Biomonitoring Equivalents – Current Activities and Use of Toxicokinetic Modeling

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Overview

- Update on current BE activities
  - Recent BE development activities
  - Use of biomonitoring data and BE values in public health and regulatory activities

- Use of toxicokinetic models in BE development and biomonitoring data interpretation
  - Empirical human data
  - Simple TK models
  - Steady-state PBPK models for VOCs
  - Fully-developed PBPK models
Recent BE Development Activities

- BE development continues under contract to Health Canada
- New or recently developed BEs
  - Selenium
  - Fluoride
  - 3-PBA
  - Silver
  - Molybdenum
- Additional compounds anticipated for late 2015-2016
  - Parabens
  - Other metals (vanadium)
Recent BE Development

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Human TK data</th>
<th>PBPK model</th>
<th>Analogue data</th>
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<tbody>
<tr>
<td>Selenium</td>
<td>✓</td>
<td></td>
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</tr>
<tr>
<td>Fluoride</td>
<td>✓</td>
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<tr>
<td>3-PBA</td>
<td>✓</td>
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<tr>
<td>Silver</td>
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<tr>
<td>Molybdenium</td>
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- BE values for selenium, molybdenium, and fluoride consider both potential toxicity AND nutritional essentiality or recommended minimal intake levels.
- 3-PBA is a non-specific metabolite of numerous pyrethroids.
- Silver evaluation addresses both ionic and nano silver exposure.
Selenium
(Hays et al. 2014, Reg. Toxicol. Pharmacol. 70:333)

- BE values for selenium in whole blood, blood plasma, and urine
- Considers both nutritional essentiality and potential toxicity (selenosis)
- Human data on biomarker concentrations as a function of exposure
  - Same datasets used to identify NOAEL for selenosis
Selenium Whole Blood BE Values

- IOM UL
- EPA RfD
- ATSDR MRL

Range of CHMS blood levels

IOM EAR

Selenium in Whole Blood, ug/L

0 100 200 300 400 500 600
Fluoride
(Aylward et al., provisionally accepted, Reg. Toxicol. Pharmacol.)

- BE values for urinary fluoride
- Considers both benefits of fluoridation for prevention of dental caries and aesthetically undesirable dental fluorosis or skeletal fluorosis following excess exposure
- Human data on urinary fluoride vs. exposure levels; consideration of age-specific relationships in fluoride excretion data
CHMS Urinary Fluoride Compared to BE Values
Silver

- BE values for urine and whole blood derived
- Current RfD and other values are based on protection against argyria (discoloring accumulation of silver in tissues) following ionic silver exposure.
  - Human data from therapeutic use of silver compounds
- Nano-silver is now widely used, but governmental exposure guidance values have not been developed
  - BE was also derived for a literature-proposed TDI
- PBPK model addressing both ionic and nano-silver was used
  
  (Bachler et al. 2013, International J Nanomedicine 8:3365)
Parallel model structures to address both ionic and nanoparticle silver

Run to steady-state at human POD

Manuscript in preparation (with Bachler and von Götz)

Figure 2 Schematic diagram of the PBPK model structures for (A) ionic and (B) nanoparticulate silver, which were used both for rats and humans.

Note: In the ionic silver model no transport of silver from the brain to the blood was modeled, to consider the blood–brain barrier.

Abbreviations: MPS, mononuclear phagocyte system; PBPK, physiologically based pharmacokinetic.
Molybdenum

- BE values for blood and urine
- Considers nutritional essentiality and potential toxic responses (increased serum uric acid in humans- USEPA; kidney alterations in rats – RIVM)
- Extensive human controlled dosing data gives empirical relationships between exposure and blood and urine concentrations.
- Manuscript in preparation.
Use of BE Values and Biomonitoring Data in Regulatory and Public Health Contexts
Health Canada

- Extensive support and use of BEs
  - Funding continues for BE development
  - BEs applied in HC Chemicals Management Plan (CMP) assessments
  - Biomonitoring data also being used with reverse dosimetry in evaluation of chemicals without BE values
- Cross chemical evaluation publication (Tox Letters 2014 231:126)
BE Review Paper

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

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

- Allows evaluation of both detected and non-detected analytes, and evaluation of both blood and urinary biomarkers
- Provides a cross-chemical perspective
- Similar to previous publication for US NHANES biomonitoring data
Cross-Chemical Evaluation Using BE Values - CHMS
Chemicals with Short Elimination Half-Lives, St-Amand et al. 2014

![Graph showing hazard quotient vs age group for various chemicals with short elimination half-lives.](image-url)
Cross-Chemical Evaluation Using BE Values - CHMS
Persistent Chemicals, St-Amand et al. 2014

[Graph showing hazard quotients for different chemicals and age groups.]

<table>
<thead>
<tr>
<th>Non-smokers</th>
<th>Smokers</th>
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<tbody>
<tr>
<td>Cadmium</td>
<td>DDT</td>
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<table>
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<tr>
<th>Age Group (years)</th>
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</table>
USEPA

- No aggregate risk assessment activities outside of Office of Pesticide Programs
  - Hazard assessment (e.g., RfD) separate from exposure and risk assessment
  - Exposure assessment done by separate offices (e.g., Office of Water, Office of Air)
  - No cross-chemical prioritization mandate or activity
  - No mandate to use or examine biomonitoring data

- Office of Pesticide Programs does address aggregate exposure, but have not assessed chemicals with available BE values
  - OPP has highly prescribed external exposure assessment paradigms in place – no direct way to inject biomonitoring data into that process
Recent evaluation of phthalate esters (PEs) which relied on NHANES urinary sampling data

- Cumulative assessment including multiple PEs based on common toxicological endpoint
- Applied reverse dosimetry rather than a BE or HBM approach
Use of Models in BE Development
Chronic risk assessment-derived POD, TDI, UFs

Model relating exposure to biomarker concentration

BE Value

No changes or evaluations

Literature search and some creativity

Characterize uncertainty and limitations

- Assumption of steady-state, consistent with chronic risk assessment guidance values
- Risk assessment interpretation for population evaluation, parallel to purpose of guidance values
Models

“Essentially, all models are wrong, but some are useful.”
- George Box

➤ Model: A graphical, mathematical (symbolic), physical, or verbal representation or simplified version of a concept, phenomenon, relationship, structure, system, or an aspect of the real world. The objectives of a model include 1) to facilitate understanding by eliminating unnecessary components, 2) to aid in decision making by simulating ‘what-if’ scenarios, 3) to explain, control, and predict events on the basis of past observations.
Approaches Used in BE Development

- Direct extrapolation from measured biomarker concentration at POD
  - HBCDD
  - PCBs
- Empirical datasets and regressions for relationships between external exposure and biomarker concentrations
  - Molybdenum, selenium, fluoride, benzene in urine
- Simple one- or two-compartment toxicokinetic models
  - Multiple short-lived analytes for urinary excretion
  - Dioxins
  - Acrylamide
- PBPK models of varying complexity
  - VOC compounds
  - Silver
Example – Simple 1 or 2 Compartment Models
Hexabromocyclododecane (HBCDD)

- Distributes largely on the basis of lipophilicity into lipid throughout the body.
  - Similar to many other persistent organochlorines.
- Peak lipid concentration resulting from a single dose easily calculated:
  \[ C_{lipid} = \frac{Abs\,Dose}{Lipid\,Volume} \]
- Est. half-life for elimination can be used to calculate long term steady state concentration:
  \[ C_{lipid\_ss} = \frac{Abs\,Daily\,Dose}{Lipid\,Volume \times k} \]
Example - Use of PBTK Modeling for VOCs - Toluene
VOC Model

- Steady-state solutions to the generic VOC PBTK model 
  *(Chiu and White 2006)*
Mass Balance Solution at Steady State

Inhalation concentration

\[ Q_p C_I + Q_L C_{VL} = (Q_p (P_B + Q_L) C_A \]

Chemical-specific parameters

\[ Abs + Q_L C_A = (Q_L + \frac{V_{max}}{Km}) C_{VL} \]

Oral absorbed dose rate

\[ C_{VSS} = C_A (1 - QLC) + C_{VL} * QLC \]

Physiologic parameters: \( Q_p, Q_L \) and \( QLC \)
Comments

- Solutions require that exposures remain in the linear range of the saturable metabolism
  - Generally not exceeded for guidance values; can be exceeded at POD

- Intra-individual variability can be examined easily:
  - 3 physiological parameters: $Q_p$, $Q_L$ and $Q_{LC}$
  - Chemical-specific parameters:
    - Metabolic parameter: $V_{max}/K_m$
    - Phys/chem parameter: $P_B$

- Steady-state slopes relating blood concentration to exposure easily calculated and can be applied to any selected guidance value:
  - $\mu g/L$ per $mg/m^3$ or $\mu g/L$ per $mg/kg\cdot d$
Toluene Steady-State Solution

<table>
<thead>
<tr>
<th></th>
<th>Oral slope μg/L per mg/kg-d</th>
<th>Inhalation slope μg/L per mg/m³</th>
<th>Upper Limit C_{VSS}, μg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>11</td>
<td>3.1</td>
<td>47</td>
</tr>
</tbody>
</table>

HBM-I: 0.8 μg/L

POD/TAF=0.26 mg/m³
Cross-VOC Results: Oral and Inhalation Slopes, 37 VOCs
Overall VOC Results – Extrapolation Possibilities

![Graphs showing blood concentration vs. oral and inhalation reference values.](image-url)
TK Variation, Children to Adults: Toluene

- Nong et al. 2006 incorporated data on the development of CYP2E1 capability and physiological parameters in neonates, infants and children into the PBTK model for toluene

*Nong et al. 2006, Toxicol Appl Pharmacol, 214:78*
Results

- Predicted blood concentrations generally bracketed measured adult concentrations and were within ~3x of adult values.
Considerations- Temporal Variability

- Variation in biomarker concentration in an individual depends on the relationship between the HL of elimination and the intervals between exposure.
Temporal Variability- Cont’d

- Modeling typically estimates steady-state average concentration
- For short-lived compounds, sampling at a particular time point may over- or under-estimate actual average biomarker concentration in the individual

- Issue is relevant for
  - VOCs in blood
  - Parabens in urine
- Not relevant for persistent compounds
Considerations - Uncertainty

- Models are uncertain
- Guidance values are also uncertain!

- Is having estimated HBM values, with their attendant uncertainties, more valuable and useful than not having them?
Considerations – HBM Values vs. BE Values

- BEs have always been envisioned as a risk assessment tool
  - Underlying guidance values are risk assessment values, not diagnostic criteria
  - Interpretation of individual results difficult, but BE values can help public health and environmental regulators to identify population-level exposures of concern
    - *Uncertainties attendant to modeling and derivation of guidance values acceptable*

- HBM values seem to be targeted more towards interpretation of individual biomonitoring data with feedback to the individual
  - *Uncertainties may be less acceptable?*