Application of Biomonitoring Data for Chemical Mixtures Assessment: Opportunities and Challenges

Presentation to the NAS Standing Committee on the Use of Emerging Science for Environmental Health Decisions

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SUMMIT TOXICOLOGY

Overview

- Characteristics of biomonitoring data for exposure and risk assessment of mixtures
- CDCP National Biomonitoring Program and NHANES data sets
- Interpreting biomonitoring data in a risk assessment framework
- Examples of application of biomonitoring data in mixtures assessment
- Tox21 applications
- Final comments and observations

Characteristics of Biomonitoring Data

The "Gold Standard"

Human Biomonitoring of Environmental Chemicals

Measuring chemicals in human tissues is the "gold standard" for assessing people's exposure to pollution

Ken Sexton, Larry L. Needham and James L. Pirkle

What chemicals in your daily routine should you be most concerned about? The volatile organic

mine the precise agent, the details of contact and the full extent of the affected population. Complicating matters,

sure also requires complex detective work to discover all kinds of details, including the chemical identity (for ex-

American Scientist, Vol. 92, p. 38, 2004

When is Biomonitoring Useful?

- When exposure is expected to be widespread and frequent in the population
  - Multi-pathway
  - Uncertainty regarding exposure sources
- In targeted studies
  - Specific populations
  - Controlled exposure situations

What Biomonitoring Can Tell Us About Chemical Exposures

- Presence or absence and levels of analyzed chemicals in biological media
  - At a given detection limit
- Trends over time
- Reflects simultaneous exposure to multiple chemicals
  - Reflects real-world distributions of both frequency and extent of exposure

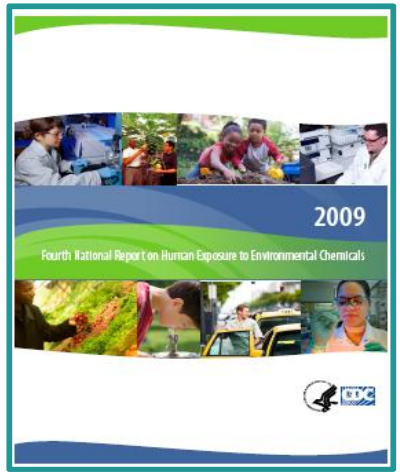
What Biomonitoring CANNOT Tell Us About Chemical Exposures

- Presence or absence of chemicals ***not*** analyzed for
- Risk of health effects
  - Requires a suitable toxicity benchmark for comparison
  - Requires understanding of longitudinal profile for individuals and relationship to toxicological endpoint(s) of interest

CDCP's NHANES Biomonitoring Data

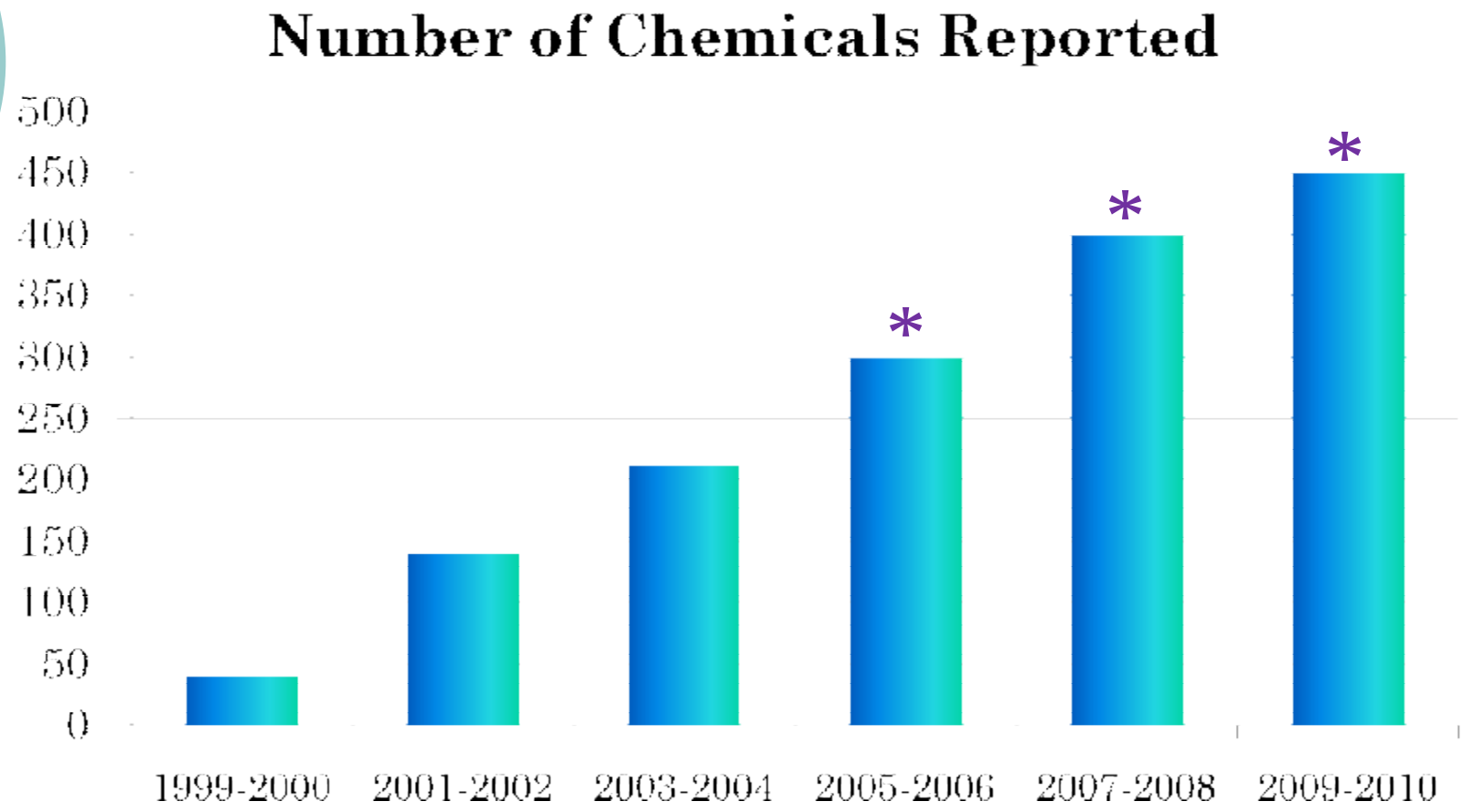
National Biomonitoring Program

- CDCP National Center for Environmental Health
- Chemical analysis of blood and urine samples from NHANES



- Continuous sample collection, ~5,000 individuals per year, population-representative
- Datasets released online and summarized in scientific publications, online summaries
- Can be merged with demographic and health endpoint data collected in NHANES

Ongoing NHANES Biomonitoring



Chemical Classes Included in NHANES

Metals

Environmental Phenols

Phthalates

Perfluorochemicals

Brominated Flame Retardants

Organochlorines

Organophosphate Insecticides

Fungicides

Acrylamide

Trihalomethanes

Pyrethroids

Phytoestrogens

PCBs

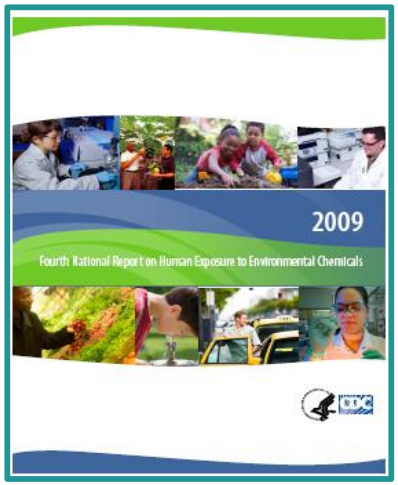
Dioxins

PAHs

Herbicides

VOCs

Perchlorate

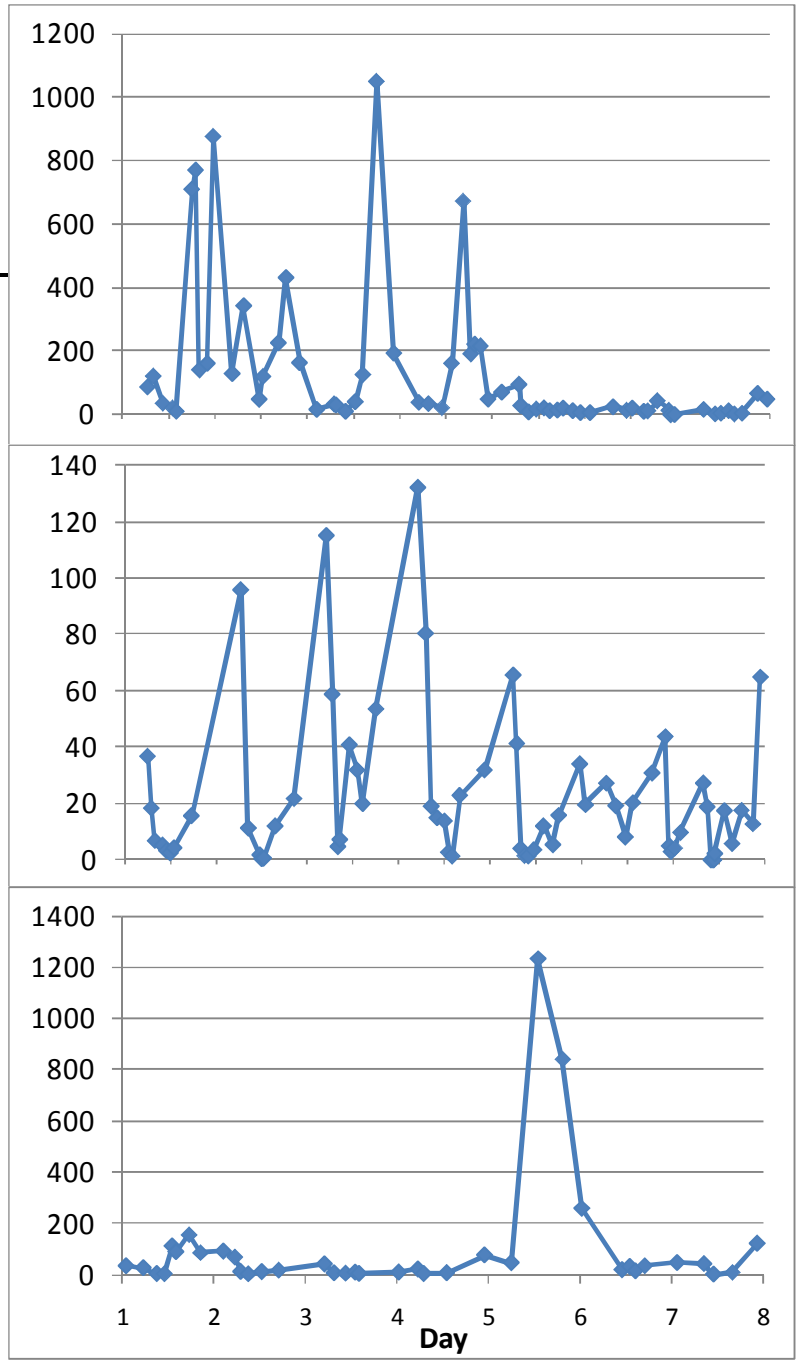


Limitations of NHANES Datasets

- Not all chemicals are measured in all individuals
- Limited data on children
- Issues with analytical sensitivity (small biological sample volumes available for analysis)
- Urinary analytes for many chemicals - perhaps less informative than blood-based analytes from a toxicological perspective
- Some analytes are non-specific
- Long lead-time for data release
- Many analytes are highly transient, reflecting the short biological half-lives of the chemicals of interest

Transient Biomarkers

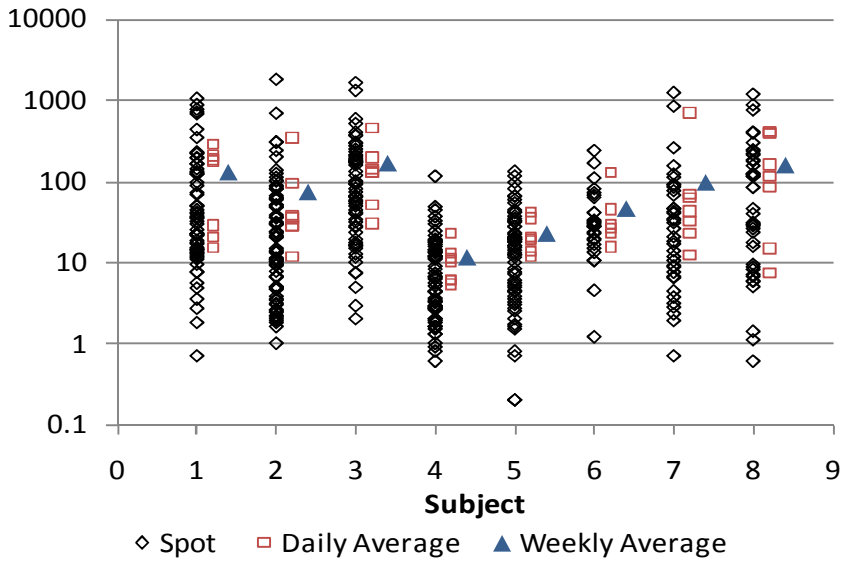
- Urinary DEHP metabolite with HL of 8-10 hrs
- Substantial within- and across day variation in spot biomarker concentrations (up to 100x within day)
  - Function of exposure frequency, half-life
- Risk assessment typically focuses on exposure levels on daily- or longer- time scales

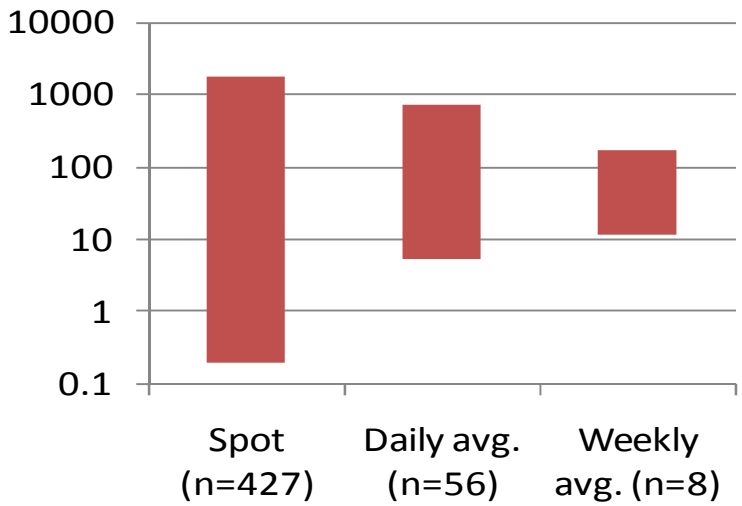


Data from CDC; see Preau et al. 2010; Environ Health Perspect. 118(12):1748-54

Transient Biomarkers (cont'd)

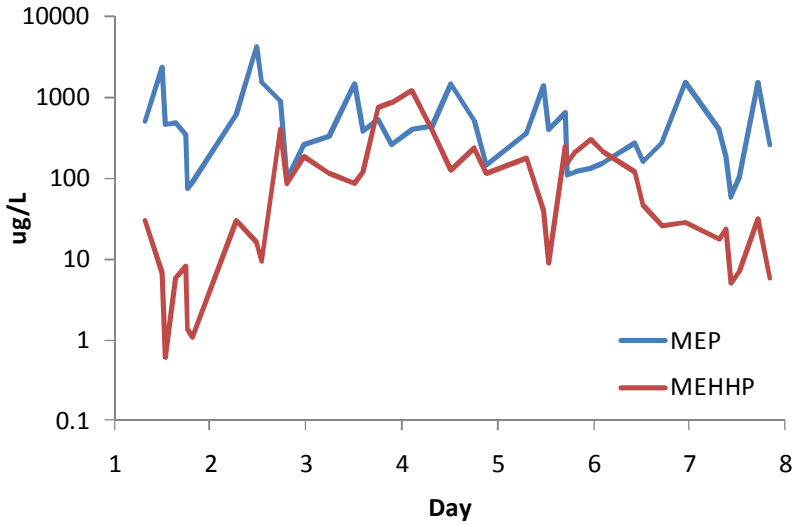
- Biomarker spot sample concentration is far more variable than daily or longer-term avg. conc. and underlying dose rates
- Focus on tails of distributions for spot concentrations likely to be misleading

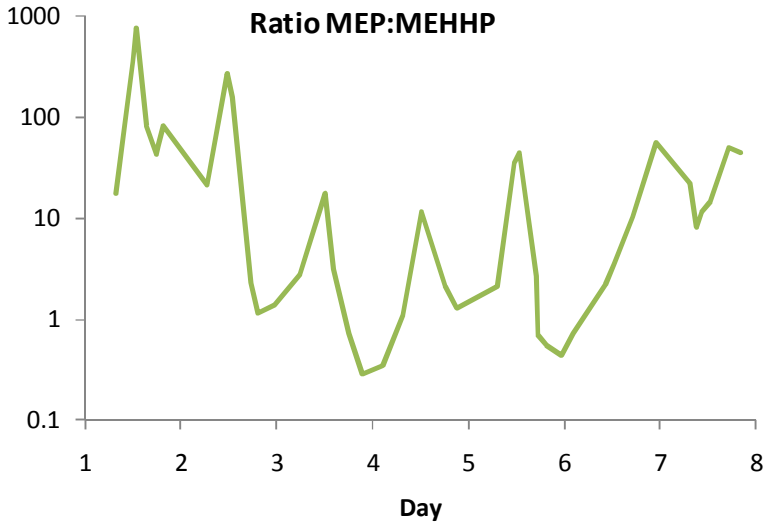




Transient Biomarkers (cont'd)

- When considering mixtures of transient biomarkers, spot samples vary widely
- Consider how instantaneous concentrations reflect longer-term averages and exposures





Interpreting Biomonitoring Data in a Risk Assessment Framework

Conventional Risk Assessment

BMDL, CSF
mg/kg-d

mg/kg-d

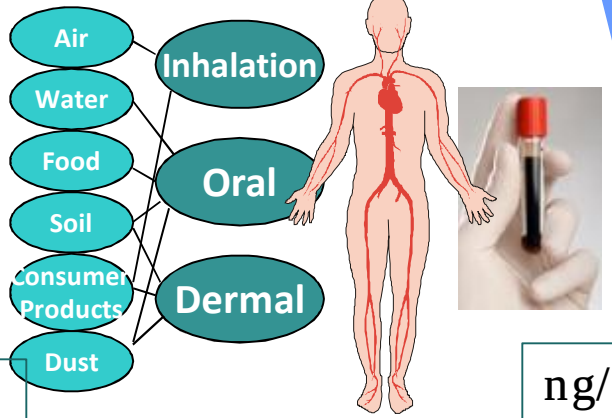
Hazard and Po cy Asse ent

Exposure Assessment

Risk Estimation

Biomonitoring Equivalents

ng/mL



Reverse Dosimetry

ng/mL

External Exposure-Based Potency Estimates

"Point of Departure"

NOAEL/LOAEL or BMD

Uncertainty Factors

100-1,000

"Tolerable" Human Dose – RfD, TDI, Risk-Specific Dose

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

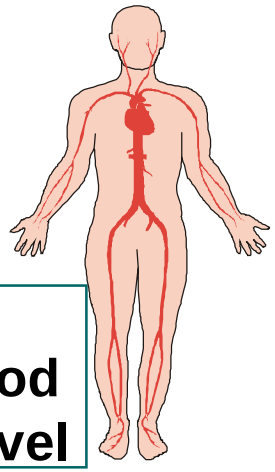
“Biomonitoring Equivalent”

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

NOAEL/LOAEL Or BMD

“Tolerable” Human Dose – RfD

BE_{RfD} Human Blood Or Urine Level



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. 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

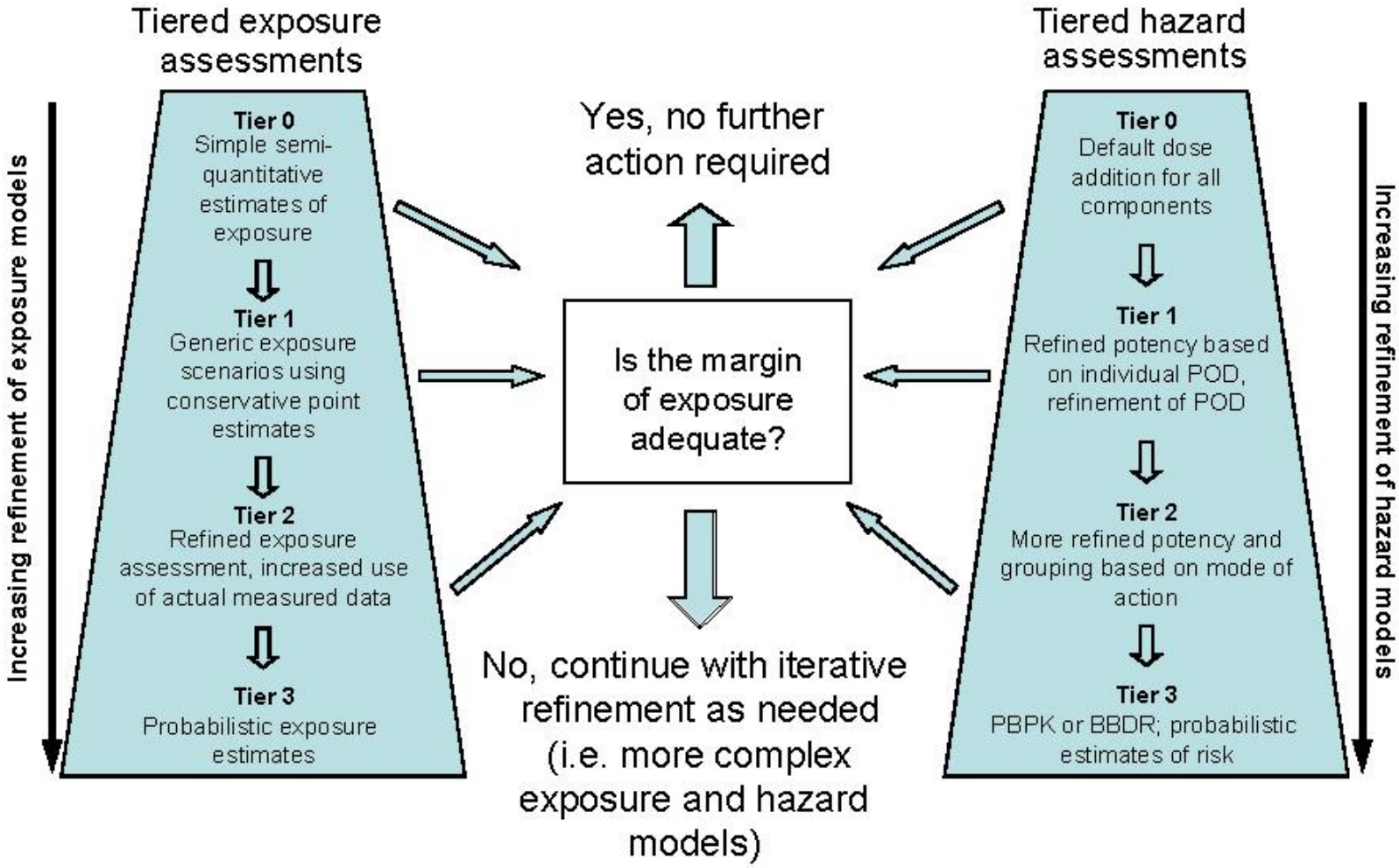
n-Nonane
1,1,1-Trichloroethane
1,1,2-Trichloroethane
n-Decane
1,2,3-Trichloropropane
1,1,1,2-Tetrachloroethane
1,1,2,2-Tetrachloroethane
1,2-Dibromoethane
Hexachloroethane
1,1-Dichloroethene
cis-1,2-Dichloroethene
trans-1,2-Dichloroethene

Trichloroethene
Tetrachloroethene
Benzene
Toluene
Styrene
Ethylbenzene
Xylenes, mixed

Dibromomethane
n-Hexane
1,1-Dichloroethane
1,2-Dichloroethane
n-Heptane
n-Octane
Acrylonitrile
Furan
Tetrahydrofuran
1,4-Dioxane
Hexabromocyclododecane
Methyl-tert-butyl ether (MTBE)
Methyl isobutyl ketone
Di-isononylphthalate
DDT/DDE/DDD
PBDE 99
Deltamethrin

Examples of Mixtures Assessment Based on Biomonitoring Data

Risk Assessment of Combined Exposure to Multiple Chemicals – IPCS Framework



Published in adapted form in Meek et al. (in press) Reg. Tox. Pharm. doi:10.1016/j.yrtph.2011.03.010

Dose Addition Assessment of Combined Exposure to Multiple Chemicals

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

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

- Combined exposures- Dose addition:

$$HI = \sum_{i=1}^{n} HQ_i$$

Screening value: HI<1

Hazard Quotient/Index Approach to Biomonitoring Data for Multiple Chemicals

- Compare biomarker concentration to BE_{RfD} to estimate a "Hazard Quotient" (HQ) for each chemical:

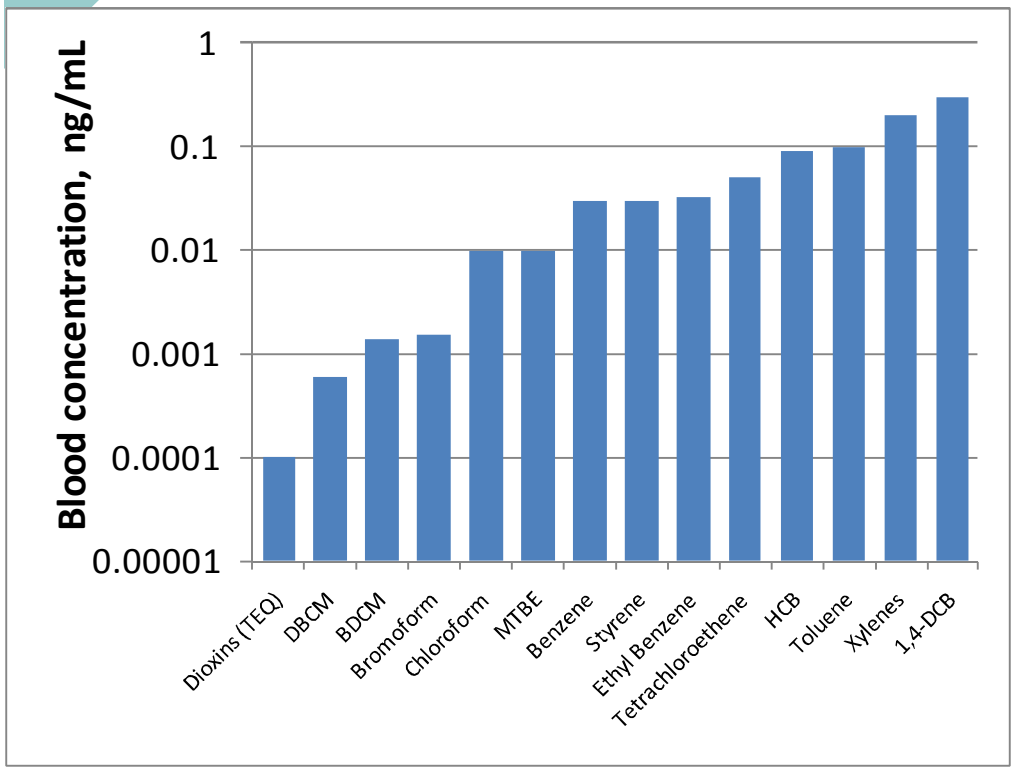
$$HQ = \frac{[Biomarker]}{BE_{RfD}}$$

- Sum across chemicals for Hazard Index (HI):

$$HI = \sum_{i=1}^{n} HQ_i$$

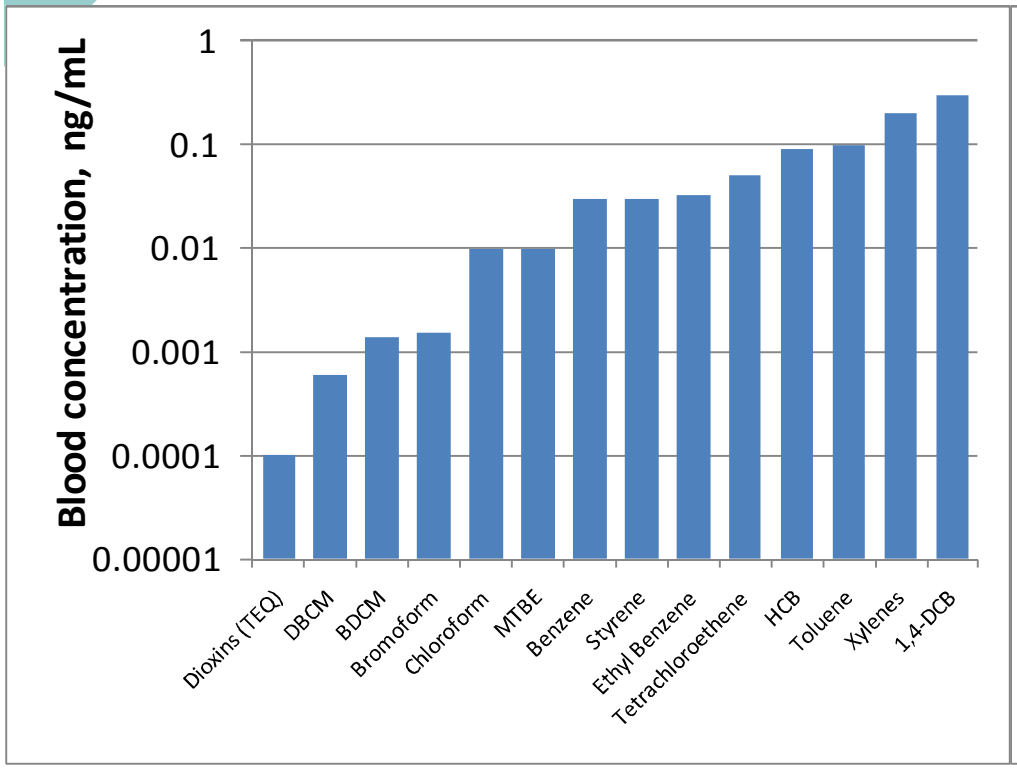
Prioritization Across Chemicals

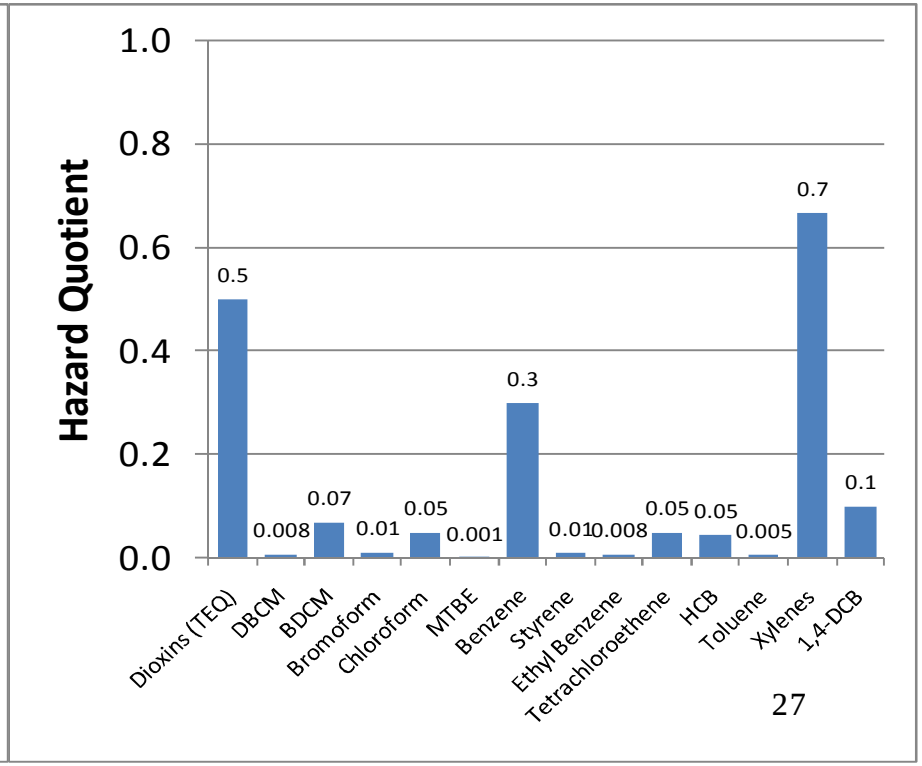
- CDC/NHANES measures >300 chemicals in blood or urine. Which ones are of greatest interest?
- Absolute concentrations tell one story…



Prioritization Across Chemicals (cont'd)

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

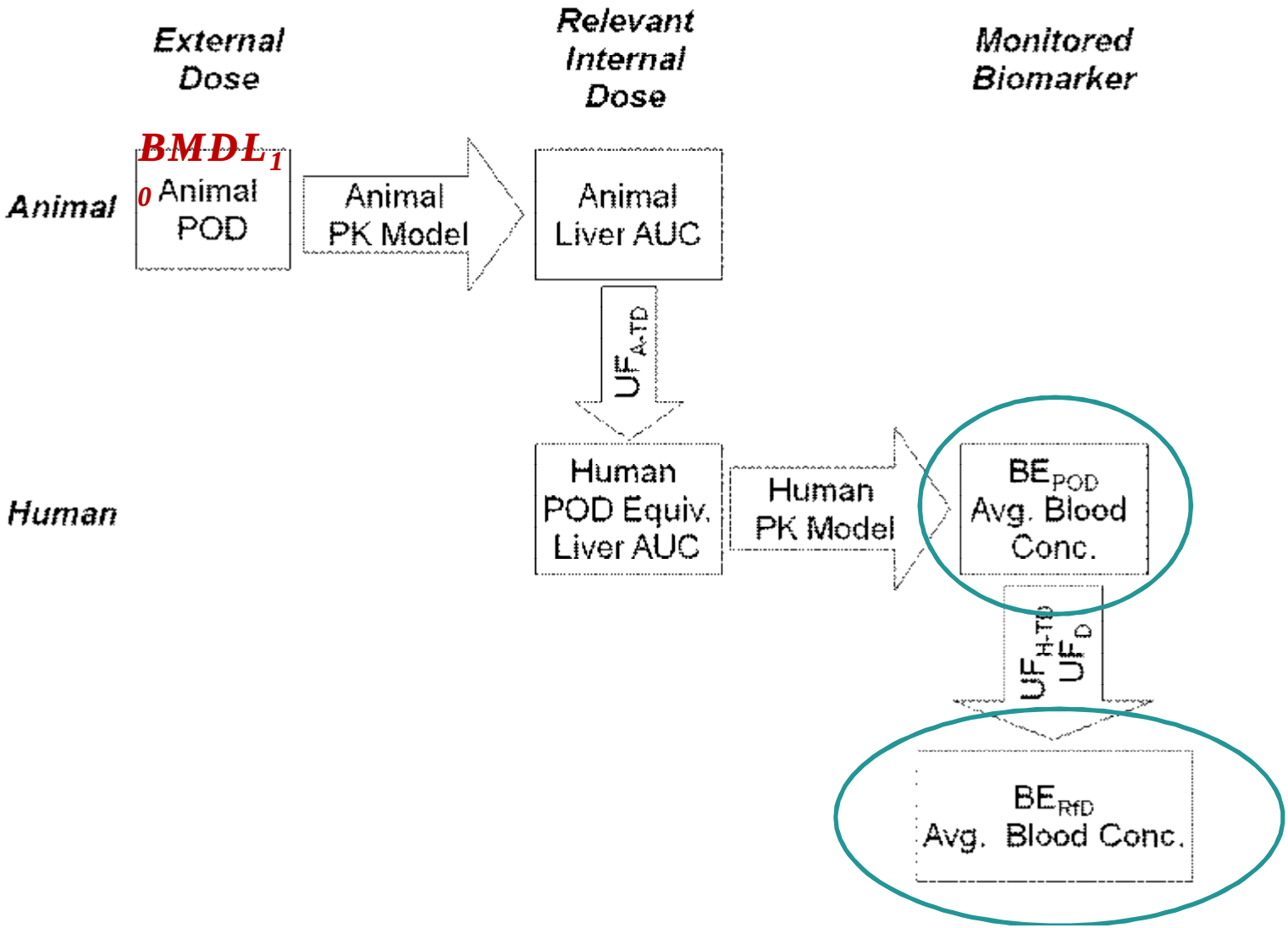




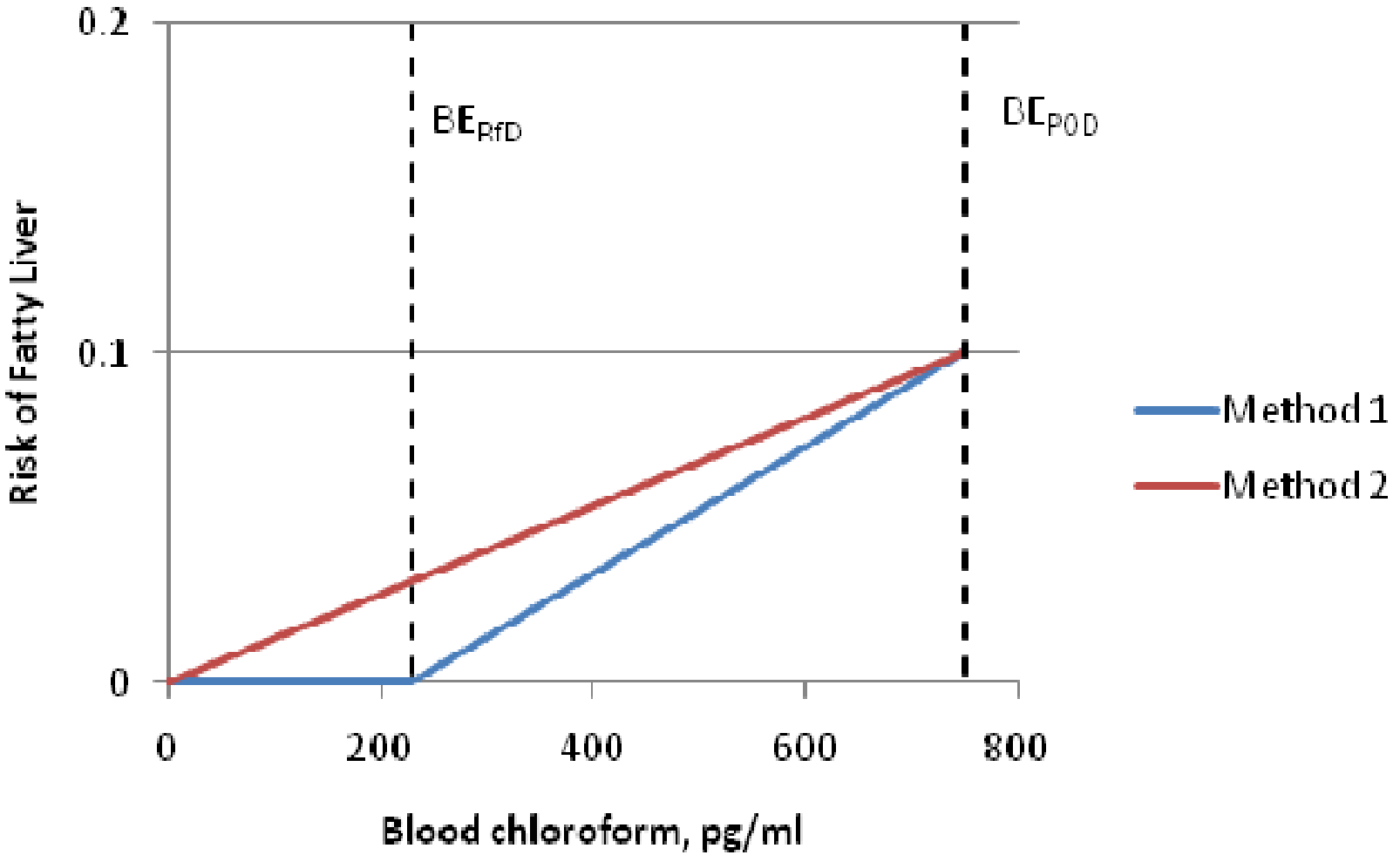
THMs Non-Cancer Critical Effects (USEPA 2001, 2005)

- Critical effect: Risk of fatty liver degeneration in rats and dogs
  - Quantal measure: yes/no
  - Point of Departure: $BMDL_{10}$
- Non-alcoholic fatty liver disease prevalent in adult US population (~10%)
- PBPK models available for humans and experimental species

BE Derivation for THMs



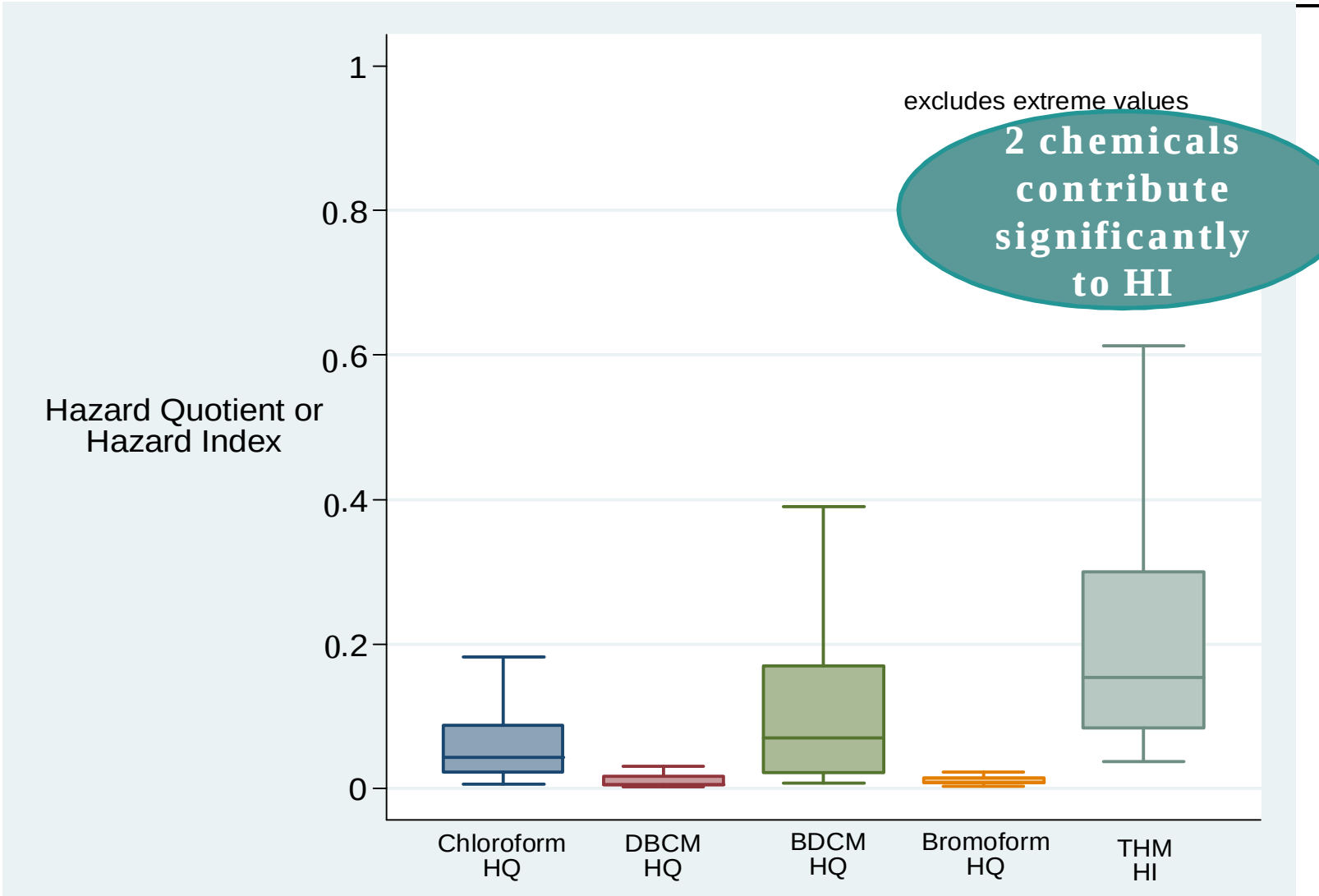
Low-Dose Extrapolation: 2 Approaches



NHANES 2003-2004 Blood THM Data

- Population representative sampling
- Allows assessment of simultaneous internal blood concentrations of all four THMs on an individual-by-individual basis
- Highly transient biomarkers

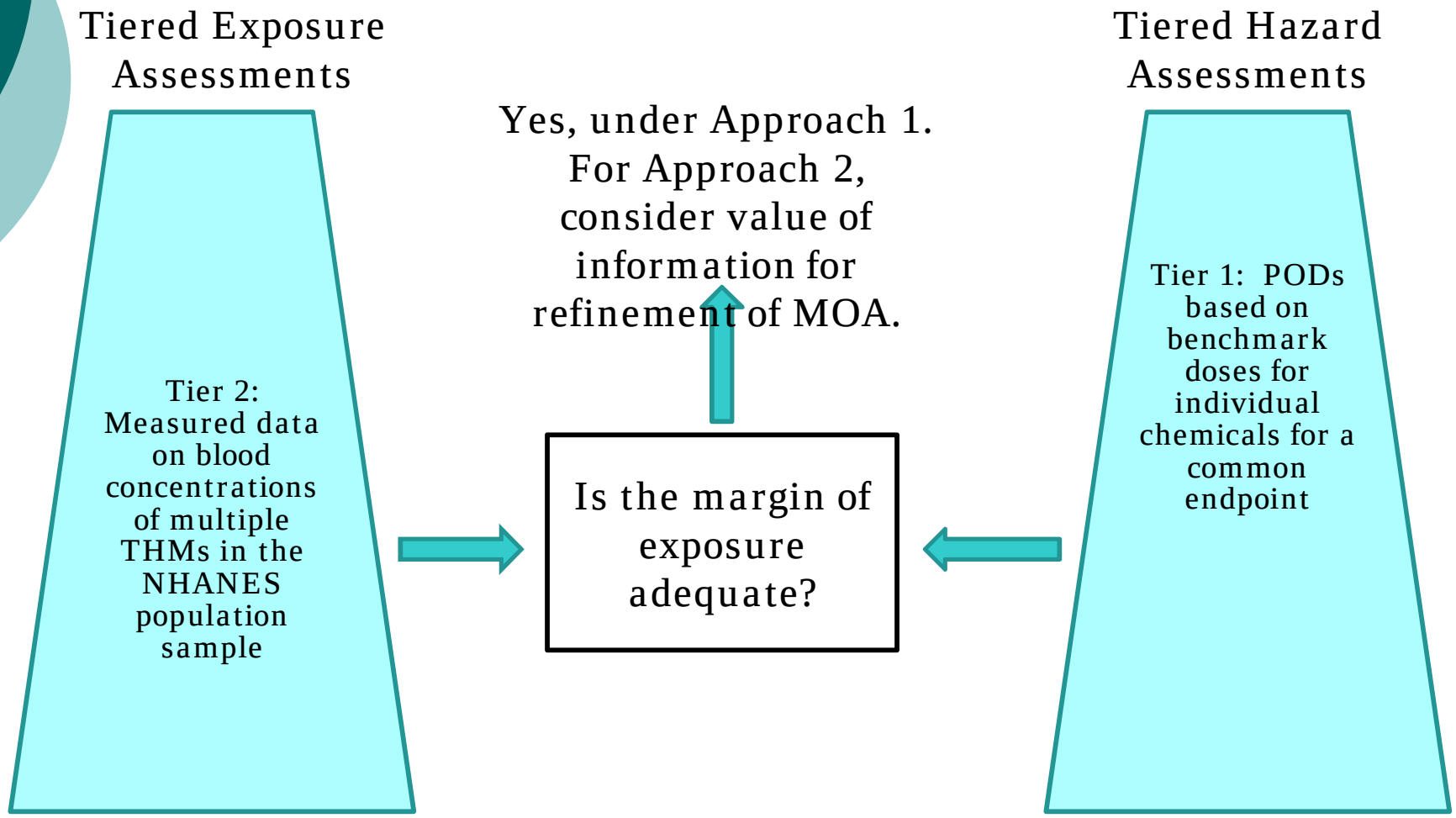
Hazard Quotients and Indices Across Individuals Based on NHANES Data



Estimated Percentiles: Risk of Fatty Liver

Chemical	Percentile 25th	50th	75th	90th	95th
Method 1 (zero risk @ RfD)					
Chloroform	0	0	0	0	0
DBCM	0	0	0	0	0
BDCM	0	0	0	0	0
TBM	0	0	0	0	0
Sum of Four THMs[a]	0	0	0	0	0
Method 2 (zero risk @ zero)					
Chloroform	0.0007	0.0013	0.0026	0.0046	0.0065
DBCM	<LOD	<LOD	0.0005	0.0013	0.0027
BDCM	<LOD	0.0007	0.0018	0.0033	0.005
TBM	<LOD	<LOD	0.0004	0.0008	0.0025
Sum of Four THMs, ND= LOD/sqrt(2)	0.0018	0.0031	0.0057	0.0096	0.015

IPCS Framework Placement

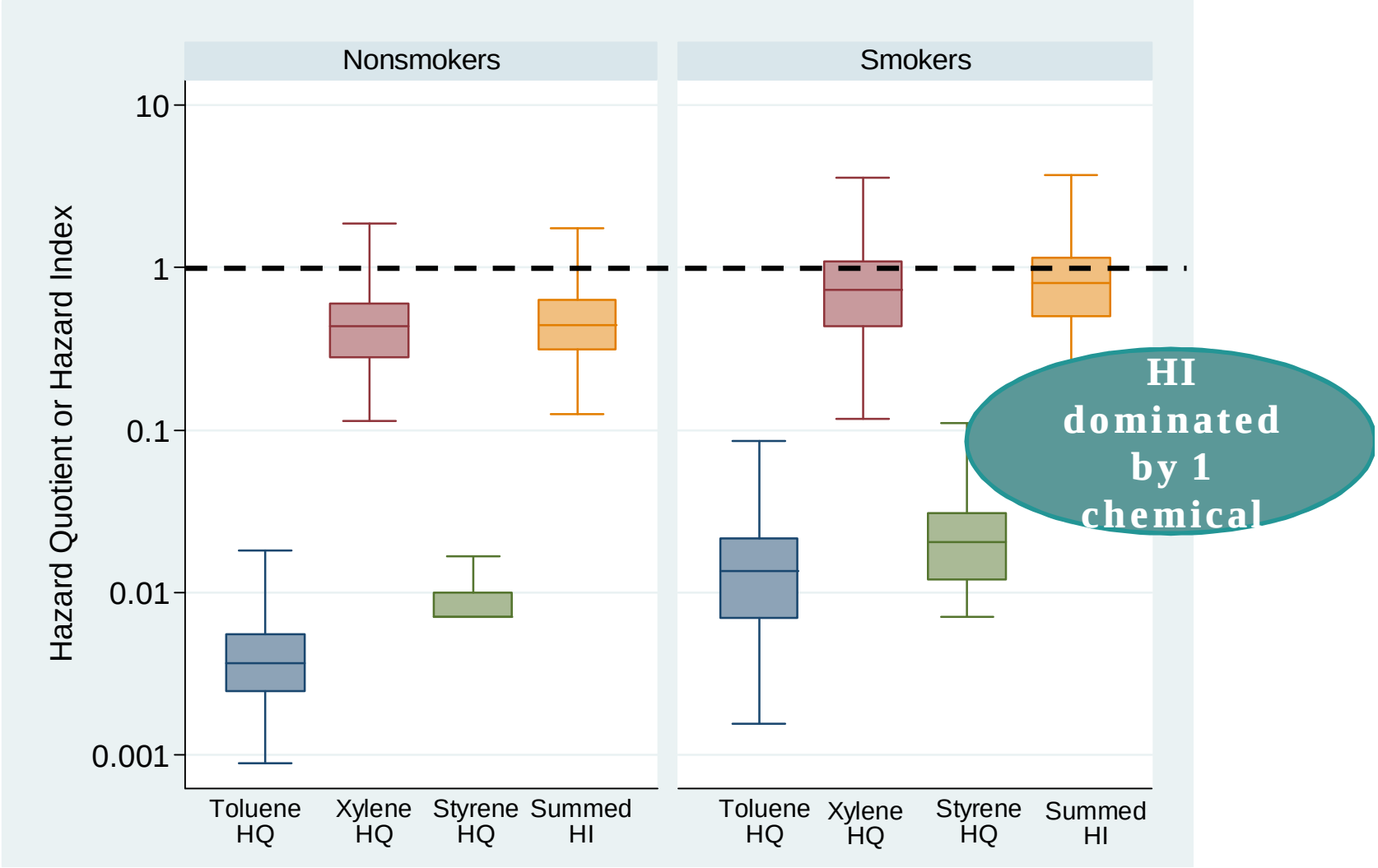


Volatile Organic Compounds

- NHANES measured ~40 VOCs (2003-2004)
- Small subset with detection rates>20%
  - Benzene, ethylbenzene, toluene, xylenes, styrene, 1,4-dichlorobenzene, MTBE
- 3 of these with neurotoxicity as a critical endpoint

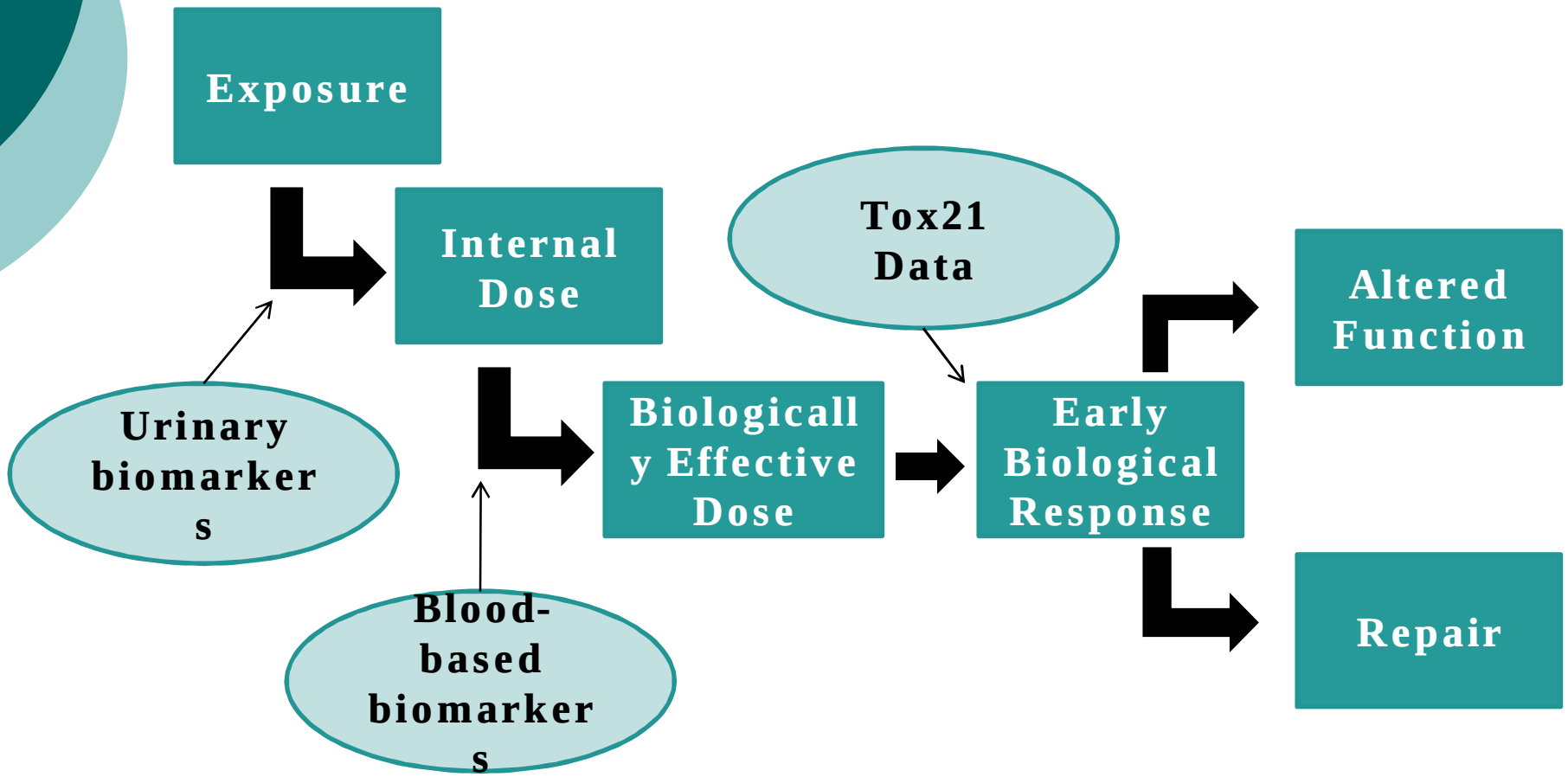
Compound	Critical Endpoint	RfC, mg/m^3	Corresponding Steady-State Blood Concentration, ug/L
Styrene	Neurological effects	1	3
Toluene	Neurological	5	20

Hazard Quotients and Indices – NHANES Blood VOC Data

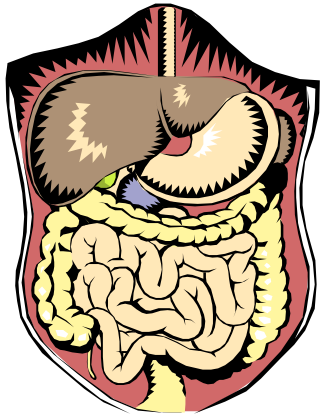


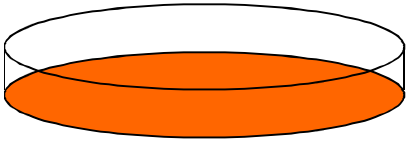
Biomonitoring Data and Tox21

Exposure-Response Continuum



Biomonitoring Data Can Inform Design and Interpretation of Tox21 Assays



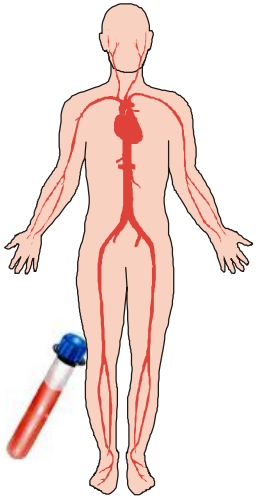


In vitro benchmark concentration

Partition coefficient

In vivo target tissue concentration

Partition coefficient



In vivo blood concentrations

Relevant exposures (internal concentrations) can help bound concentrations and mixtures of interest in *in vitro* tox test systems

Tox21 Applications of Biomonitoring Data

- Relevant mixture identification
  - *Qualitative:* Presence of potentially relevant mixture components
  - *Quantitative:* Environmentally relevant concentrations, proportions
- Various biomonitoring data sources
  - NHANES
  - Targeted studies
  - Pooled sample studies
- Blood-based data are of direct relevance; urinary data less relevant

Biomonitoring and Tox 21 Approaches to Mixtures

Hazard Identification	Relative Potency Assessment	Exposure Assessment	Hazard Quotient or MCR Approach
¡ Identify compounds of interest for a given toxicity endpoint or pathway based on – Conventional toxicology – Tox21 Assays – QSAR	¡ Apply Tox21 tests to identify active concentrations ¡ Rank compounds of interest with respect to relative potency for pathways of interest ¡ Or, test real-world mixtures identified from biomonitoring data in Tox 21 assays at relevant concentrations and	¡ Analyze blood or serum for compounds of interest – Pooled samples – NHANES population data	¡ Apply relative potencies from Tox21 to measured concentrations to calculate HQs ¡ Assess whether one or a few chemicals dominate HI, or whether a broader suite is relevant ¡ Assess whether HI approaches 1 – Proceed to higher tiers of mixtures assessment approaches

Tox21 and Biomonitoring in Risk Assessment

BMDL, CSF mg/kg-d

mg/kg-d

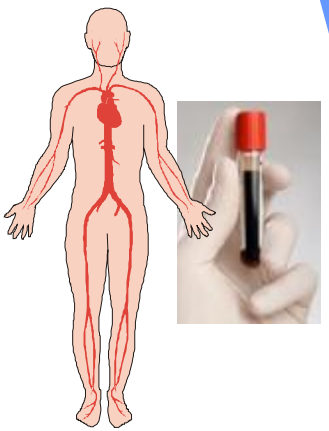
Hazard and Potency Assessment

Exposure Assessment

Risk Estimation

Tox21-Derived Hazard, Potency Estimates

ng/mL



ng/mL

Final Thoughts

- Biomonitoring is an exposure tool
  - does not solve challenges associated with toxicological assessment of mixtures (validity of additivity, linear extrapolation of dose-response, interactions, pathway vs. endpoint vs. MOA, etc.)

HOWEVER…

- Biomonitoring data provide a reflection of exposure directly relevant to
  - Internal dose-based risk assessments
  - Tox21 assays
- *Relevant* mixtures- qualitative and quantitative- can be identified based on biomonitoring data