Biomonitoring for Exposure Assessment: Challenges and Future Directions

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Biomonitoring

- Exposure Assessment Approach
- Assessment of internal dose by measuring the parent chemical (or its metabolite or reaction product) in human specimens
  - Integrates all sources/routes of exposure
  - Trace concentrations (vs environmental levels)
- We measure concentrations, not exposures
Optimal Characteristics of an Analytical Method

- Sensitive
- Specific/Selective
- Accurate
- Precise/Reproducible
- Rugged
- Cost effective

- Minimal sample volume*
- Simple*
- Instrumentation
- Multianalyte*
- Compromise
- High throughput*
- Automation
- QA/QC program*
- Interlaboratory comparisons

*Biomonitoring
Analytical Steps

- **Sample workup**
  - Deconjugation

- **Preconcentration**
  - Extraction

- **Separation**
  - Chromatography

- **Quantification**
  - Isotope dilution – mass spectrometry
  - Other

- Matrix, chemical & instrumentation influence the choice of analytical method
## Analytical Chemistry vs Biomonitoring

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Biomarker</th>
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</thead>
<tbody>
<tr>
<td>Validated method</td>
<td>Adequate facilities &amp; instrumentation</td>
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<td>Qualified personnel</td>
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<td>QA/QC (e.g., laboratory blanks)</td>
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<td>Available analytical standards</td>
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<td>Analyte metabolism &amp; toxicokinetics</td>
<td>Biomarker selection</td>
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<tr>
<td></td>
<td>Variability in concentrations</td>
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<tr>
<td>Matrix factors</td>
<td></td>
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<tr>
<td>Sampling factors</td>
<td>Timing/place of collection</td>
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</tbody>
</table>
Biomarker & Matrix Selection

- **Biomarker choice**
  - Most abundant/relevant compound for target population
    - Minimize exposure misclassification

- **Matrix choice**
  - Urine: non-persistent chemicals
  - Blood: persistent chemicals
  - Other matrices?
    - Endogenous matrix components can affect the analytical results
      - Phthalates (esterases)
  - Stability, collection issues

Variability in Urinary Concentrations: BPA Example

- **8 adults: regular (uncontrolled) setting**
  - Collected all urine voids (N = 427 including 56 FMV) for 7 days in 2005
    - Between-day/within-person variability: 77% (FMV) & 88% (24-h) of total variance
    - Within-day variance (70%) > between-person (9%) & between-day/within-person (21%) variances for spot collections
  - Multiple collections per person to better categorize exposure?
    - Episodic exposures (e.g., diet)
    - Similar data for other NPPs
    - Time of collection and last urination

Ye et al. EHP 2011, 119:983-8
Variability in Urinary Concentrations: Phthalates as a Case Study

- **DEHP (MEHHP) vs DEP (MEP)**
  - **Distinct patterns**
    - MEP: between-person variability accounted for > 75% of total variance
    - MEHHP: within-person variability contributed 69–83% of total variance
    - Spot samples intra-day variability: MEHHP (51%) & MEP (21%)
  - Nature of the exposure (diet vs. other) & timing of collection

Preau et al. EHP 2010, 118(12):1748-54
Exposures Based on 24-h Collections Also Vary

BPA total daily exposure (µg)

<table>
<thead>
<tr>
<th>Day</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
<th>P7</th>
<th>P8</th>
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<tbody>
<tr>
<td>Mon</td>
<td>5.9</td>
<td>3.3</td>
<td>4.4</td>
<td>9.5</td>
<td>4.1</td>
<td>7.6</td>
<td>3.6</td>
<td>4.4</td>
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<tr>
<td>Tue</td>
<td>3.1</td>
<td>4.3</td>
<td>1.7</td>
<td>7.0</td>
<td>5.6</td>
<td>5.2</td>
<td>1.8</td>
<td>6.5</td>
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<td>3.9</td>
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<td>1.9</td>
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<tr>
<td>Thu</td>
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<td>4.7</td>
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<td>4.6</td>
<td>5.8</td>
<td>8.1</td>
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<tr>
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<td>8.7</td>
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<td>3.0</td>
<td>3.8</td>
<td>3.4</td>
<td>11.3</td>
<td>5.2</td>
<td>11.0</td>
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<tr>
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<td>4.6</td>
<td>2.0</td>
<td>3.2</td>
<td>4.9</td>
<td>4.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Sun</td>
<td>1.5</td>
<td>1.2</td>
<td>19.7</td>
<td>4.0</td>
<td>4.5</td>
<td>3.8</td>
<td>4.5</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Mean (Mon–Sun) ± SD

- 4.5±2.2
- 3.5±1.3
- 5.9±5.7
- 4.9±2.3
- 4.6±1.1
- 6.7±2.3
- 5.1±3.4
- 4.2±3.2

- 24-h collections reflect “current” exposure, but not necessarily past or future exposures

Ye et al. EHP 2011, 119:983-8
NPPs Urine/Serum Concentrations: BPA Example

- **20 adults (controlled setting)**
  - Healthy, non-smokers, no dental work
  - Housed for 24-h at clinical facility (2009)
    - Ingested one of 3 specified meals of standard grocery store food items
    - All voided urine collected at regular intervals over 24 h (N = 389)
    - Serum samples taken until 10 pm of the study day (N = 321)
  - Urinary elimination (~1h time lag) correlated to serum time-course
  - Variable \([\text{urine}] \) & \([\text{serum}] \)
  - \([\text{Urine}]_{\text{av}} \sim 42 \times [\text{serum}]_{\text{av}}\)

Sampling Strategies (NPPs)

- One specimen, but multiple biomarkers
- Does a single sample adequately characterize an individual’s average exposure for a given time period?
  - 24-h vs spot collections
- Suitability of one sample approach depends on biomarker, exposure scenario and population
  - For chronic exposures, probably
  - For episodic exposures, maybe, depending upon type (e.g., diet), frequency and magnitude of exposure
    - Time of collection and last urination for spot collections
    - Age-related variability
- Can we overcome variability?
  - Multiple urine collections per person
    - Cost (storage, analysis) & compliance considerations
  - “Pooling” several spot samples
  - Is variability even known?
Despite Variability, Biomonitoring Data Show Exposure Differences: Case of Methyl Paraben (NHANES 2005-2006)

Calafat et al. EHP 2010, 118:679-85
Collection Protocols & Data Interpretation

- **Collection in clinical settings**
  - Birth, surgeries, IVF treatments, other
  - Medical devices, IVs, catheters

- **Plasticizers (e.g., DEHP, BPA) can leach from tubing**
  - \([\text{DEHP metabolites}] >> [\text{DEHP metabolites}]_{\text{background levels}}\)
  - \([\text{Other phthalate metabolites}]\) unremarkable
  - \([\text{BPA}] >> [\text{BPA}]_{\text{background levels}}\)

- **Biomonitoring data reflect a true exposure, but not “general” environmental exposures**

Collection & Storage Matter

- Biomonitoring integrates all sources/routes of exposure
  - Also from external contamination

- Contamination before analysis
  - Unknown sources/routes of exposure
  - Ubiquitous chemical & trace levels in humans
  - Collection procedure may be the source
    - Setting (e.g., medical interventions)
    - Matrix cross-contamination
  - Archived specimens

- We can’t completely rule out external contamination
  - Consistent use of field blanks & blind QCs
  - Describe collection setting & sampling procedures
    - How/when/where?

Calafat and Needham EHP 2009, 117:1481-5
Take Home Messages – Future Directions

- Biomonitoring is one tool for exposure assessment
  - Integrates sources/routes of exposure
  - Trace vs environmental levels
  - Requires complex analytical methods

- Many analytes can be measured, but not all analytes are good exposure biomarkers

- Interpretation of Biomonitoring data
  - Selection of appropriate biomarkers
    - Biomarker metabolism & matrix factors
  - Multiple samplings may be needed (NPPs)
  - Collection & handling considerations (how/when/where?)
    - Stability (analyte & matrix)
    - Ubiquitous & unknown potential contamination sources
    - Archived specimens & field blanks

- Used properly, biomonitoring undoubtedly improves exposure assessment
THANK YOU!

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov    Web: www.cdc.gov

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