Interpreting Biomonitoring Data in a Risk Assessment Context Using Biomonitoring Equivalents

Biomonitoring California Workshop
Understanding and Interpreting Biomonitoring Results

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Outline

- Approaches for interpreting biomonitoring data (chemical concentrations)
- Biomonitoring Equivalents
- Examples
- Development of interpretation website resource

Audiences for Biomonitoring Interpretation

- Risk assessors/risk managers
- Public health officials
- Physicians
- Individuals who receive their own biomonitoring data
- General public

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)

Approaches for Interpreting Biomonitoring Data

Reference Range	• Statistical description of levels in general population • Classify measures as “Typical” or “Atypical” • No information on potential health impacts
Human Biomonitoring-Based Benchmarks	• “Gold standard”; human exposure-response data • Resource intensive • Available for very few chemicals
Risk Assessment-Based Benchmarks	• Leverages existing chemical toxicology and risk assessments • Requires animal or human pharmacokinetic data

Examples of Available Screening Values

- Reference Ranges:
  - German Human Biomonitoring Council
  - US CDC
- Human Biomonitoring-Response-Based Benchmarks
  - German HBC: cadmium, mercury, thallium, pentachlorophenol
  - US CDC: Blood lead guideline
  - ACGIH Biological Exposure Indices for workplace
- Risk Assessment-Based Benchmarks
  - German HBC: DEHP, others in development
  - Biomonitoring Equivalents: ~80 chemicals

Evolution of Risk Assessment

Chemical-by-chemical
External exposure and response assessments
High uncertainty
Focus on observable adverse effects

Aggregate and cumulative risk assessments
Internal dose-based exposure and response assessment
Increasing focus on subtle biological alteration; population risks

Biomonitoring data; BE Approach

Integrated assessment of "exposome" across life stages
Integration of "omics" and HTS data, individual genetic susceptibility
Assessment of social and community factors

Increasing sophistication
Increasing difficulty, data demands

Biomonitoring Equivalents

Risk Assessment-Based Benchmarks
A Practical Interim Approach

Existing Chemical Risk Assessment Paradigm

"Point of Departure"

Rat Dose NOAEL/LOAEL

100-1,000

Uncertainty Factors

"Safe" Human Dose – RfD, TDI

Reference Dose or Concentration: "An estimate of an exposure …to the human population (including susceptible subgroups) that is likely to be *without an appreciable risk of adverse health effects over a lifetime*."

http://www.epa.gov/iris/help_gloss.htm#r

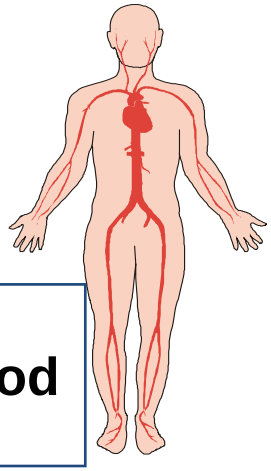
“Biomonitoring Equivalent”

Concentration of biomarker that is consistent with existing exposure guidance or reference values such as RfDs, TDIs, etc.

Rat Dose NOAEL/LOAEL

“Safe” Human Dose – RfD

BE_{RfD} Human Blood Level



Goals of BE Approach

- Leverage and integrate existing datasets and risk assessments
  - Substantial body of data and information
- Provide translational approaches between external and internal dose-based risk assessments
- Enable biomonitoring data to be screened as input to prioritization of research efforts using modern epidemiologic and biological research methods

Application to Distributional Risk Metrics

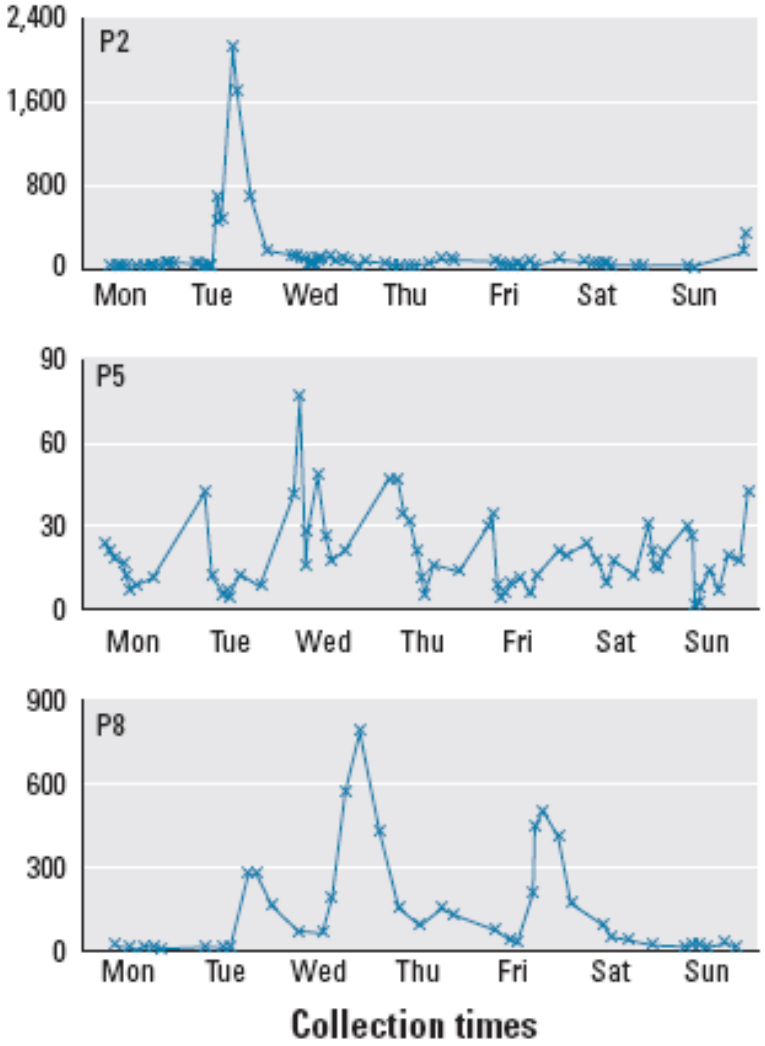
- BE values can and have been derived corresponding to risk-specific dose estimates
  - Cancer risk-specific doses
  - Non-cancer estimates of risks of adverse outcomes (e.g., under Silver Book approaches)

Considerations, Context, Limitations

- BEs are screening tools for use in a screening level risk assessment context, not bright lines separating “safe” from “unsafe” levels.
- BEs are derived from a variety of data using a variety of approaches, and are no more reliable or precise than the risk assessment values to which they correspond or the data used in their derivation.
- Most appropriately applied to population data, rather than to assessment of data for an individual.
- Most effective in a prioritization context, along with complementary information and assessments.
- Biologically transient compounds present special challenges.
- Additional caveats and considerations discussed in BE Derivation and Communications Guideline documents (Hays et al. 2008, LaKind et al. 2008; Reg. Tox. Pharm. Vol. 51, No. 3, Suppl. 1) and chemical-specific articles.

Transient Biomarkers - Challenges

- Biologically transient chemicals
  - Significant intra-individual temporal variation



MEHHP in urine over one week, 3 individuals.
Preau et al. 2010, *EHP* 118:1748

Biomonitoring Equivalents Pilot Project Expert Workshop, 2007

- Experts in risk assessment, pharmacokinetics, communication, medical ethics
- Provided guidance on the BE concept, methods, and communication
- Results from pilot project available in *Regul. Toxicol. Pharmacol*., Vol. 51, No. 3, Supplement 1 (2008)
  - Guidelines for Derivation
  - Guidelines for Communication
  - Case Studies

Chemicals with BE Values

Completed and Published

2,4-D
Cyfluthrin
Cadmium
Inorganic arsenic
Hexachlorobenzene
Bisphenol A
Triclosan
Diethyl phthalate
Dibutyl phthalate
Benzyl butyl phthalate
Di-2(ethylhexyl) phthalate
Dioxin TEQ (29 compounds)
Acrylamide
Chloroform
Bromoform
Dibromochloromethane
Bromodichloromethane
Methylene chloride
Carbon tetrachloride
Methyl-tert-Butyl Ether (MTBE)
n-Nonane
1,1,1-Trichloroethane
1,1,2-Trichloroethane
n-Decane
1,2,3-Trichloropropane
1,1,1,2-Tetrachloroethane
1,1,2,2-Tetrachloroethane
1,2-Dibromoethane
Hexachloroethane
1,1-Dichloroethene
cis-1,2-Dichloroethene
trans-1,2-Dichloroethene
Trichloroethene
Tetrachloroethene
Benzene
Toluene
Styrene
Ethylbenzene
Xylenes, mixed
Methyl isobutyl ketone
Dibromomethane
n-Hexane
1,1-Dichloroethane
1,2-Dichloroethane
n-Heptane
n-Octane
Acrylonitrile
Furan
Tetrahydrofuran
1,4-Dioxane
Hexabromocyclododecane

In Submission or Preparation

Uranium
Di-isononylphthalate
DDT/DDE/DDD
PBDE 99
Deltamethrin

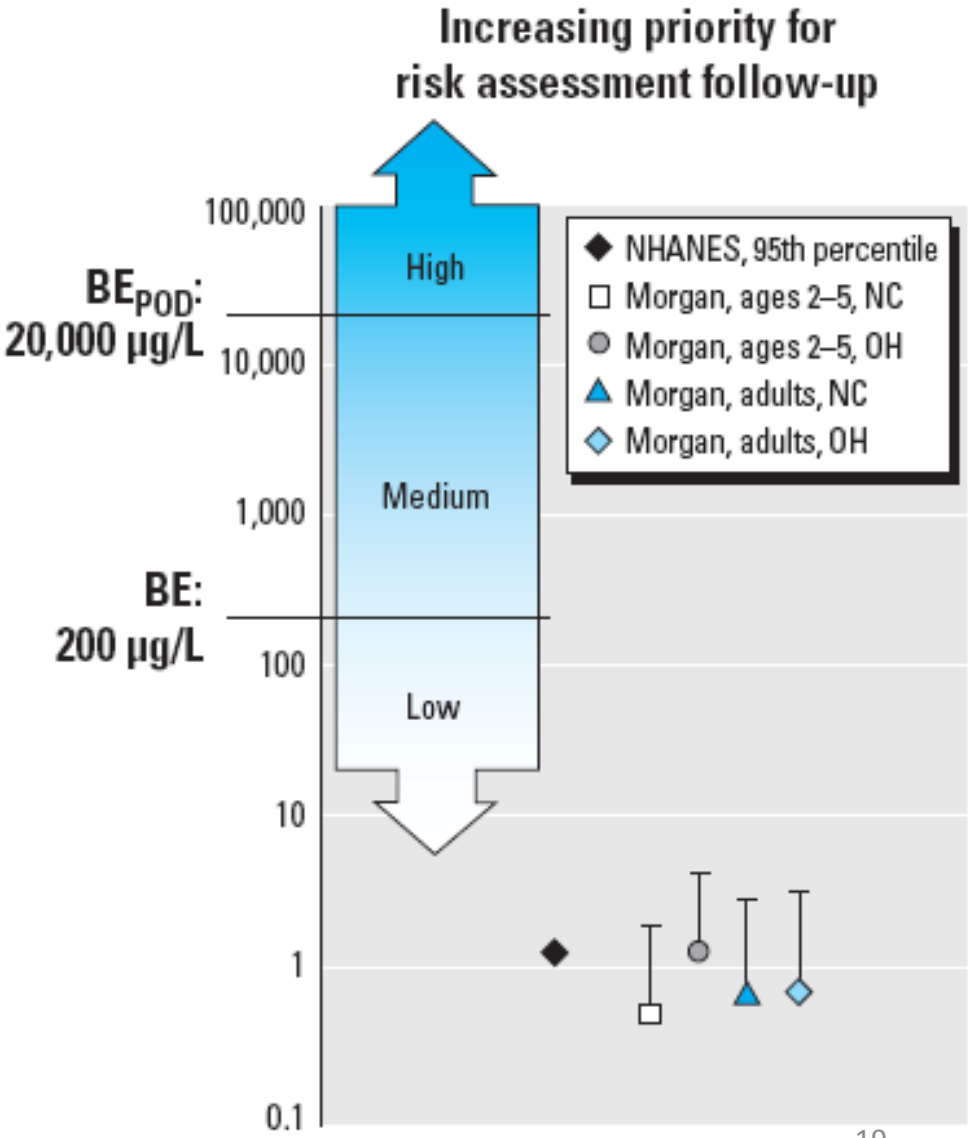
Examples of the Use of BE Values

2,4-Dichlorophenoxyacetic acid

- Herbicide with recent USEPA risk assessment
- RfD: 0.005 mg/kg-d
  - Derived from rat data
  - No-observed-effect level for bodyweight changes and biochemical endpoints: 5 mg/kg-d
  - 1000-fold UF applied
- Biomonitoring data for general population:

  <1 to 3 µg/L in urine
- Do these levels indicate exposures near or above the RfD?

2,4-Dichlorophenoxyacetic acid



Aylward, Morgan, Arbuckle, Barr, Burns, Alexander, Hays (2010; EHP 118:117-181)

BEs in the Risk Assessment Paradigm

- Compare estimated dose to RfD to estimate a "Hazard Quotient" (HQ):

$$HQ = \frac{Dose}{RfD}$$

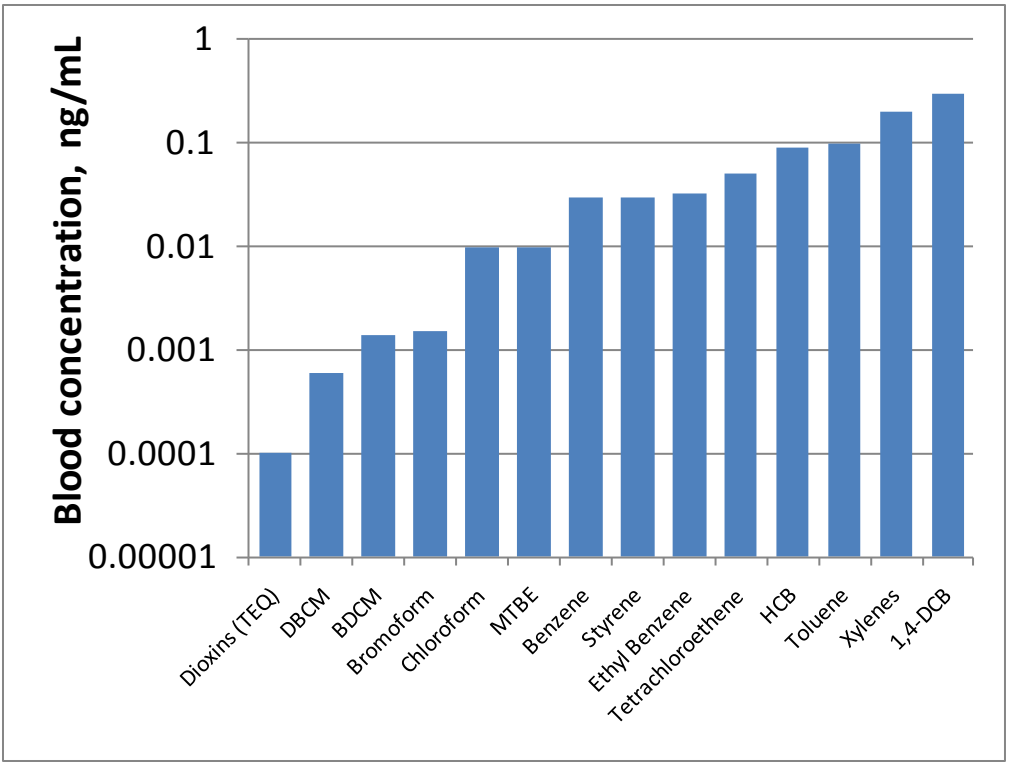
- Compare measured biomarker concentration to BE_{RfD}:

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

Allows comparison across chemicals of relative levels of exposure compared to screening value.

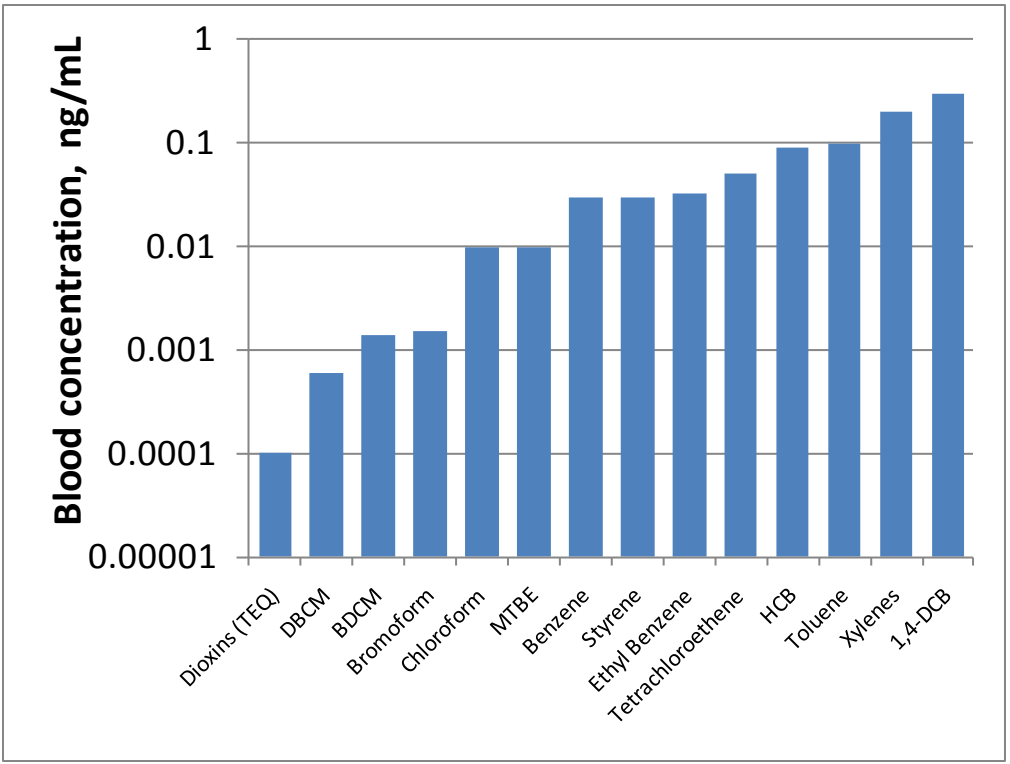
Prioritization Across Chemicals

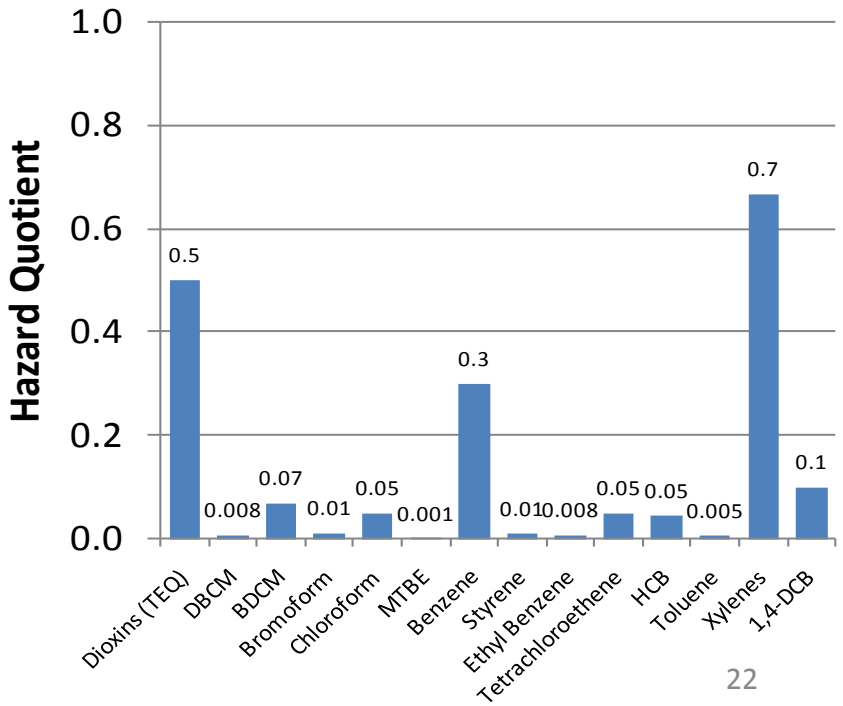
- CDC/NHANES measures >300 chemicals in blood or urine. Which ones are of greatest interest?
- Absolute concentrations tell one story…



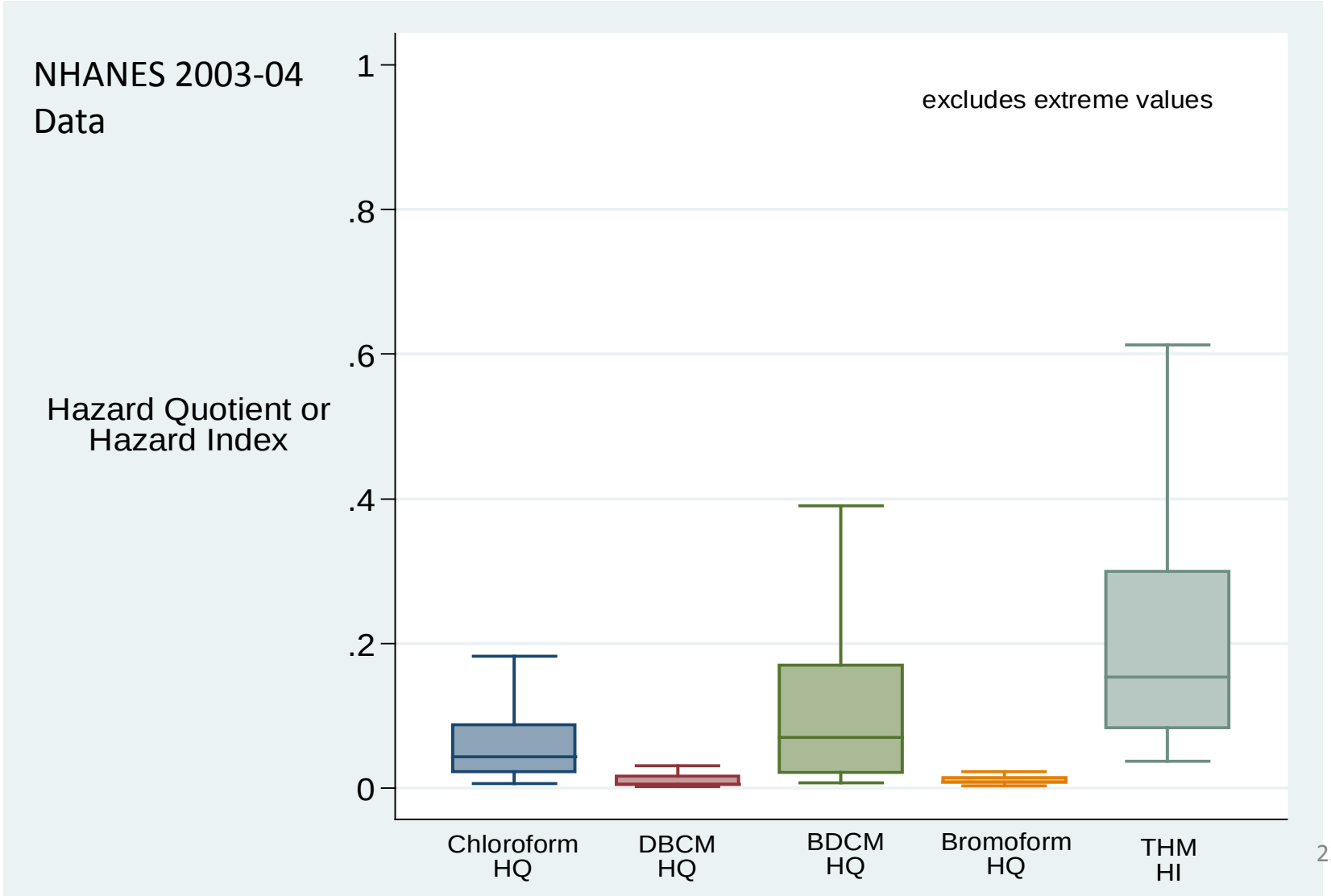
Prioritization Across Chemicals (cont'd)

- Hazard Quotients provide a different perspective
- Informed by the risk assessments for these compounds

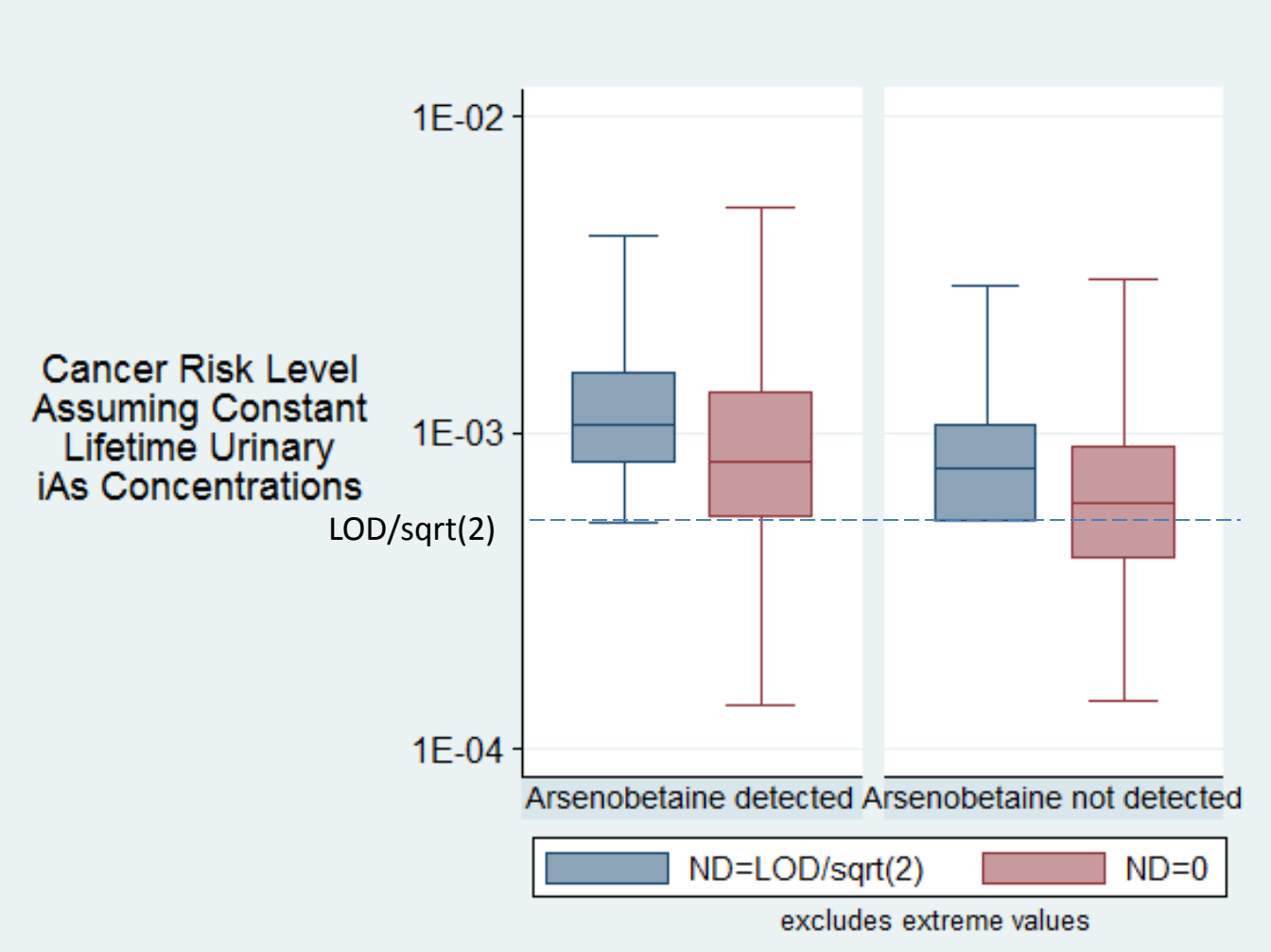




Combined Exposures - THMs in Blood Compared to BE Values



BEs and Risk Estimates
Urinary Inorganic Arsenic Species
NHANES 2007-2008



Next Steps

- BEs provide a risk assessment-based interpretation tool useful for
  - Risk assessors/risk managers
  - Public health officials

However,

- A more complete picture is needed for communication to physicians and individuals who receive biomonitoring results

Communicating to Individuals

- When biomonitoring results are conveyed to individuals, they will want to know:
  - Are my levels “high”?
  - How am I exposed, and how do I reduce exposure?
  - What health effect(s) does the chemical cause in people? In laboratory animals? At what levels?
- Physicians may be asked to interpret biomonitoring data for individual patients, but…
  - Few reliable resources
  - Available information is likely to be inappropriate in depth, detail, and focus
  - Physicians generally have limited training in principles of environmental health and risk assessment

Biomonitoring Interpretation Web Site Development

- Focus on physicians as the “front line” in interpretation for individuals
- Goal: Assemble chemical-specific web pages with reliable information on
  - Sources of exposure
  - Health effects
  - Biomarker-based exposure-response information
  - Links to additional information
- Challenges:
  - provide reliable, reviewed information
  - in an easily accessible format
  - for many chemicals, including perhaps a majority with little available data

Expert Workshop

- Planned for July, 2011
- Convene experts in clinical and occupational toxicology, risk communication, ethics, biomonitoring
- Work from draft case studies to develop guidelines for content, format, process
- Identify potential sponsoring agencies and organizations

Conclusions

- Biomonitoring has become a centerpiece of chemical exposure assessment
- BEs are a practical tool that can increase the value of chemical biomarker data
  - Prioritization of risk assessment and risk management efforts
  - Inform resource allocation for next-generation research efforts
- Additional work remains to develop and provide information to physicians and individuals