Biomonitoring Equivalents as Screening Tools for Interpretation of Human Biomonitoring Data

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Sean M. Hays, M.S., M.S.
Lesa L. Aylward, M.S.
Exposure-Response

Exposure

↓

Internal Dose

↓

Biologically Effective Dose

↓

Early Biological Response

Repair (no adverse effects)  Permanently Altered Function

↓

Adverse Effect or Clinical Disease

Biomonitoring Data
Valuable Biomonitoring Data: Lead

Blood lead, µg/dl

Frequency

CDC Screening value: 10 µg/dl
Valuable Biomonitoring Data

- Dioxins/Furans
- PCBs
- Metals
- VOCs
- PBDEs
- Pyrethroid Pesticides
- Organophosphate Pesticides
- Carbamate Insecticides
- Phthalates
- Herbicides
- PAHs
- Environmental Phenols
- Organochlorine Pesticides (~12)
- Perfluorinated compounds
- Fungicides
- Halogenated Phenolic compounds
Reasons for Conducting Population Based Biomonitoring Studies

► 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)
Interpretation in a Health Risk Context

- Reference ranges (general population) do not provide health risk context
- Biomonitoring-based health risk benchmarks are available for VERY FEW chemicals
  - Lead
  - Mercury
  - ??

![Graph showing Blood lead concentration vs. Frequency]

- CDC Screening value: 10 µg/dl
External Dose vs. Biomarker Concentrations

Rat Dose
NOAEL/LOAEL

Safety Factors

“Safe” Human Dose – RfD, TDI

Human Blood Level
“Biomonitoring Equivalent”

Lay definition: What concentration of a chemical (or metabolite) is expected in blood or urine when the average human is exposed to the RfC, RfD, etc.?

Or

Technical definition: What concentration of biomarker is consistent with existing exposure guidance or reference values such as RfCs, RfDs, TDI s, etc.?
Deriving a Biomonitoring Equivalent: Utilizing Human PK Data/Model

Rat Dose
NOAEL/LOAEL

Safety Factors

“Safe” Human Dose – RfD, MRL

Human pharmaco-kinetic data

Human Blood Level
Deriving a Biomonitoring Equivalent: Utilizing Animal PK Data/Model

Rat Dose
NOAEL/LOAEL

Animal pharmaco-kinetic data

Rat Blood Level

Modified Safety Factors

Human Blood Level
External Dose Risk Assessment

**External Dose**

- Animal
  - NOAEL$_{adj}$ or POD
  - UF$_{A-PD}$
  - UF$_{A-PK}$

- Human
  - NOAEL$_{adj}$
  - POD
  - UF$_{H-PD}$
  - UF$_{H-PK}$

**Relevant Internal Dose**

**Monitored Biomarker**

RfC
Internal Dose-Based Risk Assessment

Animal

External Dose

Animal NOAEL_{adj} or POD

Animal PK Model or Data

Relevant Internal Dose

Animal Internal Dose

Human

Human Internal Dose

U_{F,PD}

U_{F,PK}

U_{F,PK}

RfC

Human PBPK/PK Model

Human Internal Dose
Biomonitoring Equivalent

**External Dose**

Animal NOAEL\textsubscript{adj} or POD

Animal PK Model or Data

**Relevant Internal Dose = Monitored Biomarker**

Animal Internal Dose

\(BE_{\text{POD,Animal}}\)

\(UF_{A\rightarrow P D}\)

Human Internal Dose

\(BE_{\text{POD}}\)

\(UF_{H\rightarrow P D}\)

Human Internal Dose

\(BE\)
Communicating Meaning of Biomonitoring Equivalent

► BE Definition is consistent with definition of underlying exposure guidance values
  ▪ Level likely to be
    ► Without adverse effects
    ► In the general population including sensitive subpopulations
    ► Over a lifetime of exposure

► Risk assessment tools, *not* diagnostic criteria or bright lines between “safe” and “unsafe”
Communication Model – Intended for Public Health Professionals

- BEs are not bright lines between safe and unsafe levels
- NOT diagnostic criteria for interpreting biomonitoring data from individuals
- Interpretation focuses on low to high priority for "risk assessment follow-up"
- Risk assessment follow-up may include
  - Exposure pathway evaluations, risk assessment re-evaluations, product stewardship, risk management
Workshop Publications

 ► Results from pilot project available in *Regul. Toxicol. Pharmacol.*, 51:S1-S77.
  ▪ Guidelines for Derivation
  ▪ Guidelines for Communication
  ▪ Case Studies:
    ► Toluene
    ► Cadmium
    ► Acrylamide
    ► 2,4-Dichlorophenoxyacetic acid
    ► Trihalomethane compounds
### Characteristics of the BE Approach and Reverse Dosimetry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BE Approach</th>
<th>Reverse Dosimetry</th>
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</thead>
<tbody>
<tr>
<td>Goal</td>
<td>Estimate steady-state biomarker concentrations consistent with exposure guidance value</td>
<td>Estimate distribution of plausible exposure concentrations consistent with distribution of biomarkers, assuming defined exposure patterns</td>
</tr>
<tr>
<td>Model Requirements</td>
<td>Can utilize animal and/or human PK/PBPK model and data</td>
<td>Requires human PK/PBPK model</td>
</tr>
<tr>
<td>Mathematical Solutions</td>
<td>Steady-state, deterministic</td>
<td>Non-steady state, nondeterministic</td>
</tr>
<tr>
<td>Biomonitoring study dependent?</td>
<td>No unique solution as a function of biomonitoring dataset</td>
<td>Unique solutions required for each biomonitoring dataset</td>
</tr>
</tbody>
</table>
Existing BEs

- Acrylamide
- 2,4-D
- Cadmium
- Toluene
- Trihalomethanes
  - Chlororom, bromoform, bromodichloromethane, chlorodibromomethane
- Dioxins and furans
BESs in Development

- Cyfluthrin
- Phthalates
  - DEHP
  - DEP
  - DBP
  - BzBP
# Approaches to BE Derivation

<table>
<thead>
<tr>
<th>Approach/ Data</th>
<th>Case Study Chemicals</th>
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<tbody>
<tr>
<td>PBPK modeling</td>
<td>Toluene</td>
</tr>
<tr>
<td></td>
<td>Trihalomethanes</td>
</tr>
<tr>
<td>Urinary mass balance</td>
<td>2,4-D</td>
</tr>
<tr>
<td></td>
<td>Acrylamide</td>
</tr>
<tr>
<td>Measured internal doses or biomarkers</td>
<td>Acrylamide</td>
</tr>
<tr>
<td></td>
<td>2,4-D</td>
</tr>
<tr>
<td></td>
<td>Cadmium</td>
</tr>
<tr>
<td></td>
<td>Dioxins/furans</td>
</tr>
</tbody>
</table>
Calculating the Cadmium BE

External Dose

Relevant Internal Dose

Monitored Biomarker

Animal

Human

Human POD Renal cortex Cd conc.

Human PK Data

Urinary Cd Conc.

Human PK Data

Blood Cd Conc.

Target Urinary Cd conc.

Target Blood Cd conc.

\( \frac{UF_{HD}}{} \)
Interpretation Using Cadmium BE

Urinary concentration, ug g\(^{-1}\) cr

- **Low**: NHANES 95th %ile
- **Medium**: BE\(_{RfD}\) with MOS >= 2
- **High**: Human BE\(_{POD}\) with Increasing priority for risk assessment follow-up
Calculating the 2,4-D BE

External Dose

Animal POD

Relevant Internal Dose

Animal POD

Monitoring Biomarker

Human Equiv. POD

Adjustment for creatinine production and urinary volume

Human Equiv. BE_{POD}

Target urinary concentration

UF_{A-PD}

UF_{A-PK}
Interpretation Using 2,4-D BE

Urinary concentration, ug g⁻¹ cr

30,000

10000

1000

100

10

1

High

Medium

Low

Increasing priority for risk assessment follow-up

Human equivalent BE$_{POD}$

BE$_{RfD}$

MOS ~300

NHANES 95th %ile

Low

Medium

High

Low urinary concentration

Medium urinary concentration

High urinary concentration
Calculating Toluene BE

External Dose

Relevant Internal Dose

Monitored Biomarker

Animal

Human

Human NOAEL_{adj} POD

Human PK Model

Human average blood concentration

Monitored Biomarker

Target avg. blood conc.

\[ UF_{PD} \]

\[ UF_{D} \]
Interpretation Using Toluene BE

Blood concentration, µg/L

- **High**: 1000
- **Medium**: 175
- **Low**: 50

Increasing priority for risk assessment follow-up:
- Human BE<sub>POD</sub>
- BE<sub>RtC</sub>

95th percentile in a sample of US children (Sexton et al. 2005)

MOS >100
Calculating Acrylamide BE

- **External Dose**
  - Animal POD
  - Animal PK Data

- **Relevant Internal Dose**
  - Avg. blood conc. AA or GA
  - UF

- **Human**
  - Human Equiv. POD
  - Avg. conc. AA or GA
  - UF

- **Monitored Biomarker**
  - Avg. blood conc. AAVal or GAVal
  - Target AAVal or GAVal
Interpretation Using Acrylamide BE

Human equivalent $\text{BE}_{\text{POD}}$

Increasing priority for risk assessment follow-up

Measured gen. population concentrations
(Hagmar et al. 2001)

AAVal, pmoles/g globin

Low

Medium

High

$\text{BE}_{\text{RfD}}$
### Application of the BE Approach

<table>
<thead>
<tr>
<th>Compound</th>
<th>MOS</th>
<th>Priority for Risk</th>
<th>Assessment Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrylamide</td>
<td>&lt;1</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Dioxins</td>
<td>~1</td>
<td></td>
<td>Medium</td>
</tr>
<tr>
<td>Cadmium</td>
<td>~2</td>
<td></td>
<td>Low - Medium</td>
</tr>
<tr>
<td>Chloroform</td>
<td>&gt;10</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Toluene</td>
<td>&gt;50</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>2,4-D</td>
<td>&gt;100</td>
<td></td>
<td>Low</td>
</tr>
</tbody>
</table>

Risk prioritization screening tool
Additional Benefits of BEs

- Inform potential risk assessment improvements (mode of action, internal dose)
- Inform biomonitoring study design
  - Identify preferred biomarker(s)
  - Identify concentrations of interest (LOD)
Application of BEs in Study Design

What detection limit should we target?

- **Low**: $8 \times \text{BE}_{\text{POD}}$
- **Medium**: $25 \times \text{BE}_{\text{RI/D}}$
- **High**: $1000 \times \text{BE}_{\text{POD}}$

- Insensitive - Not informative
- Overkill – wastes resources
Application of BE Concept to 21st Century Tox Initiatives

- Dose-response data are important for setting screening levels
- Only limited toxicokinetic data may be needed for screening - fully-developed PBPK models may not be required
Biomonitoring Data and BEs Can Help Inform Concentration Selections for 21st Century Tox Initiatives

Relevant exposures (internal doses) can help bound and BEs can help to “anchor” concentrations of interest in *in vitro* tox test systems.
Conclusions

► Biomonitoring Equivalents leverage existing chemical risk assessments
  ▪ Reproduces risk assessment based on internal dose, mode of action considerations

► BEs provide a tool for prioritization for risk assessment follow-up

► BEs can inform study design
  ▪ Selection of biomarkers, detection limit targets

► The BE concept may be applicable to “21st Century Tox” approaches
Resources

► www.biomonitoringequivalents.net
  - Home of Registered Biomonitoring Equivalents
  - Information on the BE concept and interpretation of biomonitoring data
  - Information for physicians
  - Chemical-specific information for BE case study compounds (in progress)

► *Regulatory Toxicology and Pharmacology* BE Pilot Project Supplement (2008)