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

*Biomonitoring

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

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

Analyte

- Validated method
  - Adequate facilities & instrumentation
  - Qualified personnel
  - QA/QC (e.g., laboratory blanks)
  - Available analytical standards

Biomarker

- Analyte metabolism & toxicokinetics
  - Biomarker selection
  - Variability in concentrations
- Matrix factors
- Sampling factors
  - Timing/place of collection

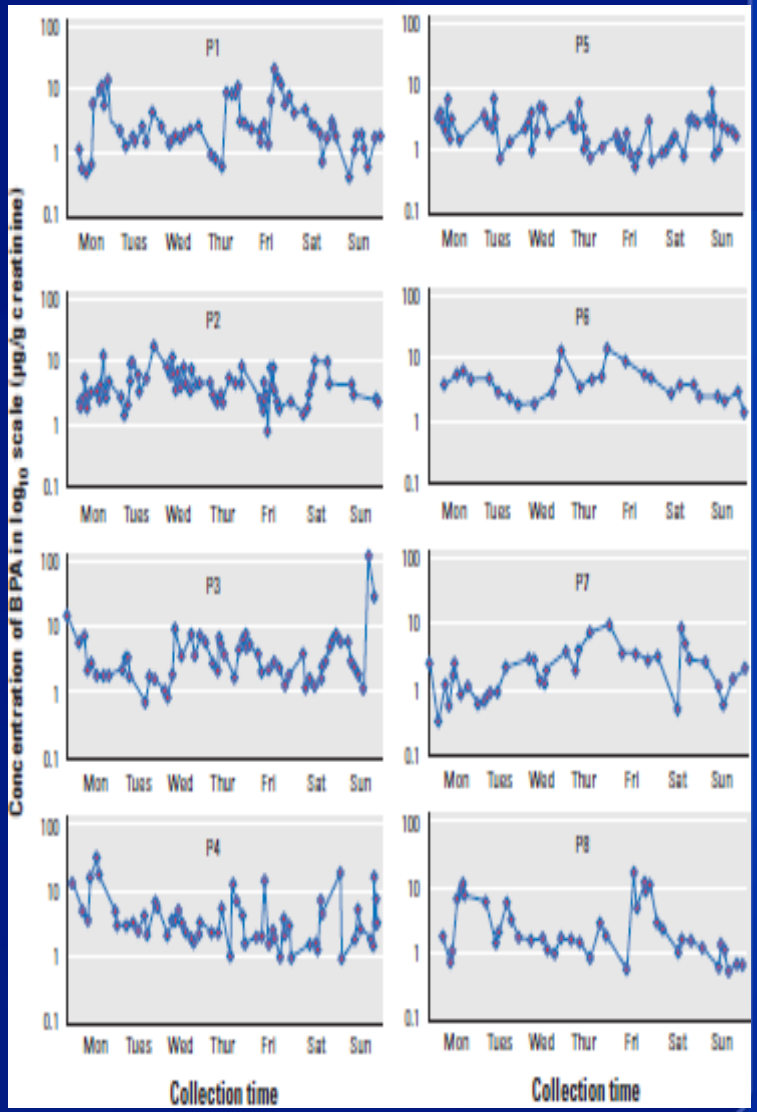
Biomarker & Matrix Selection

- **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

Calafat and Needham. Int J Androl. 2008, 31(2):139-43

Variability in Urinary Concentrations: BPA Example

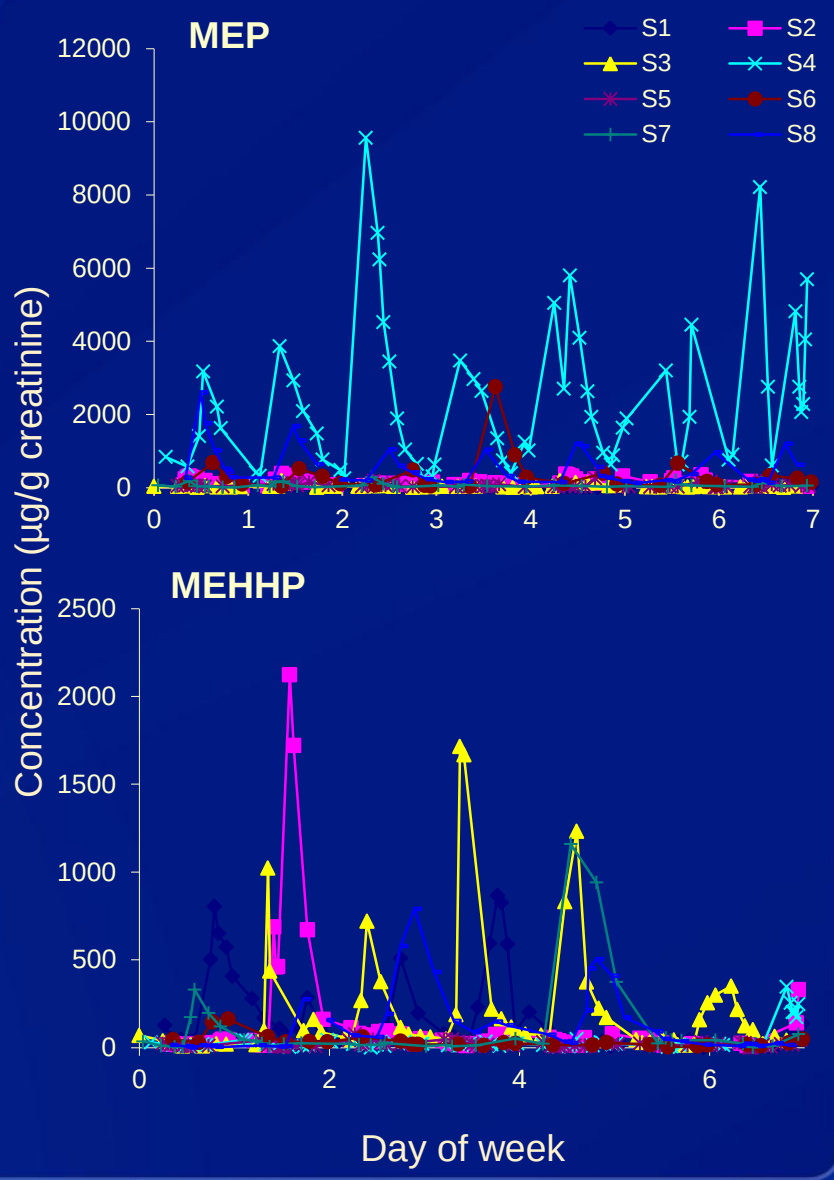
- **8 adults: regular (uncontrolled) setting**
  - Collected all urine voids (N = 427 including 56 FMV) for 7 days in 2005
    - Between-day/within-person variability: 77% (FMV) & 88% (24-h) of total variance
    - Within-day variance (70%) > between-person (9%) & between-day/within-person (21%) variances 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)

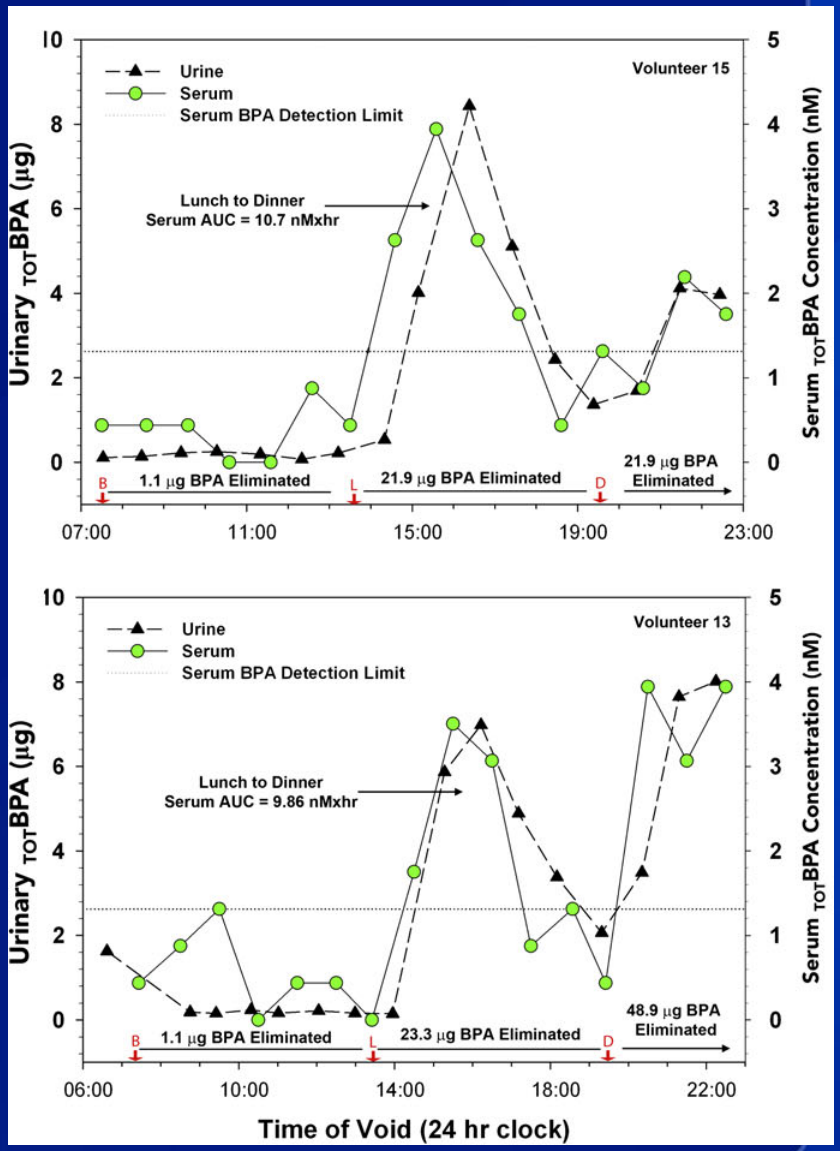
Day	P1	P2	P3	P4	P5	P6	P7	P8
Mon	5.9	3.3	4.4	9.5	4.1	7.6	3.6	4.4
Tue	3.1	4.3	1.7	7.0	5.6	5.2	1.8	6.5
Wed	2.8	5.2	3.9	3.6	5.8	6.1	3.3	1.9
Thu	5.5	4.7	4.0	4.6	5.8	8.1	13.0	2.3
Fri	8.7	2.5	3.0	3.8	3.4	11.3	5.2	11.0
Sat	3.9	3.7	4.6	2.0	3.2	4.9	4.4	2.0
Sun	1.5	1.2	19.7	4.0	4.5	3.8	4.5	1.1
Mean (Mon–Sun) ± 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 [urine] & [serum]
  - $[Urine]_{av} \sim 42*[serum]_{av}$

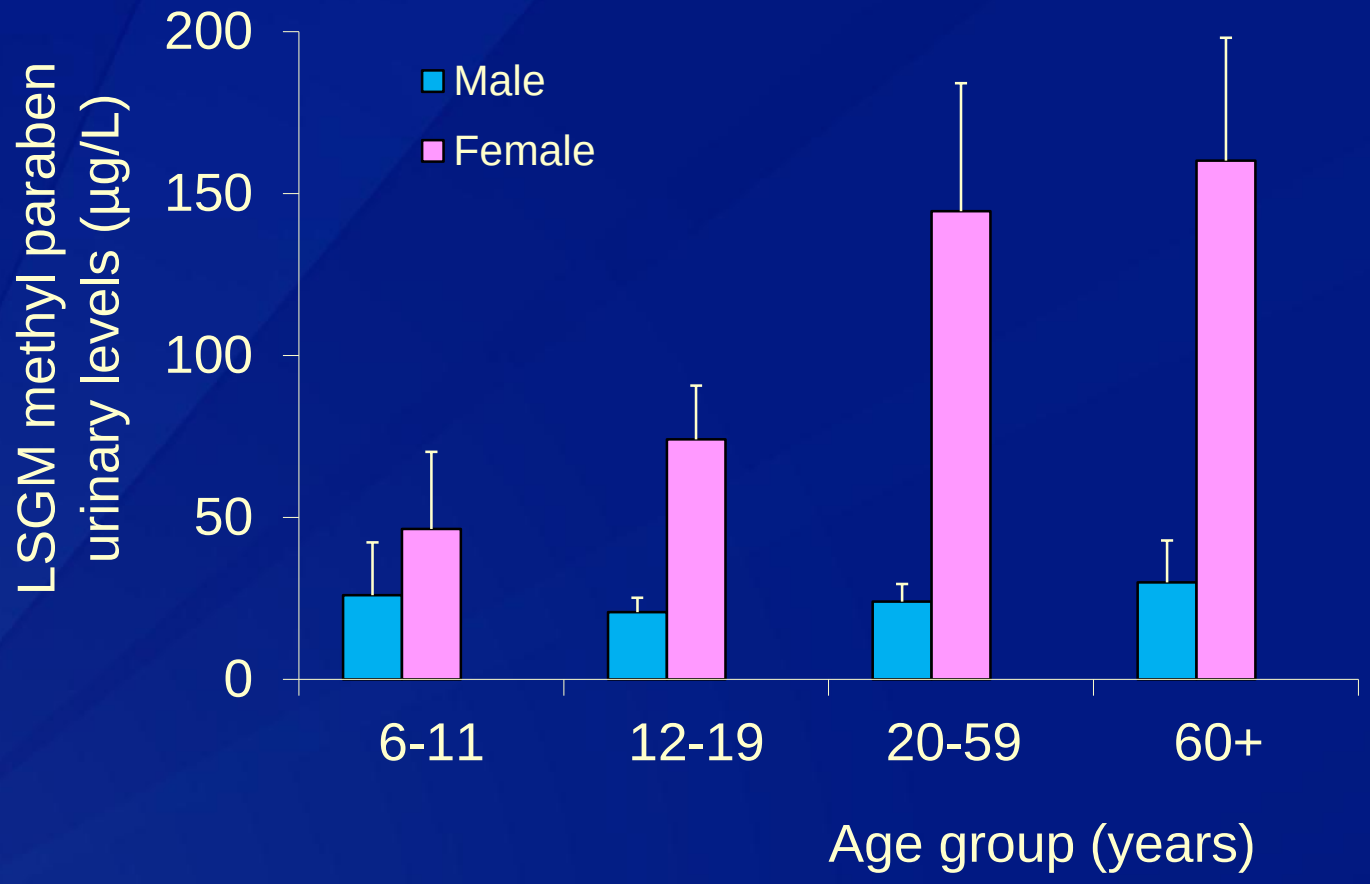


Teeguarden et al. Toxicol Sci 2011, 123(1):48-57

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**
  - [DEHP metabolites] >> $[\text{DEHP metabolites}]_{\text{background levels}}$
  - [Other phthalate metabolites] unremarkable
  - [BPA] >> $[\text{BPA}]_{\text{background levels}}$
- **Biomonitoring data reflect a true exposure, but not "general" environmental exposures**

Yan X et al. Hum Ecol Risk Assess 2009,15:565–78; Vandentorren et al. Environ Res 2011,111:761-4

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

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