Risk Assessment of Exposure to Trihalomethane Drinking Water Disinfection By-Products: Use of Biomonitoring Equivalents and Biomonitoring Data from NHANES

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Lesa L. Aylward

Sean M. Hays

Chris R. Kirman

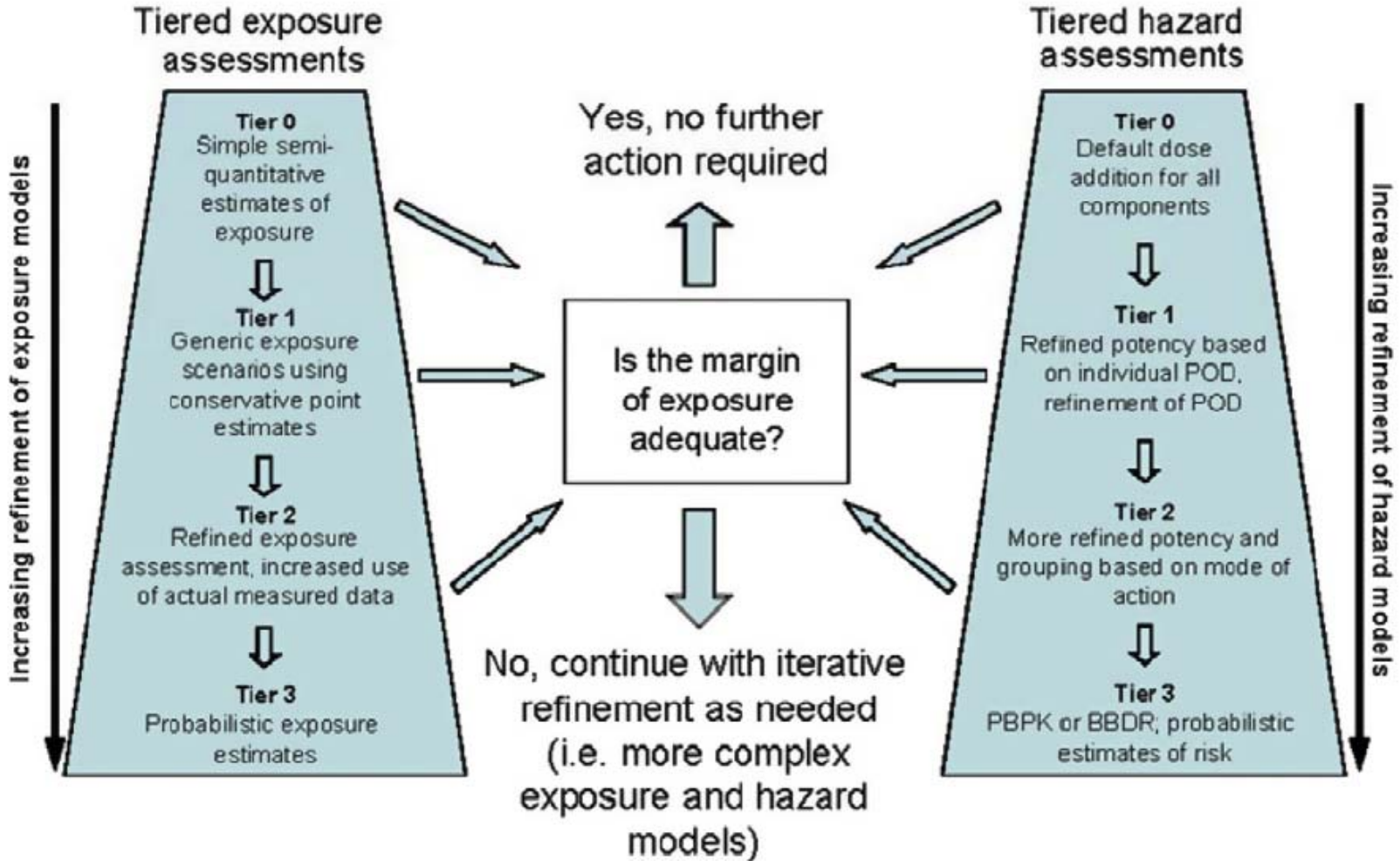
SUMMIT TOXICOLOGY

Purpose and Approach

- Case Study developed for the Alliance for Risk Assessment workshop series "*Beyond 'Science and Decisions': From Issue Identification to Dose-Response Assessment*"
- Goals:
  - Conduct a screening-level internal dose-based risk assessment of potential non-cancer risks from population THM exposures
  - Demonstrate use of internal dose measures for both
    - Dose-response – Biomonitoring Equivalents (BEs)
    - Exposure metrics – NHANES blood THM data
  - Apply WHO/IPCS Framework for assessing risks from combined exposure to multiple chemicals for screening four THMs ("Assessment Group") in blood

WHO/IPCS Risk Assessment of Combined Exposure to Multiple Chemicals

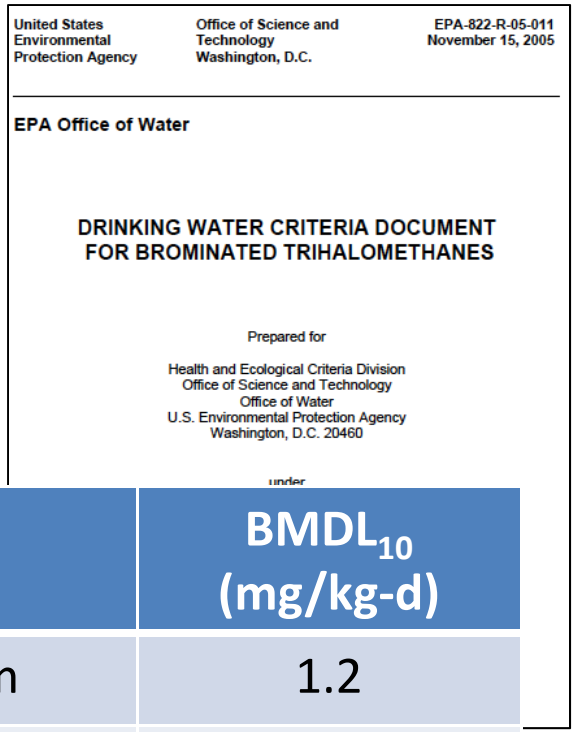
(*Meek et al. 2011, Reg. Toxicol. Pharmacol.*)



Dose-Response: THMs Non-Cancer Critical Effects

(USEPA 2001, 2006)

- Critical effect: Fatty liver degeneration* in rats and dogs
  - Quantal measure: yes/no
  - Point of Departure: $BMDL_{10}$
- No explicit MOA analysis or formal relative potency assessment *(IPCS Tier 1)*
  - But similar pathology, and similar potencies



United States Environmental Protection Agency | Office of Science and Technology Washington, D.C. | EPA-822-R-05-011 November 15, 2005

EPA Office of Water

DRINKING WATER CRITERIA DOCUMENT FOR BROMINATED TRIHALOMETHANES

Prepared for

Health and Ecological Criteria Division
Office of Science and Technology
Office of Water
U.S. Environmental Protection Agency
Washington, D.C. 20460

under

THM	$BMDL_{10}$ (mg/kg-d)
Chloroform	1.2
DBCM	1.6
BDCM	0.8
Bromoform	2.6

* *For bromoform, hepatic vacuolization*

Relevance of THM Non-Cancer Critical Effects

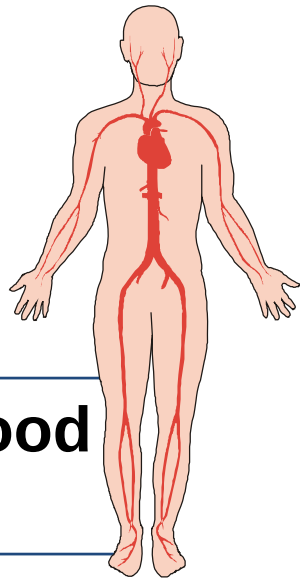
- Non-alcoholic fatty liver disease prevalent in adult US population (~10%) *(Clark 2006, J. Clin. Gastroenterol. 40(Suppl. 1):S5)*
  - Risk factors include obesity, diabetes, age
  - Range of severity: benign to clinically adverse
  - Case of interest in the context of Silver Book considerations: high background prevalence of endpoint

External Dose vs. Biomarker Concentrations

Rat Dose NOAEL/LOAEL

Safety Factors

"Tolerable" Human Dose – RfD, TDI



Human Blood Level

“Biomonitoring Equivalent”

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

Hays et al. 2008; Reg. Tox. Pharm. 51 (3 Suppl. 1):S4.

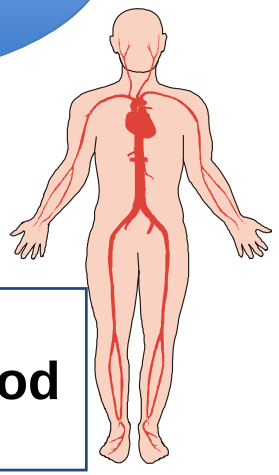
Rat Dose NOAEL/LOAEL

Tolerable Human Dose – RfD

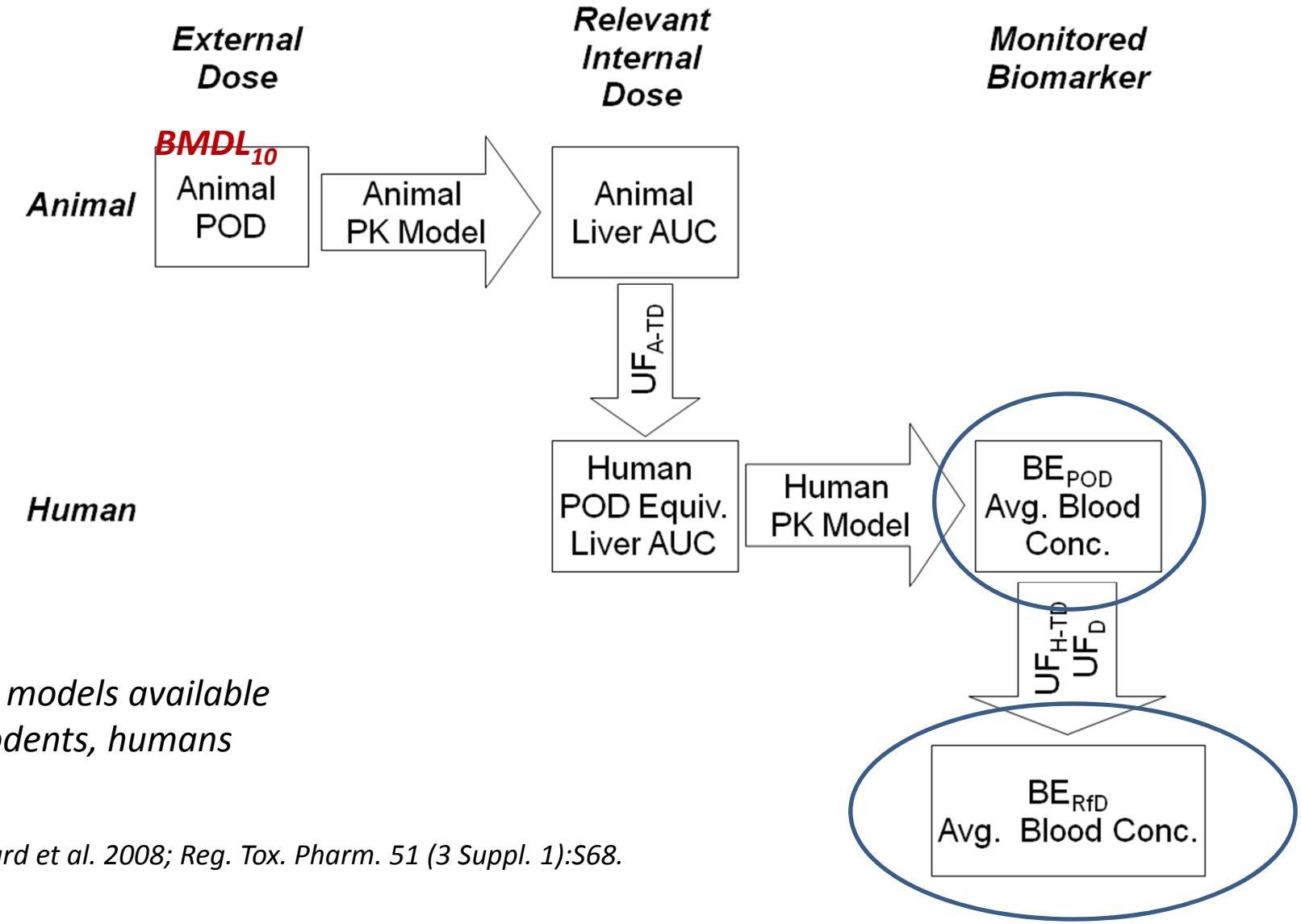
PK data or model

BE_{RfD} Human Blood Level

Screening tool!



BE Derivation for THMs

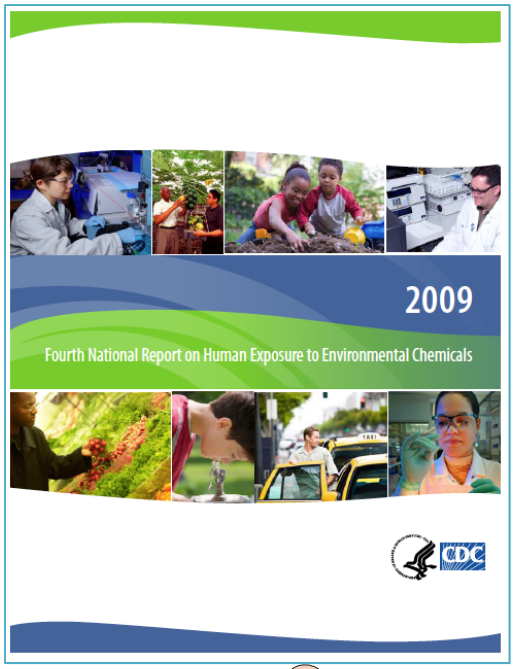


PBPK models available for rodents, humans

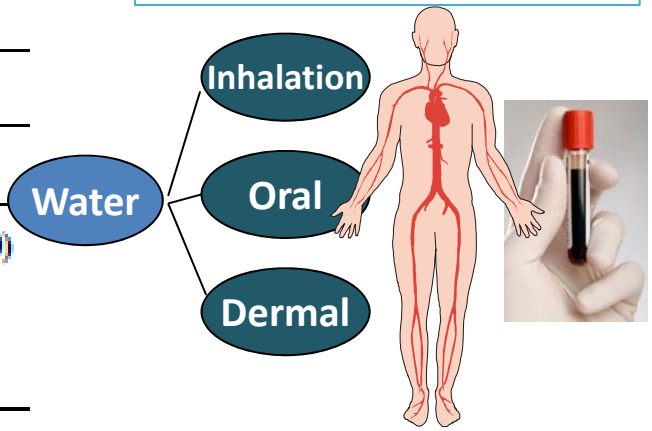
Aylward et al. 2008; Reg. Tox. Pharm. 51 (3 Suppl. 1):S68.

Exposure Assessment: NHANES 2003-2004 Blood THM Data

- Population-representative sampling
- Reflects exposure from all routes and pathways of exposure
- Allows assessment of simultaneous internal blood concentrations of all four THMs on an individual-by-individual basis *(IPCS Tier 2)*
- Highly transient biomarkers



	Blood THM levels, pg/ml (95% CI[a])	
	Median	95th percentile
Chloroform	10.0 (9.0, 10.6)	50.0 (43.0, 56.0)
Bromodichloromethane	1.4 (1.2, 1.5)	9.5 (8.0, 11.6)
Dibromochloromethane	< LOD[b]	7.2 (6.3, 9.1)
Bromoform	< LOD[c]	6.4 (5.1, 7.8)



LaKind et al. 2010; JESEE 20:255

Two Risk Assessment Approaches Investigated

- Hazard quotient/Hazard index approach
  - Does not provide estimates of risk, just assessment of above/below RfD
- Low dose risk extrapolation
  - Two approaches

Hazard Quotient/Hazard Index Approach

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

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

- Compare measured biomarker concentration to BE_{RfD}:

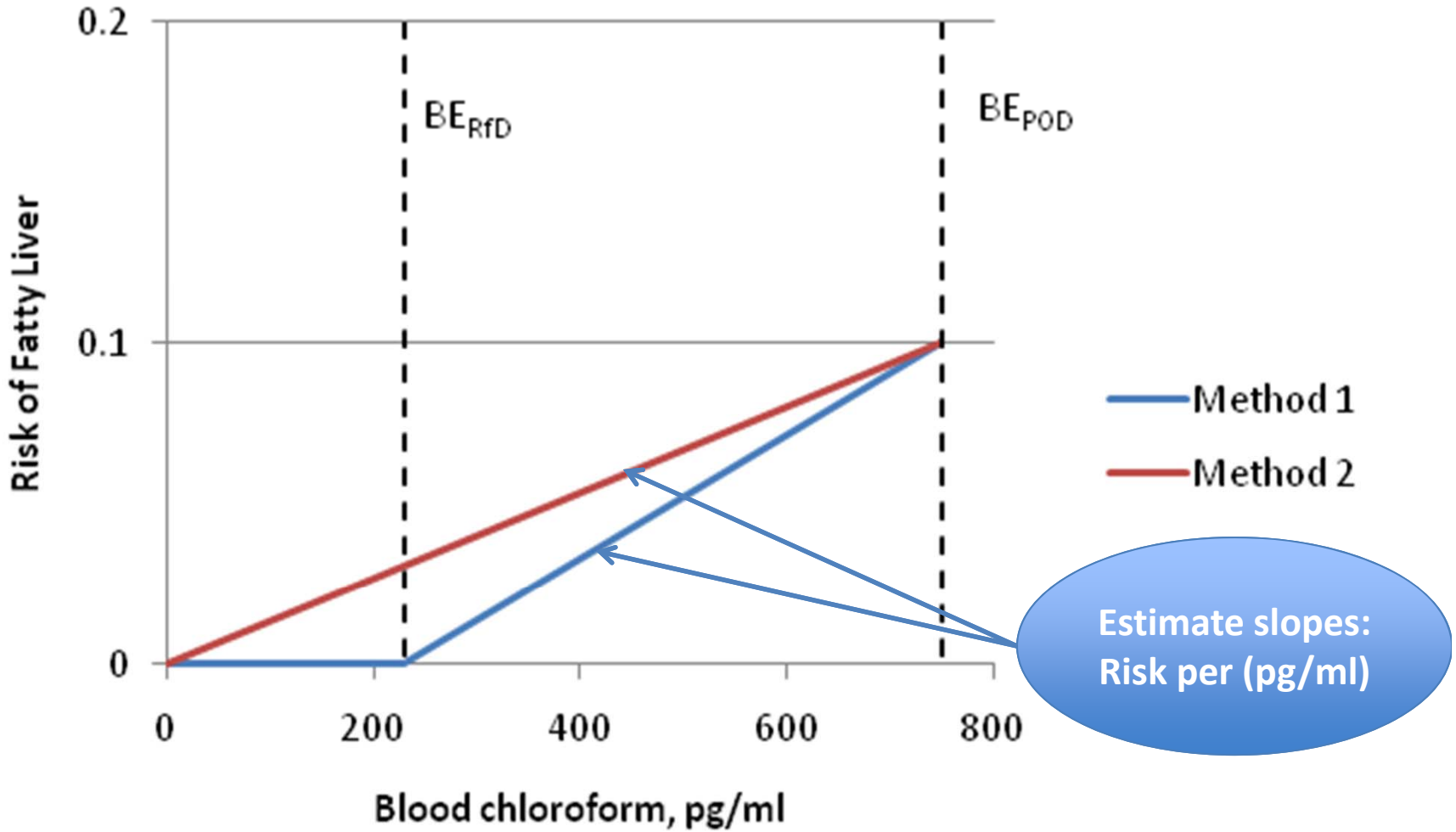
$$HQ = \frac{[Biomarker]}{BE_{RfD}}$$

- Sum across THMs (IPCS Tier 1-2 approach; assumes dose addition):

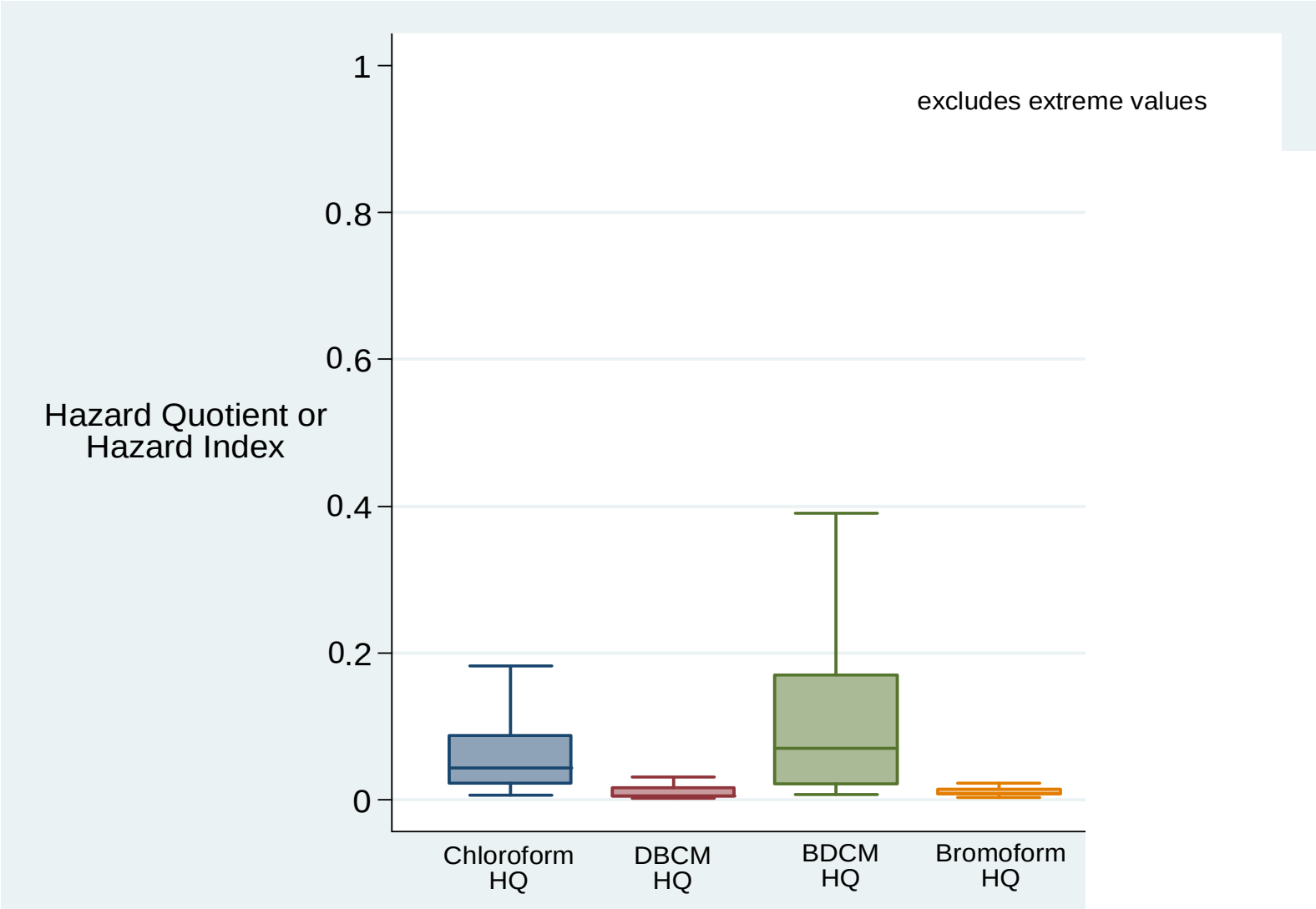
$$HI = \sum_{i=1}^{4} \frac{[THM_i]}{BE_{RfD\_i}}$$

Calculated for each individual in the NHANES dataset

Low-Dose Extrapolation: Two Approaches



Results: Hazard Indices, Quotients Across Individuals Based on NHANES Data

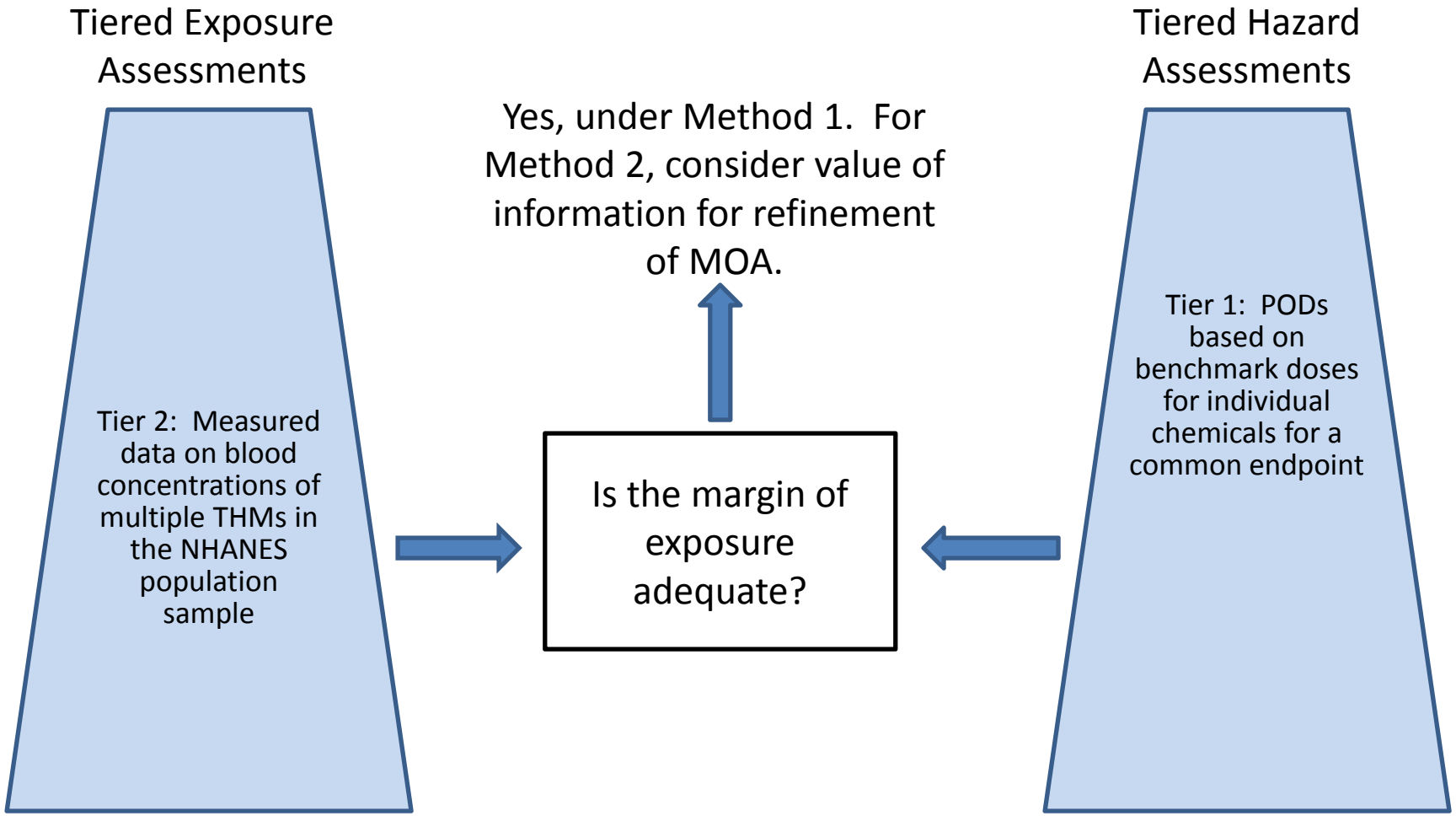


Predicted Risk of Fatty Liver

	NHANES Blood Concentration Percentile				
Chemical	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		
TBM	0	0	0		
Sum of Four THMs	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
Sum of Four THMs (ND=0)	0.0014	0.0028	0.0055	0.0094	0.015

Background rate of NAFLD ~0.1 (10%)

WHO/IPCS Framework Context



Issues in Interpretation

- Risk management for THMs must consider benefits
- Highly transient biomarker: comparison to estimates of steady-state avg. blood conc. (BE_{POD}, BE_{RfD})
  - How representative are spot blood samples of long term avg. blood conc. for each individual?
  - Is this better/worse/complementary to external exposure-based assessments?
- POD: quantal risk – continuous measure of effect would be preferable
- Low-dose extrapolation procedure: How does MOA for fatty liver occurrence inform selection?

What About Data-Poor Chemicals?

- Biomonitoring studies, dose-response assessments, pk data, available only for a limited set of chemicals
- 21st Century Tox testing provides a source of response data on a ***concentration*** basis (e.g., AC_{50})
  - Could be compared to serum concentrations as a crude screening tool to identify priorities for more refined screening
- Can we develop more efficient biomonitoring strategies to broaden the suite of chemicals examined?
  - Pooled serum samples (examine average levels and co-occurrence of chemicals) (Reduce the "n")
  - Analytical techniques that are more "quick and dirty"?

Conclusions

- Biomonitoring data can be used in conjunction with BEs to examine potential risks of co-exposure to multiple chemicals
  - Hazard Quotient, Hazard Index approach can be applied
  - Approach may be applicable for other assessment groups with biomonitoring data and appropriate screening values
    - BE values have been derived for ~80 chemicals from the NHANES analyte list
  - Biomarkers provide a window on real-world mixture exposures
    - Simultaneous measurement of multiple analytes in samples from individuals
- HI values for THM assessment group consistently below 1 based on NHANES data
  - But estimated potential risks (non-cancer) depend on low-dose extrapolation method