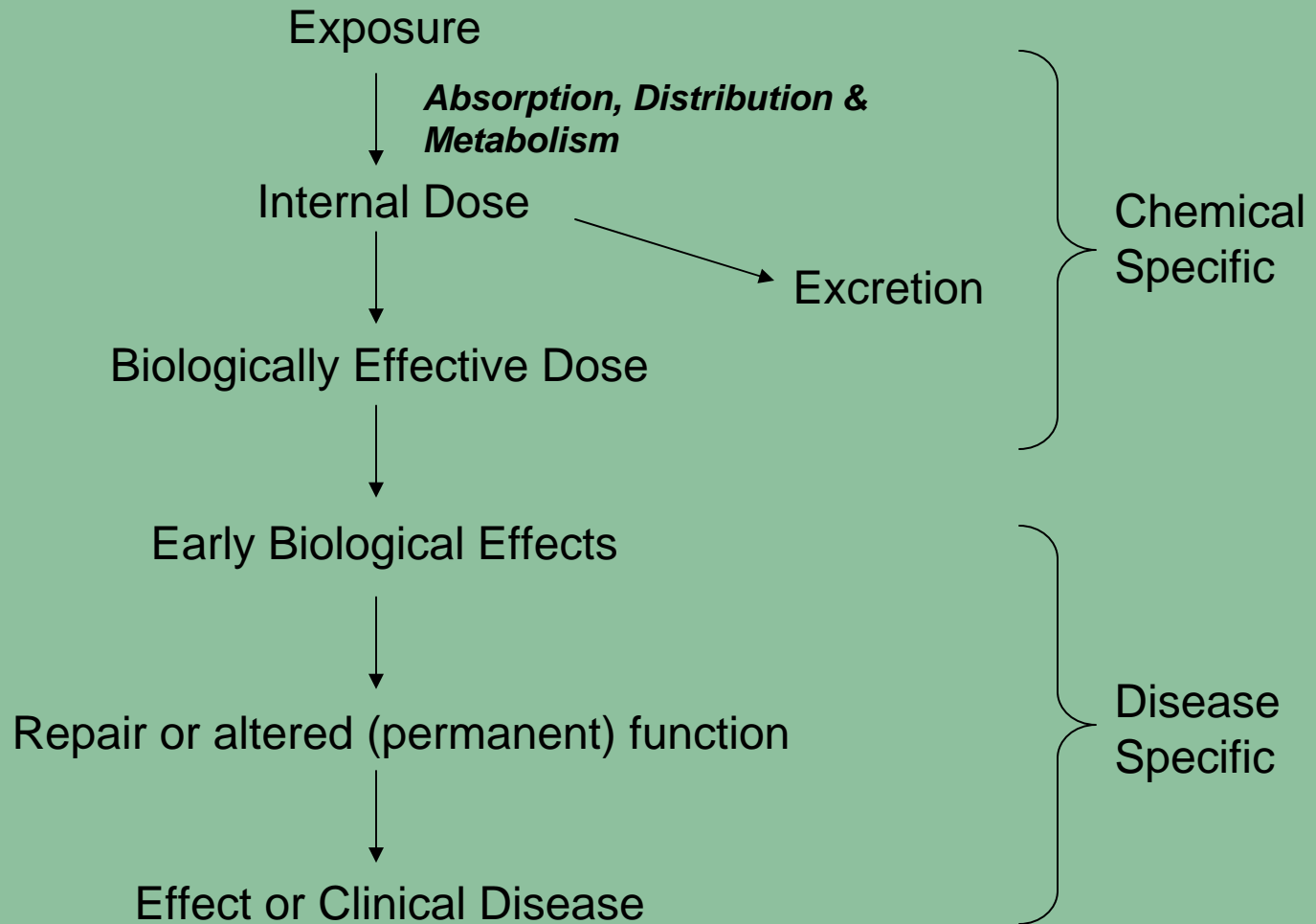
- Predictive
 - Epidemiology-based biomonitoring guidance values (e.g., lead, ethanol, mercury)
 - Usually robust, but take many years to develop
 - Requires robust datasets on biomonitoring-based epidemiology studies
- Screening
 - Internal-dose based risk assessment
 - Can be very sophisticated and robust
 - Forward & Reverse Dosimetry: Leverage existing risk assessment paradigm
 - Can be easy
 - Generic screen:
 - Leverage limited toxicology database
 - Threshold for Toxicological Concern
 - Something is needed for the “data poor” compounds

Increasing Level of Uncertainty for Interpreting Risks

With Perfect Knowledge

- Epidemiology based standards
 - Great, but takes a long time to build robust database on biomonitoring based epidemiology and to build consensus
- Internal dose based risk assessments
 - Informed by an understanding of
 - Mechanism of action
 - Critical dose metric
 - Species differences in pharmacokinetics
 - Species differences in pharmacodynamics
 - Basis of drug development industry

Relating Exposure & Effect



“The closer the human exposure estimate is to the toxicity endpoint the more accurate the exposure estimate must be” Linda Sheldon

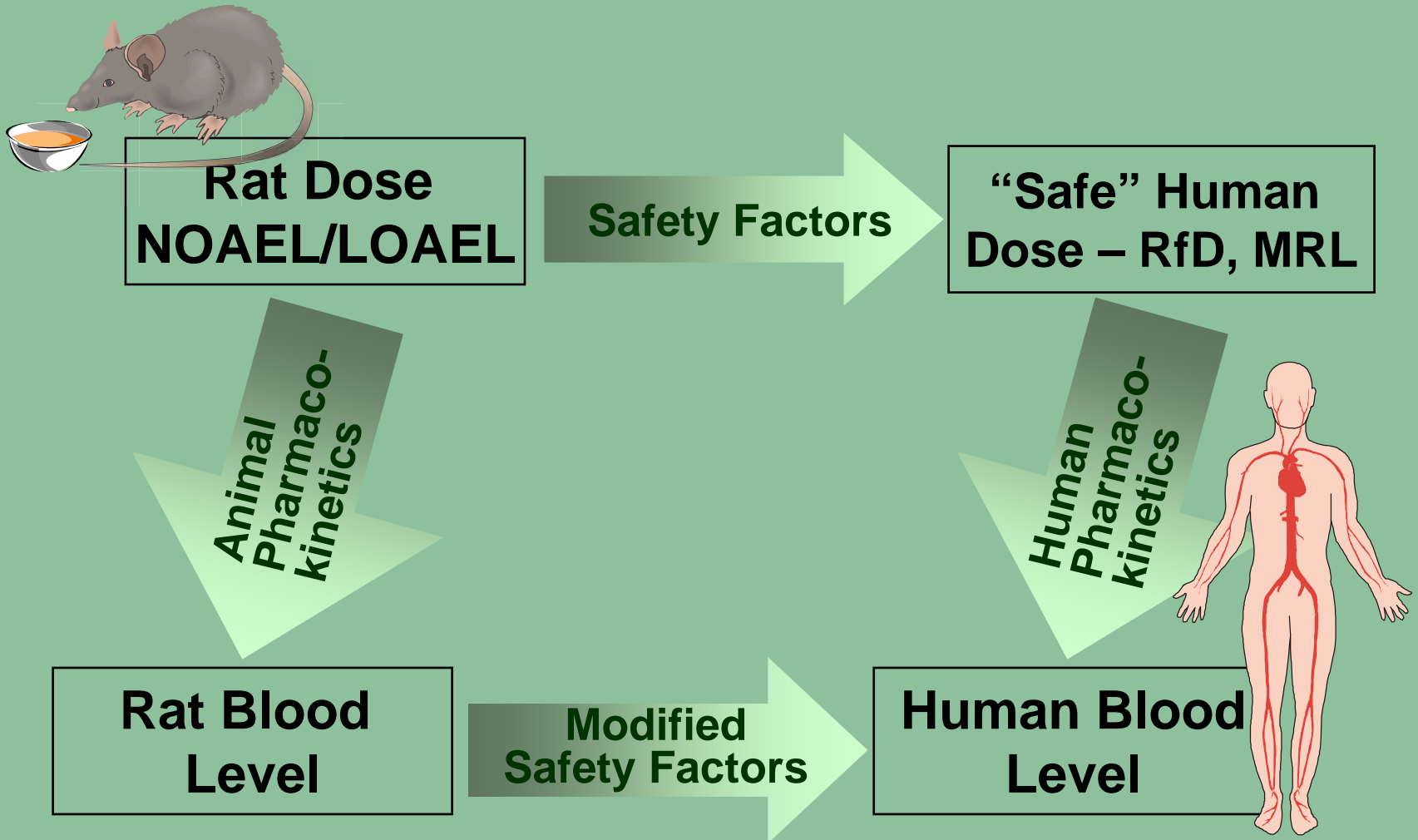
Recent Publication

“Biomonitoring Equivalents: A Screening Approach for Interpreting Biomonitoring Results from a Public Health Risk Perspective” - Hays et al., 2007, *Reg. Tox. Pharm.* Vol. 47, pp. 96-109.

- Presents rationale, background, and methods for development of biomonitoring equivalents (BEs):
- The concentration of a chemical in a (human) biological medium consistent with exposure at an exposure guidance value (e.g., RfC, RfD, UCR, MRL, TDI, etc.)



Forward Approach: Moving from RfD Based on Administered Dose to Screening Blood Levels





Questions Raised by BE Paradigm



**Rat Dose
NOAEL/LOAEL**

Safety Factors

What types of exposure guideline values should be used?

**“Safe” Human
Dose – RfD, MRL**

**Animal
Pharmaco-
kinetics**

Does one pathway (animal or human) provide more reliable means of extrapolation over the other internal doses (e.g., PKA-H, PKH)

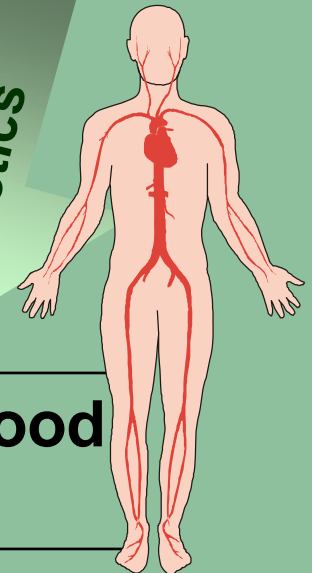
**Human
Pharmaco-
kinetics**

How do we use BE_{POD}?

**Rat Blood
Level**

**Modified
Safety Factors**

**Human Blood
Level**



Additional Questions Raised by Original BE Paradigm

- Does the cancer slope factor approach pose unique challenges?
- How should BEs for short-lived compounds be derived?
- How should these BEs be communicated to the various audiences?
 - What is a BE?
 - What does it mean if biomonitoring levels exceed the BE?

BE Pilot Project

- Sponsoring partners
 - EPA, Health Canada, ACC, CropLife America, RISE, API, Soap and Detergent Association
- Develop guidelines for derivation and communication of BEs
- Expert workshop held June, 2007
 - Participants from government, academia, industry, NGOs
 - Addressed charge questions
 - Informed by draft BEs for four case study compounds: 2,4-D, acrylamide, cadmium, and toluene
 - Develop guidelines for BE derivation and communication

BE Pilot Project - Publications

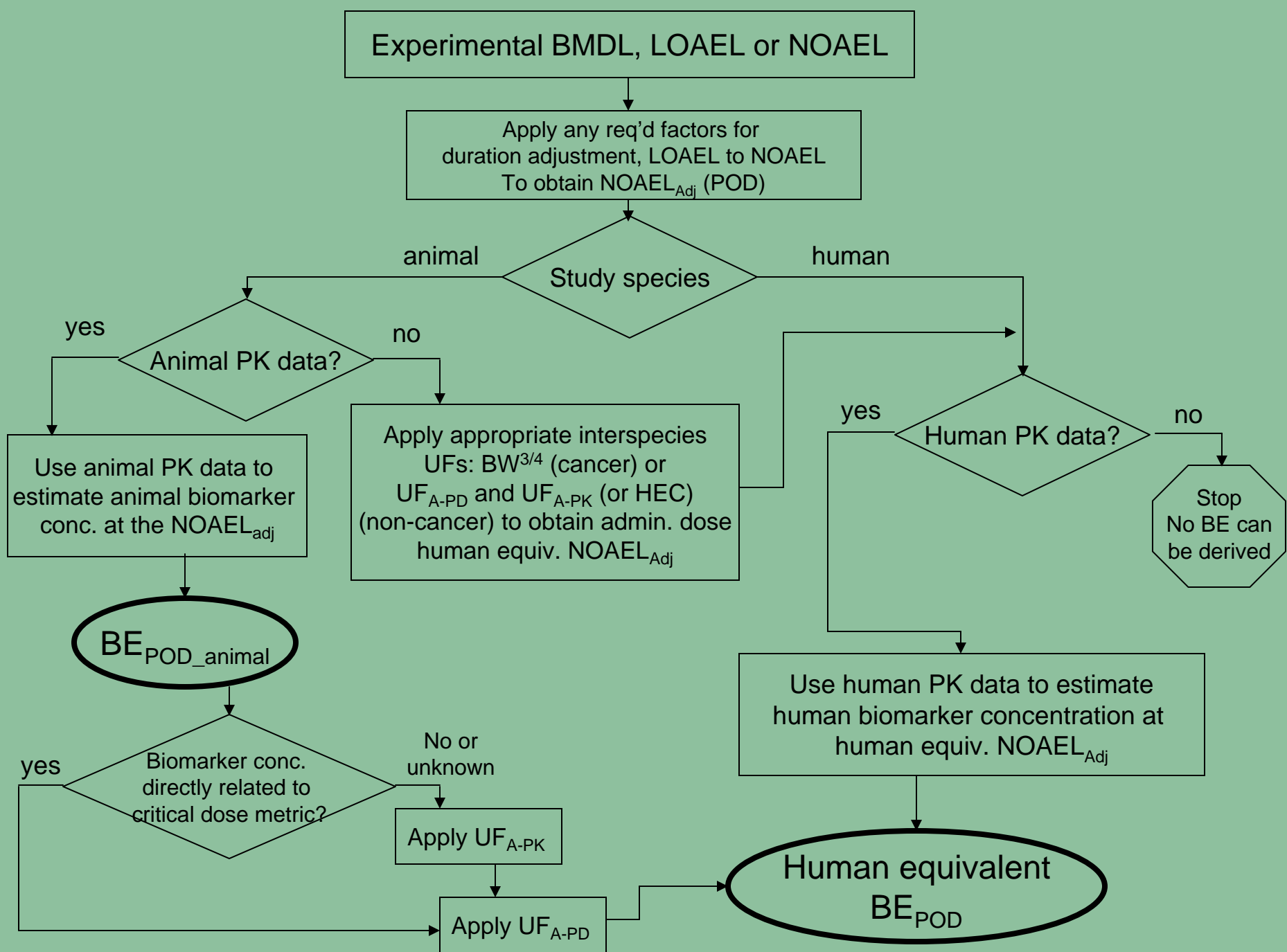
- Dedicated issue of *Regulatory Toxicology and Pharmacology*, early 2008
- Guidelines Manuscripts
 - Technical derivation guidelines
 - Communication guidelines
- Case Studies
 - Toluene
 - Cadmium
 - Acrylamide
 - 2,4-D

Findings From Expert Workshop: Derivation

- Calculate BE values associated with
 - $BE_{\text{POD-Animal}}$ - POD in animals
 - Biomarker concentration expected in animals at POD (NOAEL or BMDL)
 - Duration- and LOAEL-to-NOAEL adjustments already incorporated
 - $BE_{\text{POD-Human}}$ - Human equivalent POD
 - Includes adjustment
 - Interspecies pharmacodynamic sensitivity
 - HEC conversion based on PK differences (if appropriate)
 - BE – Fully populated BE
 - Accounts for
 - Intraspecies pharmacodynamic sensitivity
 - Intraspecies variability in pharmacokinetics (if appropriate),
 - Database uncertainties (if appropriate)

Key Considerations for Derivation

- Availability of animal and/or human PK data/model
- Understanding of MOA and critical dose metric
- Understanding of relationship between biomarker and critical dose metric



Is the BE Approach Practical?

- Requires existing toxicity guidelines and some pharmacokinetic understanding
 - CDC currently has about 460 chemicals on its analyte list
 - An initial survey shows that toxicity criteria such as RfDs and RfCs have been set for at least 150 compounds;
 - Another 40 to 60 represented by criteria for a parent compound (i.e., the analytes are metabolites of compounds with toxicity values)
- Pharmacokinetic data or models are available for many compounds of interest

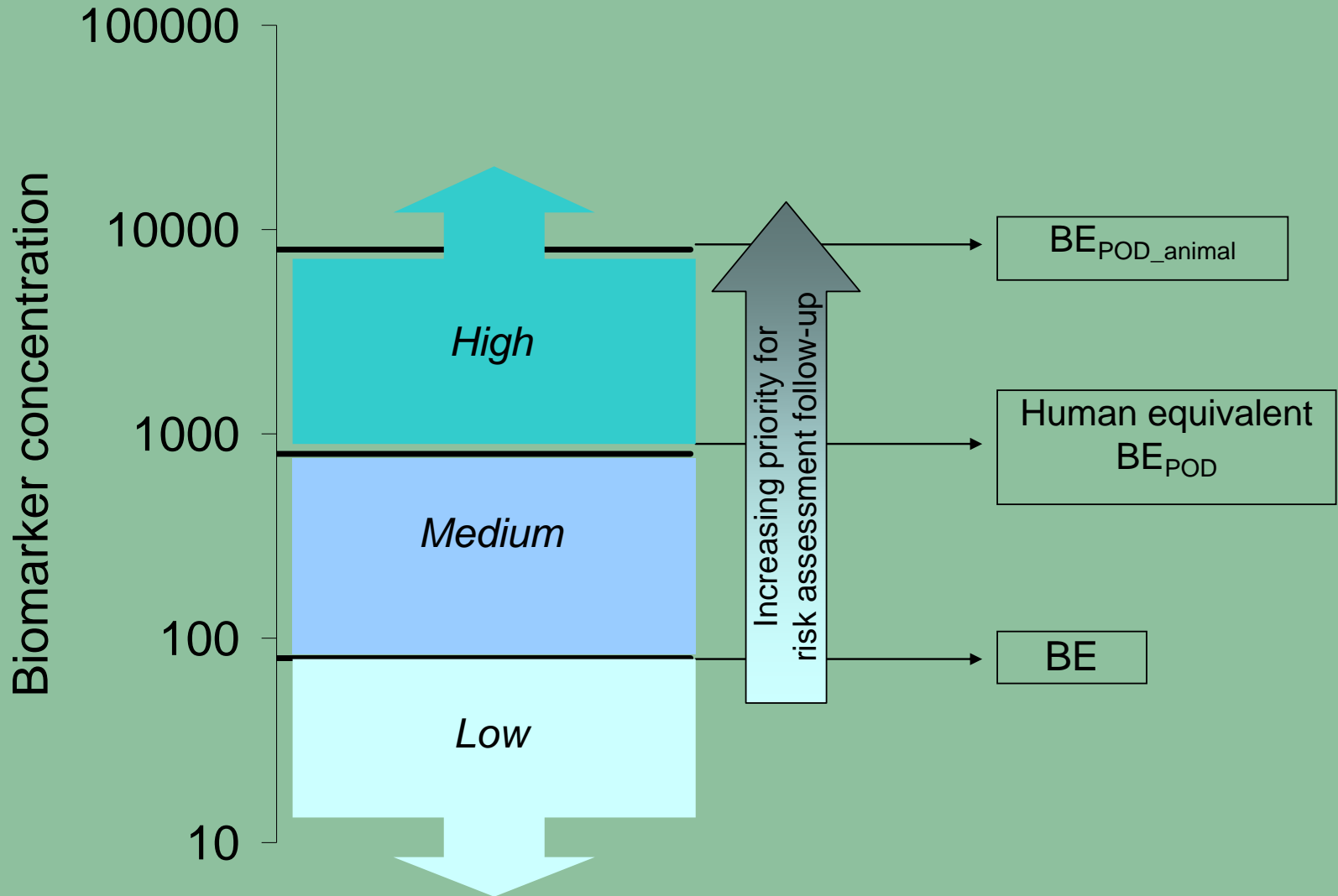
Approaches for Data-Poor Compounds

- BE approach does NOT require robust PBPK models
- Where no PK data exist, bridging studies can be conducted
 - Replicate key animal toxicity study dosing regimens
 - Measure blood concentrations
 - Provides an internal dose metric to facilitate extrapolation to target human blood concentrations
- Where no health-based guidance values exist, develop target MOEs from available toxicity data
 - Provisional approach to allow screening
 - NOT a definitive risk assessment

Findings From Expert Workshop: Communication

- BEs are not bright lines between safe and unsafe levels
- Should not be used for interpreting biomonitoring data from individuals
- Interpretation focuses on low to high priority for “risk assessment follow-up”

BE Communication Model



Case Study

Toluene Biomonitoring Data

- Sexton et al. (2005)
- Elementary school-aged children (n=60 to 160)
- Four samples during two seasons over two years

Blood toluene	
Median (ug/L)	Upper 95th (ug/L)
0.10	0.25
0.08	0.20
0.11	0.19
0.17	0.37

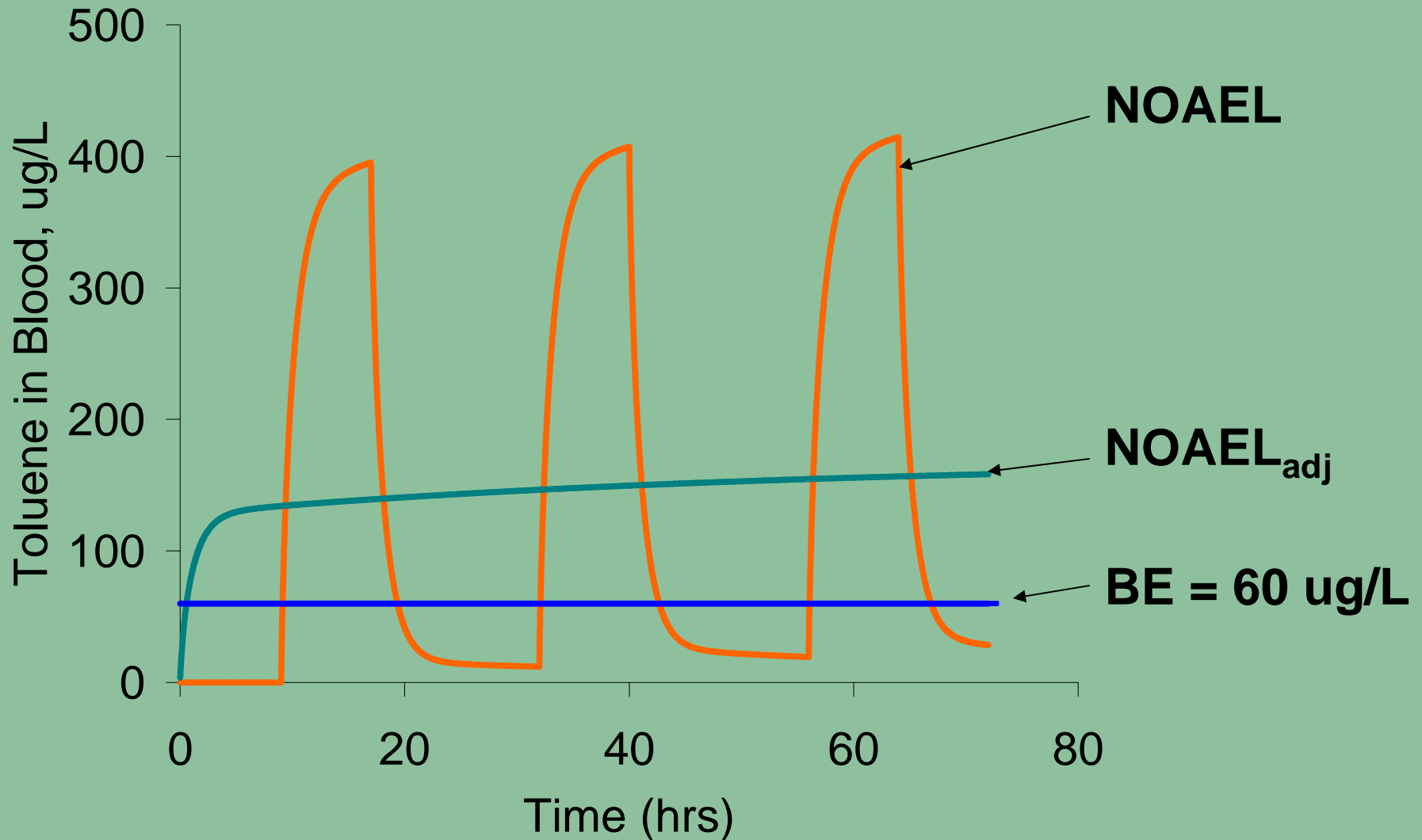
Example: Derivation of a BE_{RfC} for Toluene

- USEPA RfC
 - Based on NOAEL for neurological effects in multiple human occupational studies
 - Toluene blood concentration relevant to effects
- Pharmacokinetics of toluene well understood
 - Human and animal PBPK models available

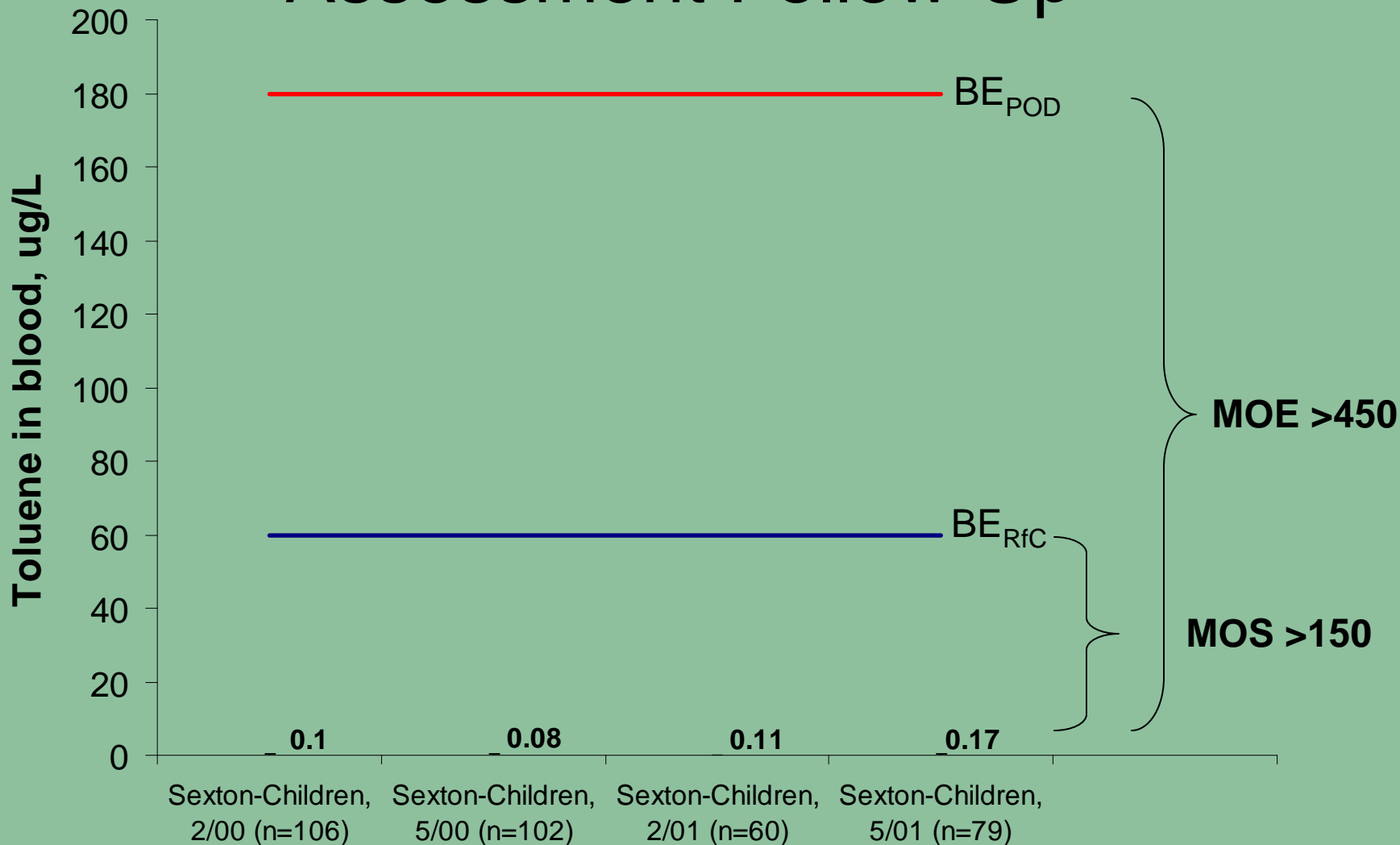
Derivation of RfC and BE_{RfC}

RfC	
Human NOAEL	128 mg/m ³ 8 hrs/d, 5 d/wk
NOAEL_{adj}	46 mg/m ³ continuous exposure
Uncertainty factors:	10 3 for P-D 3 for P-K
Result	5 mg/m³

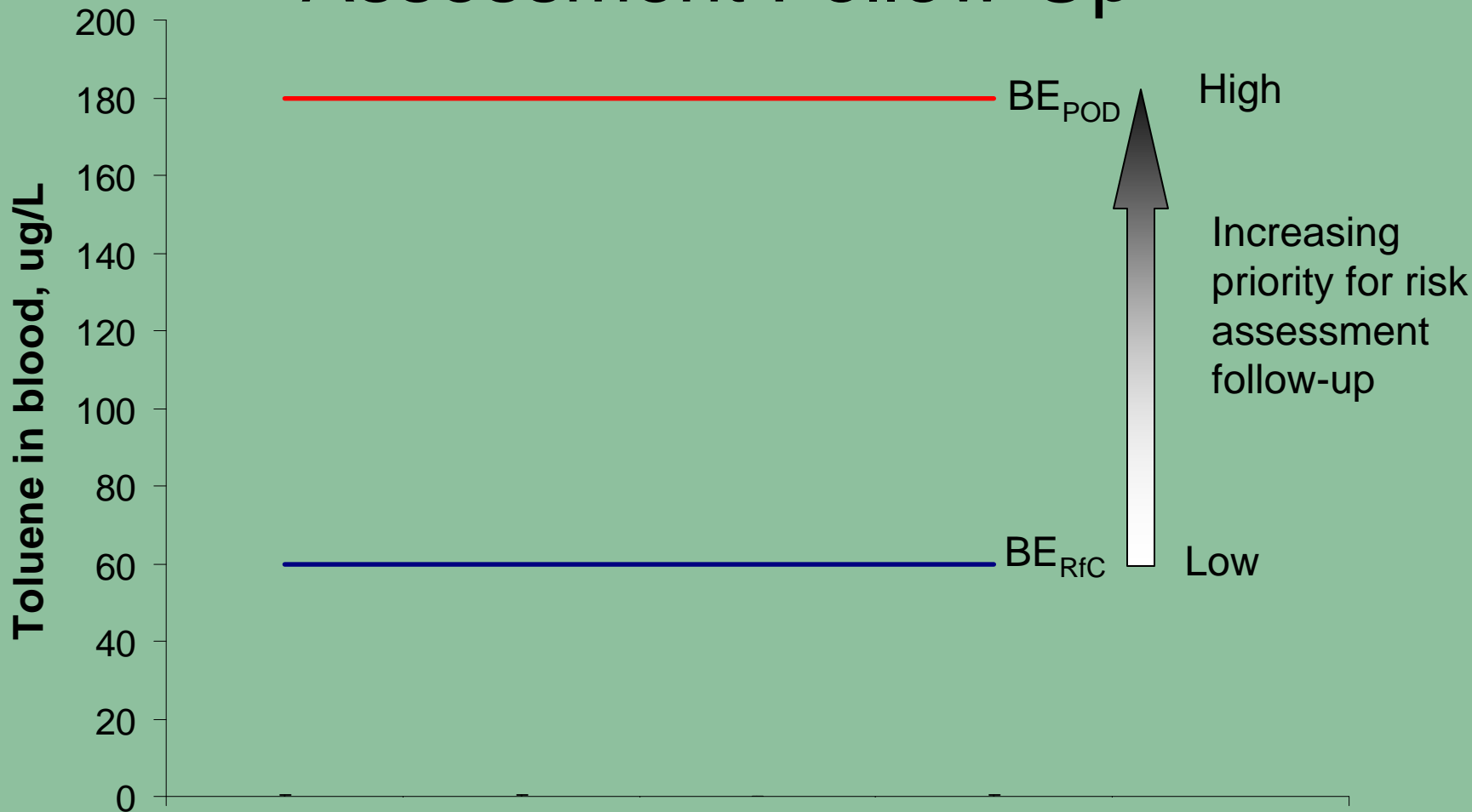
Estimated Blood Concentrations of Toluene



Interpreting Biomonitoring Data and Communicating Priority for Risk Assessment Follow-Up



Interpreting Biomonitoring Data and Communicating Priority for Risk Assessment Follow-Up



The Value of the BE as a Screening Tool

- **Risk Assessment**
 - Identify areas of potential improvement for risk assessments
- **Biomonitoring Studies**
 - Identify preferred biomarker(s)
 - Identify concentrations of interest (LOD)
- **Risk Communication and Context**
 - Provide context for biomonitoring study results
- **Risk Management**
 - Prioritize risk assessment and research efforts
 - Compounds with low margin of safety – potentially invest in risk assessment follow-up (exposure and epi studies)
 - Compounds with large margin of safety – move to lower priority list
 - Identify types of studies/data that will reduce uncertainties