Challenges Faced in Interpreting Biomonitoring Data in a Risk Context

Sean M. Hays
Summit Toxicology

Understanding Human Biomonitoring
A Workshop Presented by ISRTP
Sacramento, CA
June 16, 2005
The Critical Question We Face

You have measured a concentration of 10 ng/mL of chemical X in blood. “Is this safe? Is this level likely to cause an increased risk of health effects? Should people be worried by this level?”

How do we as toxicologists, risk assessors, epidemiologists, public health officials, industry representatives and physicians answer this question?
What we know
"All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy." Paracelsus (1493-1541)

What we don’t know
Is the dose we are observing in our bodies lower than those thought to cause adverse effects?
The Disconnect

• There is a disconnect
  – Exposure guidelines for chemicals are currently set based on concentrations in the external environment
  – Biomonitoring tells us how much of a chemical we have in our bodies

• Is there a way to get from one to the other?

• And can this help interpret biomonitoring levels in a health risk context?
Outline

• What should we calculate?
• Methods for calculating “safe” biomarker levels
• Challenges with interpreting the various types of medium used for biomonitoring
• Challenges with communicating the interpretation of biomonitoring levels in a risk context
Possible Approaches

Forward Approach: Calculate “safe” concentration of chemical in body

Safe Concentration of Chemical in External Medium (e.g., RfC) or Safe Applied Dose (e.g., RfD)

Backward Approach: Calculate exposure required to yield biomonitoring level

Concentration of Chemical in Body
Which is Best

• Should we calculate “safe” biomonitoring levels from “safe” exposure levels, or should we calculate the exposure required to yield the biomonitoring level and then compare to “safe” exposure levels?
Some Thoughts

• The toxicology and pharmacology communities have known for a long time that the critical dose measures are related to the concentration of the toxic/therapeutic chemical/metabolite at the target organ

• Calculating the exposure required to yield the biomonitoring level holds several areas of uncertainty/variability
  – The routes (inhalation, oral, dermal) and sources of exposure are not known
  – Projecting backwards yields a range of potential exposures…for each individual measurement
The approach obviously depends on the objective.

However, if the objective is to put biomonitoring levels in a health risk context, a forward extrapolation from an established “safe” external exposure, assuming steady-state, is going to yield the more reasonable and scientifically enlightening result.
Methods for Calculating “Safe” Biomarker Levels

- Extrapolations from workplace standards (e.g., BEIs, BATs, etc.)
- Actual human (or animal) pharmacokinetic studies
- Simple pharmacokinetic models (one-compartment)
- Physiologically Based Pharmacokinetic (PBPK) models
“Safe” Biomonitoring Levels Established for the Workplace

- The ACGIH has set Biological Exposure Indices (BEIs) for 42 chemicals
- Not all are quantitative
- It may be possible to extrapolate from an occupational exposure limit (TLV) to a lower environmental exposure limit
- Germany has set Biological Tolerance Values (BATs) to correspond with their Maximum Workplace Concentration (MAK) - > 800 chemicals?
Example from BEIs

- EGEE, EGEEA – BEI = 100 mg EEA/mg creatinine (end of workweek),
- EGEE – TLV = 27 mg/m$^3$
- EGEE RfC = 0.2 mg/m$^3$
- Critical issue: Is biomarker linear down to 0.2 mg/m$^3$ exposures. Possible answers from existing literature, PK modeling, or additional studies
Methods Used to Set BEIs

• Methods used to set BEIs can provide some insights for setting “safe” biomonitoring levels for environmental exposures
• Many of them have relied on actual workplace observational studies
Pharmacokinetic Studies

Groeseneken et al. (1986)

\[ RfC = 0.2 \text{ mg/m}^3 \]
Fig 3  Correlation between time weighted individual uptake of EGEE at rest (○, ●) and during physical exercise (△, ▲), and urinary excretion of ethoxyacetic acid at maximal excretion (open symbols) and next morning (closed symbols).
Pharmacokinetic Studies

• There is a wealth of data available for workplace exposures and from volunteer human exposure studies.

• If linear relationships are found, extrapolating to lower environmental standards can be achieved.

• Caution using workplace observational studies….exposure monitoring was not always robust.

• Sometimes, the serum concentration of a chemical in animals is available for the critical studies (extrapolate from NOAEL in animals).
Steady-State Pharmacokinetic (PK) Models

• PK models are used in pharmaceutical industry
• The only parameters needed;
  – Half-life or k (first-order rate of elimination)
  – Vd (volume of distribution) or F (fraction of volume)
  – Bioavailability (f)

\[ C_{ss} = \frac{ADD \times f \times t_{1/2}}{\ln(2) \times Vd} \]
Steady-State PK Models

Similarly, for inhalation exposures

\[
Cvss = \frac{Qp \times Ci \times (1 - QLC \times E)}{(Qp/Pb) + (QL \times E)}
\]

\[
E = \frac{CLint}{CLint + QL}
\]

Where,
- **QP** – alveolar ventilation
- **QL** – Liver blood flow rate
- **QLC** – fraction of cardiac output flowing to liver
- **Ci** – inhalation concentration
- **Pb** – blood:air partition coefficient
- **E** – hepatic extraction coefficient
- **CLint** – intrinsic hepatic clearance (defined as Vmax/Km)
Steady-State PK Models

- **Dioxin**
  - Using steady-state equation for oral exposures,
  - Half-life = 7.5 years
  - $f = 0.5$
  - $V_d = 0.25$
  - TDI = 1 pg/kg/day (ATSDR)
  - “safe” biomonitoring level = 8 ppt lipid

- **Toluene**
  - Using steady-state equation for inhalation exposures,
  - $C_{vss} = C_i/0.2998/1000$ (L/m$^3$)
  - RfC = 0.4 mg/m$^3$
  - “safe” biomonitoring level = 1.3 ug toluene/L blood
Steady-State PK Models

• Much of the necessary information required for using these models is already available
  – Toxicology Profiles (ATSDR)
  – PK studies published in peer-reviewed literature

• Can be very useful as a screening tool
PPBK Modeling
Example With Multiple Sites for Biomonitoring

2-ME

Inhaled air

Exhaled air

2-ME

Lung

Fat

Richly Perfused

Poorly Perfused

Liver

Arterial Blood

Venous Blood

Kegc

EG

ka

GI tract oral dose

2-MAA

Fat

Richly Perfused

Poorly Perfused

Liver

Arterial Blood

Venous Blood

Urine

ke

Kmaac

2-MAA
Number of Chemicals for Which PBPK Models Have Been Developed
PBPK Models

- Acetone
- Acrylonitrile
- Arsenic
- Benzene
- Benzo(a)pyrene
- Bromobenzene
- Butadiene
- 2-butoxyethanol
- Cadmium
- Carbon tetrachloride
- Chlorfenvinphos
- Chloroalkanes
- Chloroethanes
- Chloroform
- Chloropentafluorobenzene
- Chromium
- DDT
- Dichlorobenzene
- Dichloroethane
- Dichloroethene
- Dieldrin
- Diisopropylfluorophosphate
- Dimethyloxazolidine2,4-dione,5,5’
- 1,4-dioxane
- Dioxin
- Ethanol
- 2-ethoxyethanol
- Ethyl acrylate
- Ethyl acetate
- Ethylene dibromide
- Ethylene oxide
- Furan
- Hexabromobiphenyl
- Hexachlorobenzene
- Hexane
- Isoamyl alcohol
- Isofenphos
- Kepone
- Lead
- Melphalan
- Mercury
- Methanol
- 2-methoxyethanol
- Methotrexate
- Methylmercury’
- Methylenechloride
- MTBE
- Napthalene
- Nickel
- Nicotine
- Physostigmine
- PCBs
- Soman
- Styrene
- Toluene
- Tetrachloroethane
- Tetrachloroethene
- Trichloroethane
- Trichloroethene
- Trichloro, trifluoroethane
- Vinyl acetate
- Vinyl chloride
- Vinylidene chloride
- Vinylidene fluoride
- Xylenes
- Zinc
Simulating Biomarker Levels With a PBPK Model

Rate of 2-MAA Excretion in Urine (ug/min) vs. Time (hrs)
Accounting for Variability

Model Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimates</th>
<th>Distributions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>QPC</td>
<td>35.0</td>
<td></td>
</tr>
<tr>
<td>QCC</td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td>Vti’s</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Qti’s</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>Pti’s</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>VmaxC</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Km</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>KfC</td>
<td>1.5</td>
<td></td>
</tr>
</tbody>
</table>
Variability in Biomarkers
PBPK and Monte Carlo

Distribution of internal dose in humans exposed to $X$ ppm for 8 hrs/day.
Variability in Predicted Biomarker Levels Can be Used to Guide Biological Equivalent Selection

<table>
<thead>
<tr>
<th>Chemical and Metabolite</th>
<th>Current BEI (mg/g creatinine)</th>
<th>Predicted Urinary Metabolite Concentrations (mg/g creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Percent of Population</td>
</tr>
<tr>
<td>Benzene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenol</td>
<td>50</td>
<td>27</td>
</tr>
<tr>
<td>Methyl chloroform</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichloroacetic acid</td>
<td>10</td>
<td>2.9</td>
</tr>
<tr>
<td>Trichloroethanol</td>
<td>30</td>
<td>37</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichloroacetic acid</td>
<td>100</td>
<td>62</td>
</tr>
<tr>
<td>Trichloroethanol</td>
<td>----</td>
<td>472</td>
</tr>
</tbody>
</table>
Pros and Cons of Various Methods

Extrapolating from BEIs

• Pros
  – Approach already established for some
  – Can be easy

• Cons
  – Have to assure linearity or shape of relationship when extrapolating to lower concentrations
Pros and Cons of Various Methods

PK Studies

• Pros
  – Can be the most direct method if the data is appropriate
  – Historical data exists for many compounds
  – New protocols at NTP will supposedly develop some of this PK data within animals

• Cons
  – Studies not always conducted at steady-state (requires some extrapolations)
Pros and Cons of Various Methods

**Steady-State PK Models**

- **Pros**
  - Easy to use
  - Minimal information required
  - Can be expanded to include urinary excretion

- **Cons**
  - Simplistic
  - Not as useful for media other than blood...and urine to some degree
  - Not as useful for metabolites
Pros and Cons of Various Methods

PBPK Modeling

• Pros
  – Most robust and comprehensive approach
  – Powerful tool for assessing various scenarios (special populations, co-exposures, etc.)
  – PBPK models already exist for many chemicals

• Cons
  – Most costly and time consuming to develop, if starting from scratch
What About Safety/Uncertainty Factors?

• When scaling from RfC, RfD, etc., should some of the uncertainty/safety factors be removed?
  – Pharmacokinetic?
  – Species?
  – Susceptible populations?
  – What about cancer?
Characteristics of a Useful Biomarker of Exposure

• Moderate half-life (not too long, not too short)
• Easy medium to sample
• Specific to chemical of interest
• Best if related to toxicity, but not critical
• Easy medium to interpret (the further away from the critical dose measure, the harder to interpret)
Ease of Collection

Easy
- Hair
- Nails
- Saliva
- Urine
- Exhaled breath
- Breast milk
- Blood
- Cord blood
- Tissue biopsy

Difficult
Ease of Interpretation

- Blood
- Exhaled breath
- Cord blood
- Tissue biopsy
- Urine
- Breast milk
- Saliva
- Hair
- Nails

Easy

Difficult
Interpretation versus Collection
The Optimal Medium for Interpreting Risk

Collection

Most Difficult

Most Difficult

Interpretation

Optimal region

- hair
- saliva
- breast milk
- urine
- exhaled breath
- blood
- BM_infant
- cord blood
- tissue biopsy

BM_infant
Biomarker Medium and Types of Compounds

- Exhaled breath
  - Volatiles with short half-lives
- Urine
  - Metabolites, parent compounds especially with short half-lives and urine is major route of elimination
- Blood
  - Parent, metabolites, long-lived compounds and compounds not readily excreted in urine
Challenges With Communicating the Interpretation of Biomonitoring Levels in a Risk Context

- Presence does not equal risk
- However, we need to establish “safe” biomonitoring levels to assist in
  - Putting biomonitoring levels in a risk context
  - Communicating public health risks
  - Risk management decisions
What’s in a Name?

• Biomonitoring Action Level (BAL)
  – Used by Finland to denote a level of the 95\textsuperscript{th} percentile of the non-occupationally exposed population

• Biological Exposure Index (BEI)
  – Used by ACGIH to indicate a biomonitoring level that would correspond with exposures at the Threshold Limit Value (TLV)

• Biological Tolerance Value (BAT)
  – German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area
What’s in a Name?

• What image should a name conjure?
  – Concern?
  – Safety?
  – Action?
  – Exposure?
  – Equivalents?
  – Risk?
  – Toxicity?

• A proposed name – “Biological Equivalents” or “Biomonitoring Equivalents”
  – There can be a BE for each regulatory guidance (RfC, RfD, CSF, MRL, TDI, etc.)
  – $BE_{RfC}$
Final Thoughts

• Biomonitoring can become the “gold standard” for exposure assessments if done correctly…and become an extremely valuable tool for risk management

• However, we need methods for interpreting results in a risk context

• The methods exist for developing some form of guidance on “safe” biomonitoring levels

• A naming convention can help in interpretation and communication
Interpreting Biomarkers of Exposure

Sean M. Hays
Summit Toxicology

ISRTP Workshop on Biomonitoring
Sacramento, CA
June 16, 2005