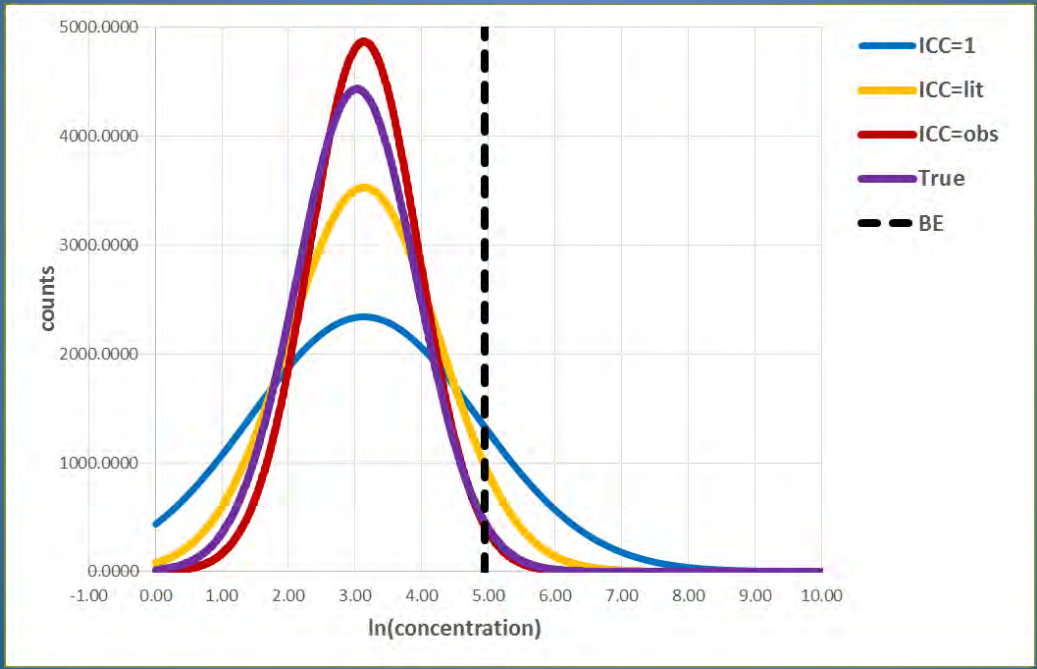
Improving the Use of Spot Biomarker Data for Environmental Epi. and Population Risk Assessment

U.S. EPA Temporal Exposures Workshop, Jan 2016



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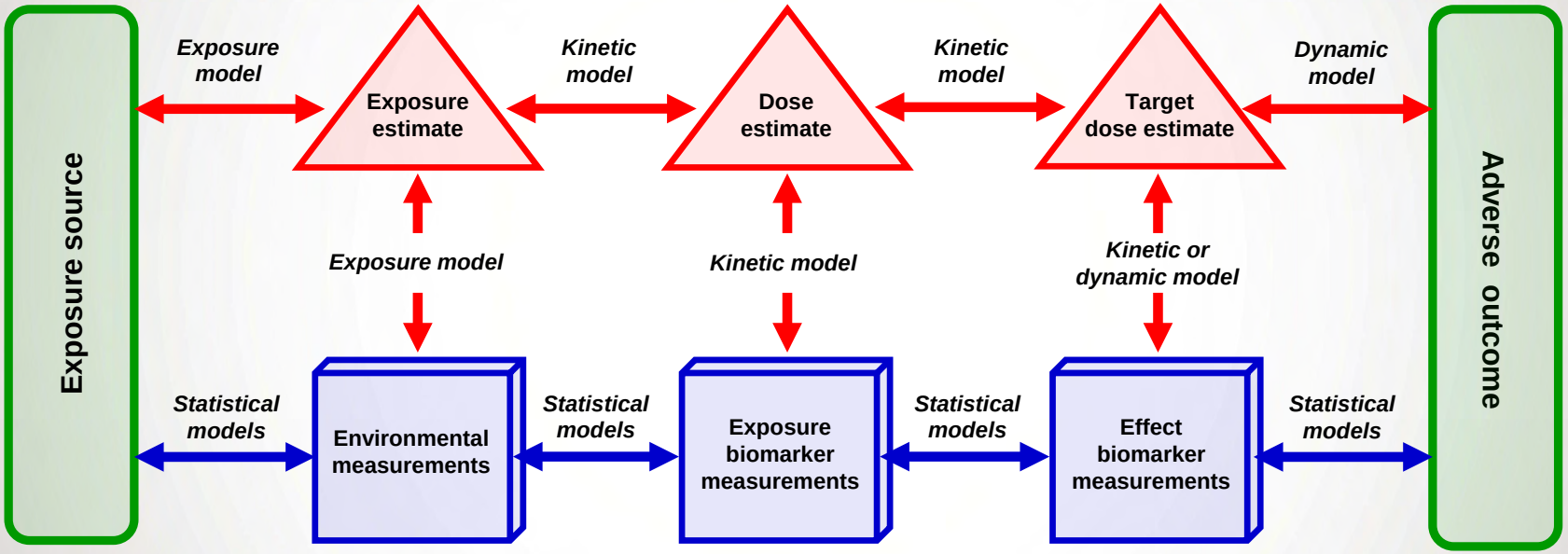
National Exposure Research Laboratory

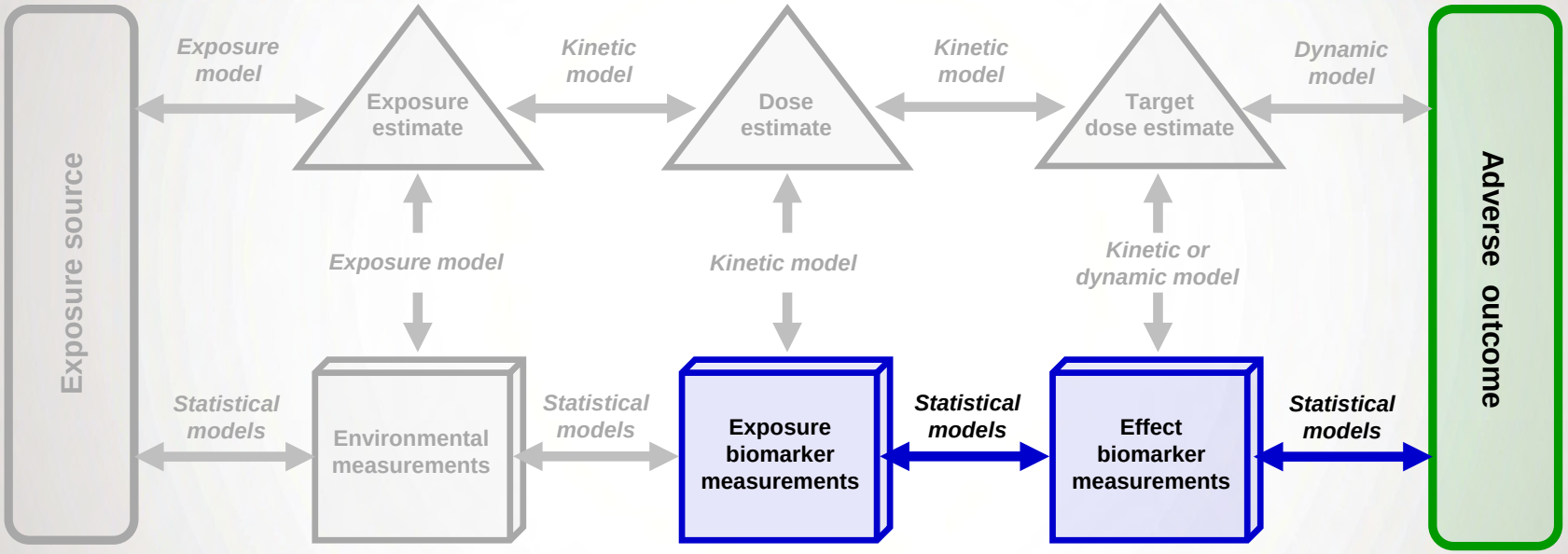
Biomonitoring Framework (2-plane source-to-outcome continuum)



Adapted from Sobus *et al.,* Sci Total Environ. 2011 Oct 15;409(22):4875-84.

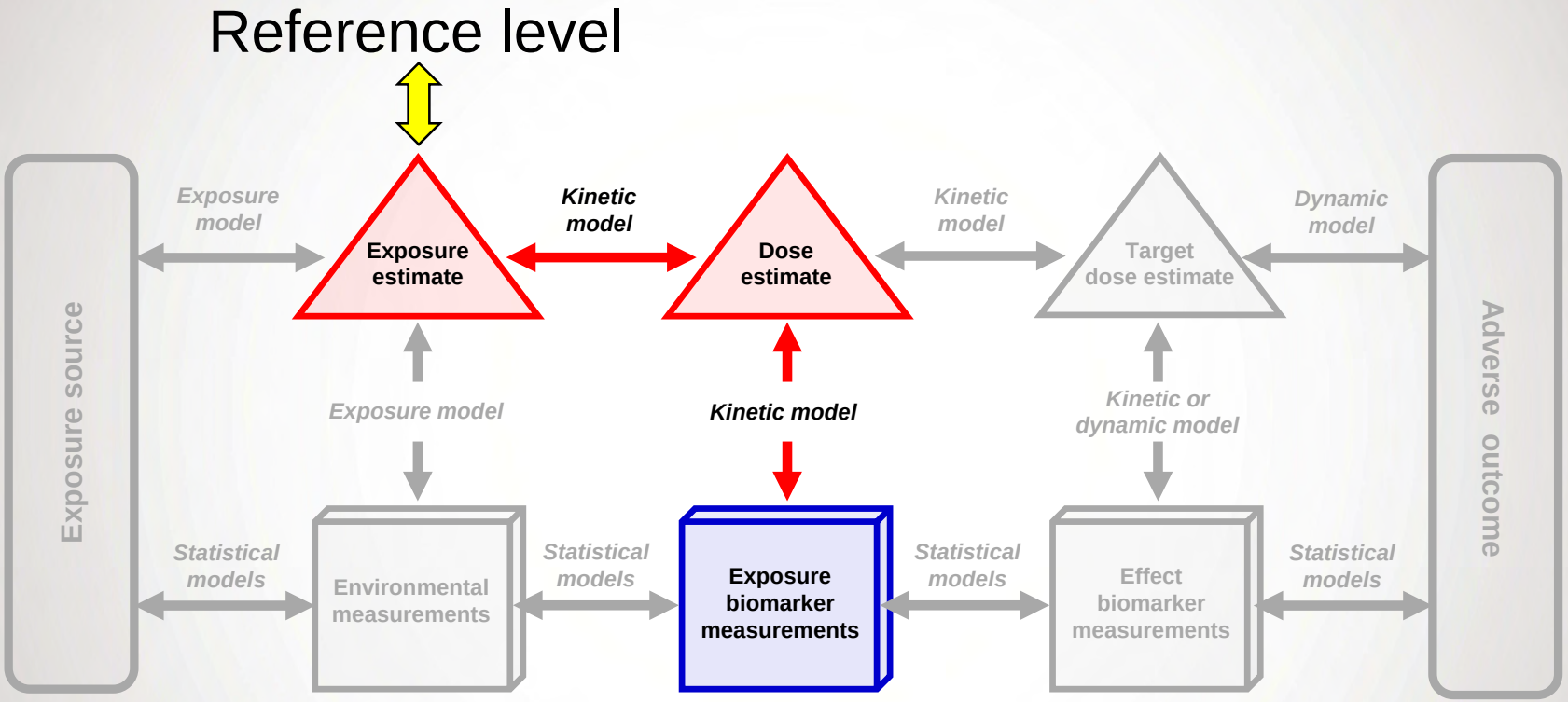
Typical Biomarker-Based Health Association Studies

a.k.a. “Environmental Epidemiology”



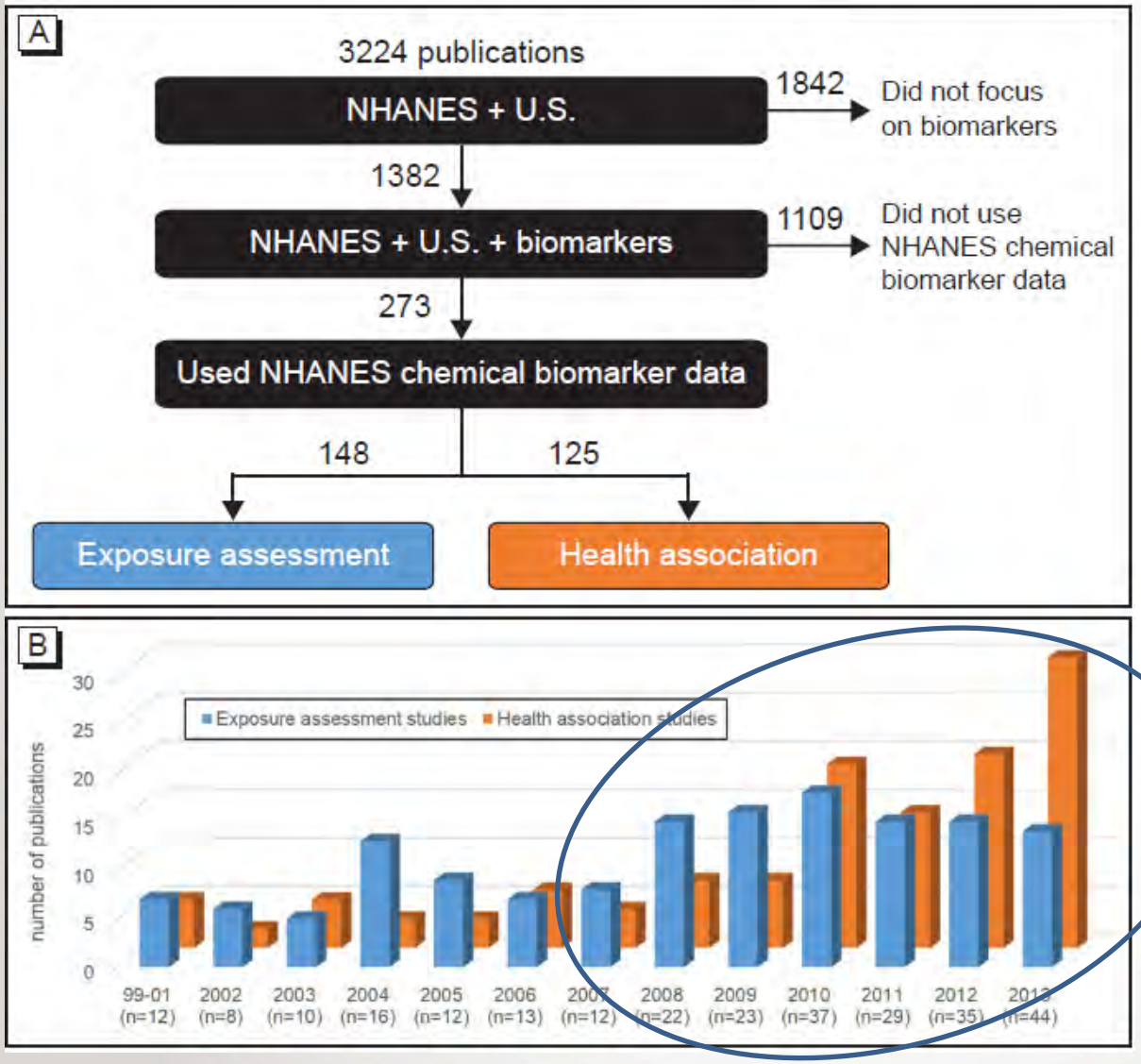
Are exposure biomarkers predictive of health outcomes?

Typical Biomarker-Based Exposure Assessment Studies



Is estimated exposure ≥ or < reference level?

Trends in Usage of Spot Biomarker Data

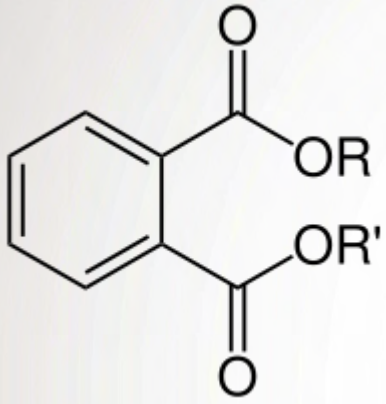


Review of sample of publications (1999-2013) using NHANES chemical biomarker data

Dramatic increase in recent years

Sobus et al. *Environ Health Perspect.* 2015 Oct;123(10):919-27.

Case Studies Using Phthalates



https://en.wikipedia.org/wiki/Phthalate

Clothing - raincoats, printed shirts, diaper covers, skirts
Footwear - rain boots, sandals, sneakers
Accessories - backpacks, handbags, packaging
Building products - floor tiles, wall covering, wiring
Household - shower curtains, tablecloths, toys
Personal care - shampoo, deodorant, lotion, nail polish
School supplies - lunch boxes, notebooks, binders
Outdoors - swimming pools, inflatables, garden hoses
Automotive - car seats, upholstery, dashboards

http://www.cleanandhealthyme.org/Portals/0/Hormones%20Disrupted/Phthalates-in-Products.jpg

Studied for relationships with cancer, reproductive effects, developmental effects, endocrine disruption, and body size (BMI, WC).

Existing exposure reference levels (e.g., EPA RfD).

Parent to Metabolite Mappings

Parent Phthalate Compound	Phthalate Monoester Metabolite
Diethyl phthalate (DEP)	Monoethyl phthalate
Di-2-ethylhexyl phthalate (DEHP) 	Mono-(2-ethylhexyl) phthalate (MEHP)
	Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)
	Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)
	Mono (2-ethyl-5-carboxypentyl) phthalate (MECPP)
Di-n-butyl phthalate (DnBP or DBP)	Mono-n-butyl phthalate (MBP)
Butylbenzyl phthalate (BBP)	Mono-benzyl phthalate (MBzP)
Di-isononyl phthalate (DiNP)	Mono-(carboxyoctyl) phthalate (MCOP)
Di-iso-butyl phthalate (DiBP)	Mono-iso-butyl phthalate (MiBP)

Case Study #1: Environmental Epi.

Environment International 73 (2014) 66–76

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Changes in epidemiologic associations with different exposure metrics: A case study of phthalate exposure associations with body mass index and waist circumference☆,☆☆

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Challenge: Different exposure metrics produce different results in epi studies

Research question: What are best practices for selecting an exposure metric?

Approaches: 1) Evaluate NHANES associations using different exposure metrics
2) Simulate random exposures and evaluate using different metrics
3) Compare simulation results to NHANES results

Results from NHANES 2009-2010

Adjusted regression coefficients for effect of phthalate levels on ln(Body Mass Index). All models adjusted for age, sex, race/ethnicity, height, and PIR. Results presented for models treating phthalate exposures as ln-transformed variables.

	Outcome is ln(Body Mass index)				
Phthalate	nmole/min: β (SE),	nmole/mL: β (SE),	nmole/mL + crt: β (SE),	nmole/g crt: β (SE),	nmole/kg-day: β (SE),
DiBP	**0.022 (0.005)****	**0.023 (0.004)*****	**0.014 (0.006)***	0.007 (0.006)	**0.040 (0.006)******
BBP	**0.019 (0.005)****	**0.021 (0.004)*****	**0.011 (0.005)***	0.006 (0.006)	**0.033 (0.006)*****
DEHP[a]	**0.019 (0.005)****	**0.025 (0.004)*****	**0.017 (0.005)***	0.008 (0.006)	**0.033 (0.005)*****
DiNP	**0.020 (0.004)*****	**0.023 (0.004)******	**0.017 (0.004)****	**0.013 (0.004)***	**0.028 (0.004)******
DBP	**0.022 (0.005)****	**0.025 (0.005)*****	**0.014 (0.006)***	0.003 (0.007)	**0.045 (0.007)******
DEP	**0.013 (0.004)****	**0.016 (0.003)****	**0.010 (0.004)***	0.005 (0.004)	**0.018 (0.004)****

[a]Represents the molar sum of 4 DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP)

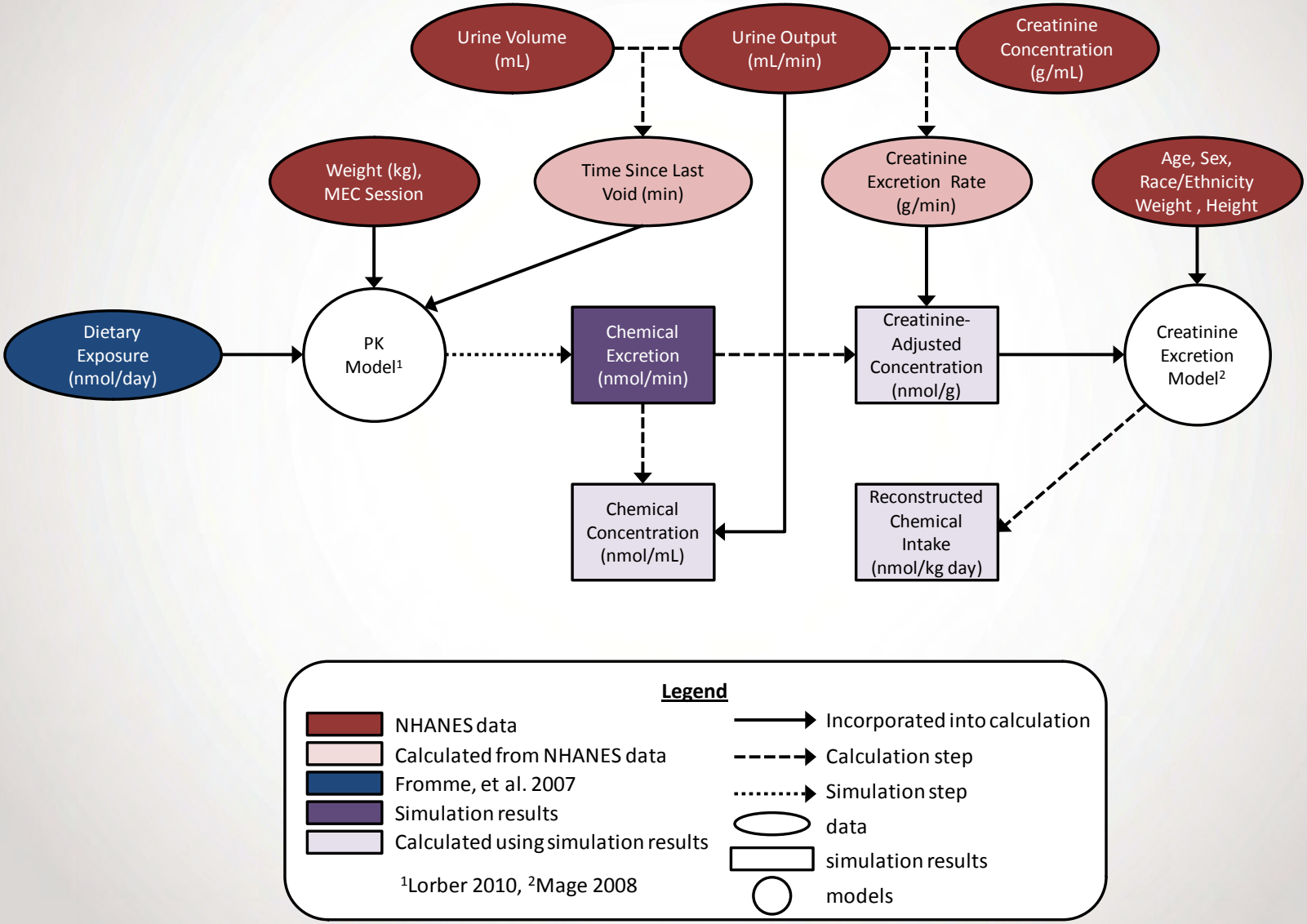
* $p < 0.05$

** $p < 0.001$ (1×10^{-3})

*** $p < 0.000001$ (1×10^{-6})

**** $p < 0.000000001$ (1×10^{-9})

Simulation Experiment (DEHP)

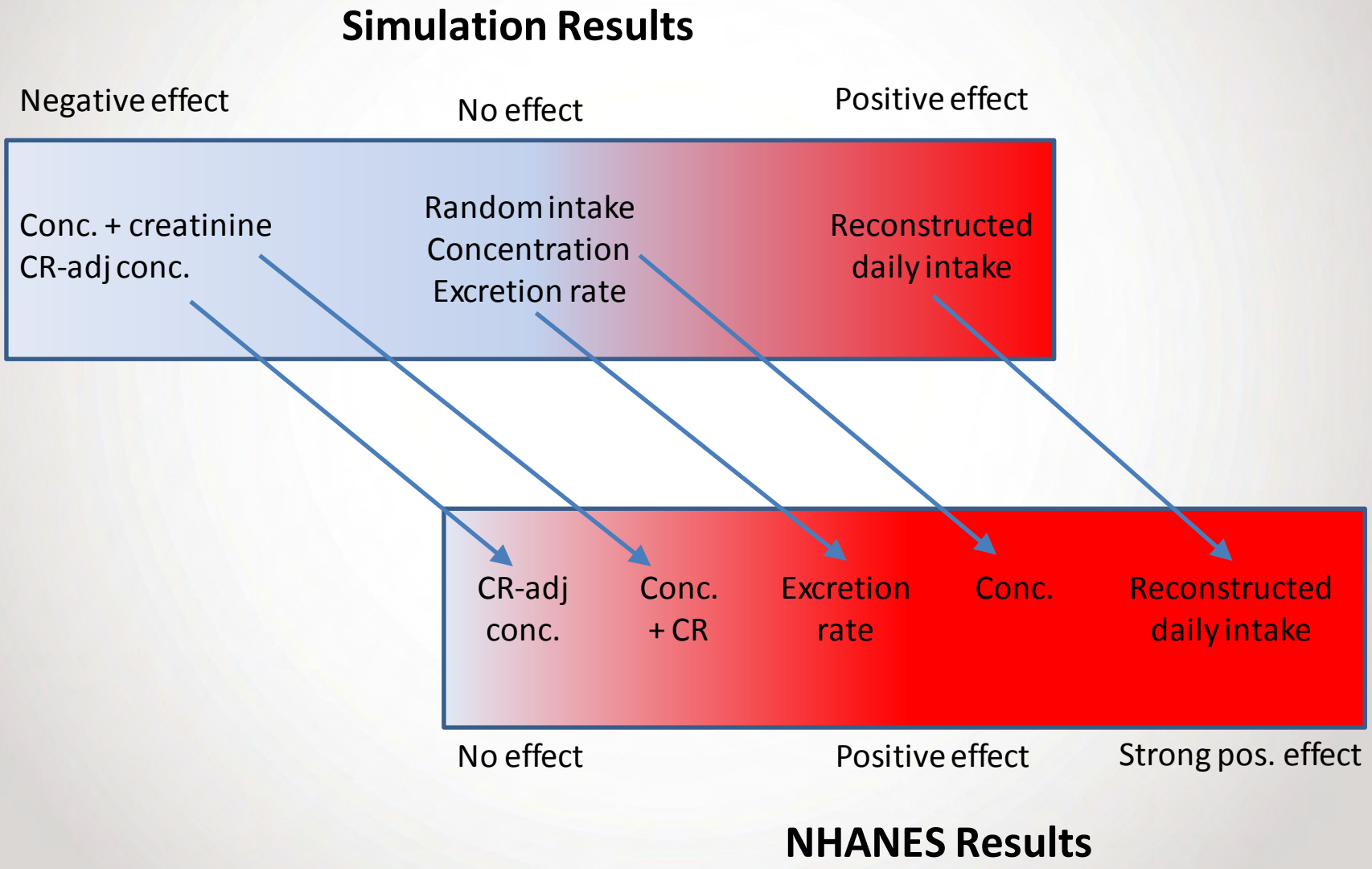


Simulation Results (DEHP)

	Unadjusted Results		Adjusted[1] Results	
	Coefficient (SE) p-value	R^2	*Coefficient (SE) p-value*	R^2
Intake, nmole/day	-0.0009 (0.0147) p = 0.95	0.0000	-0.0036 (0.0145) p = 0.81	0.0416
nmole/min	-0.0039 (0.0050) p = 0.43	0.0004	-0.0042 (0.0050) p = 0.39	0.0420
nmole/mL	-0.0004 (0.0045) p = 0.92	0.0000	-0.0027 (0.0044) p = 0.54	0.0418
nmole/mL + crt	**-0.0126 (0.0048) p = 0.01**	**0.0235**	**-0.0168 (0.0049) p = 0.0005**	**0.0681**
nmole/g cr	**-0.0174 (0.0048) p = 0.0003**	**0.0084**	**-0.0203 (0.0048) p < 0.0001**	**0.0522**
nmole/kg-day	**0.0325 (0.0058) p < 0.0001**	**0.0199**	**0.0371 (0.0057) p < 0.0001**	**0.0667**

[1]Adjusted models include age, sex, race/ethnicity, height, and PIR.

Results Comparison



Case Study #1: Summary and Conclusions

- Spot urinary biomarker data often require adjustment
- Choice of adjustment method is likely to influence study results
- Biased results may be expected when examining certain endpoints
- Rigorous analyses should be performed across multiple exposure surrogates
- Careful consideration should be given to all results to inform selection of the “best” surrogate, and most informative model(s).

Case Study #2: Exposure Assessment

Journal of Toxicology and Environmental Health, Part A, 76:747–766, 2013
ISSN: 1528-7394 print / 1087-2620 online
DOI: 10.1080/15287394.2013.821394

Taylor & Francis
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ESTIMATING LIFETIME RISK FROM SPOT BIOMARKER DATA AND INTRACLASS CORRELATION COEFFICIENTS (ICC)

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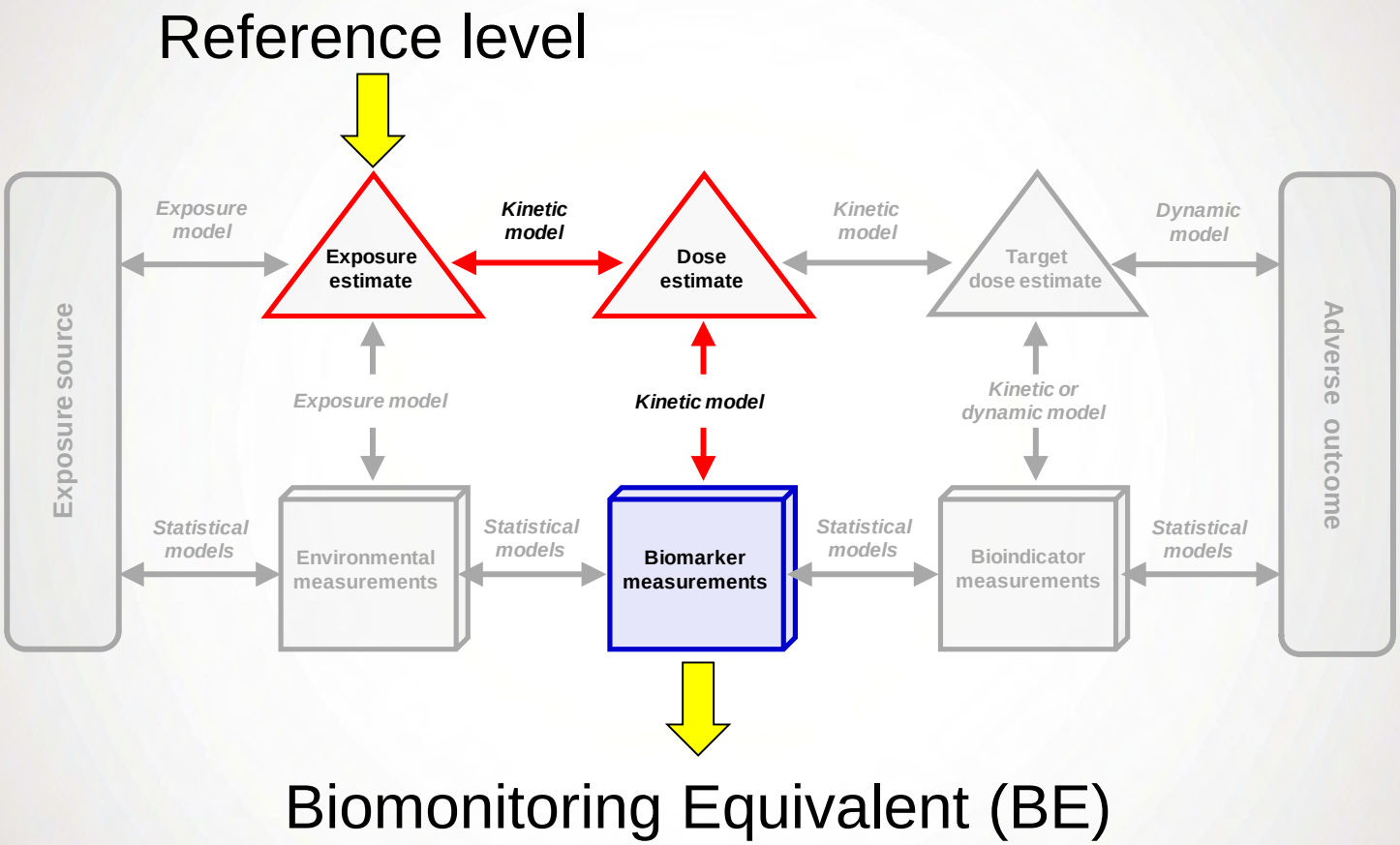
Challenge: Difficult to compare spot biomarkers with ref. levels based on long-term exposures

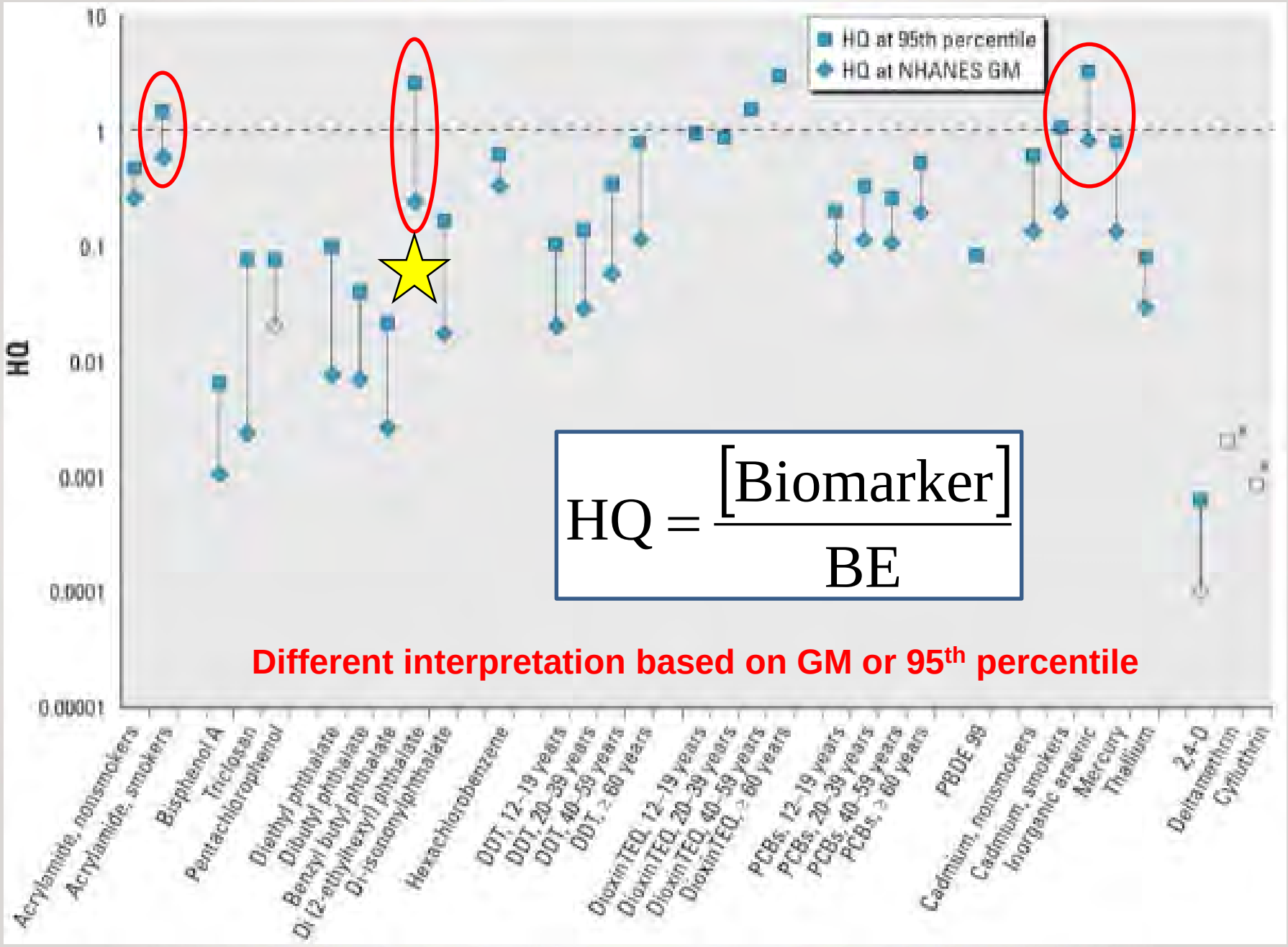
Research question: How do we better interpret "tails" of biomarker distributions?

Approaches: 1) Acquire/develop repeat measures data sets
2) Build and calibrate distribution conversion model
3) Evaluate model performance using real repeat-measures data

Biomonitoring Equivalents Concept

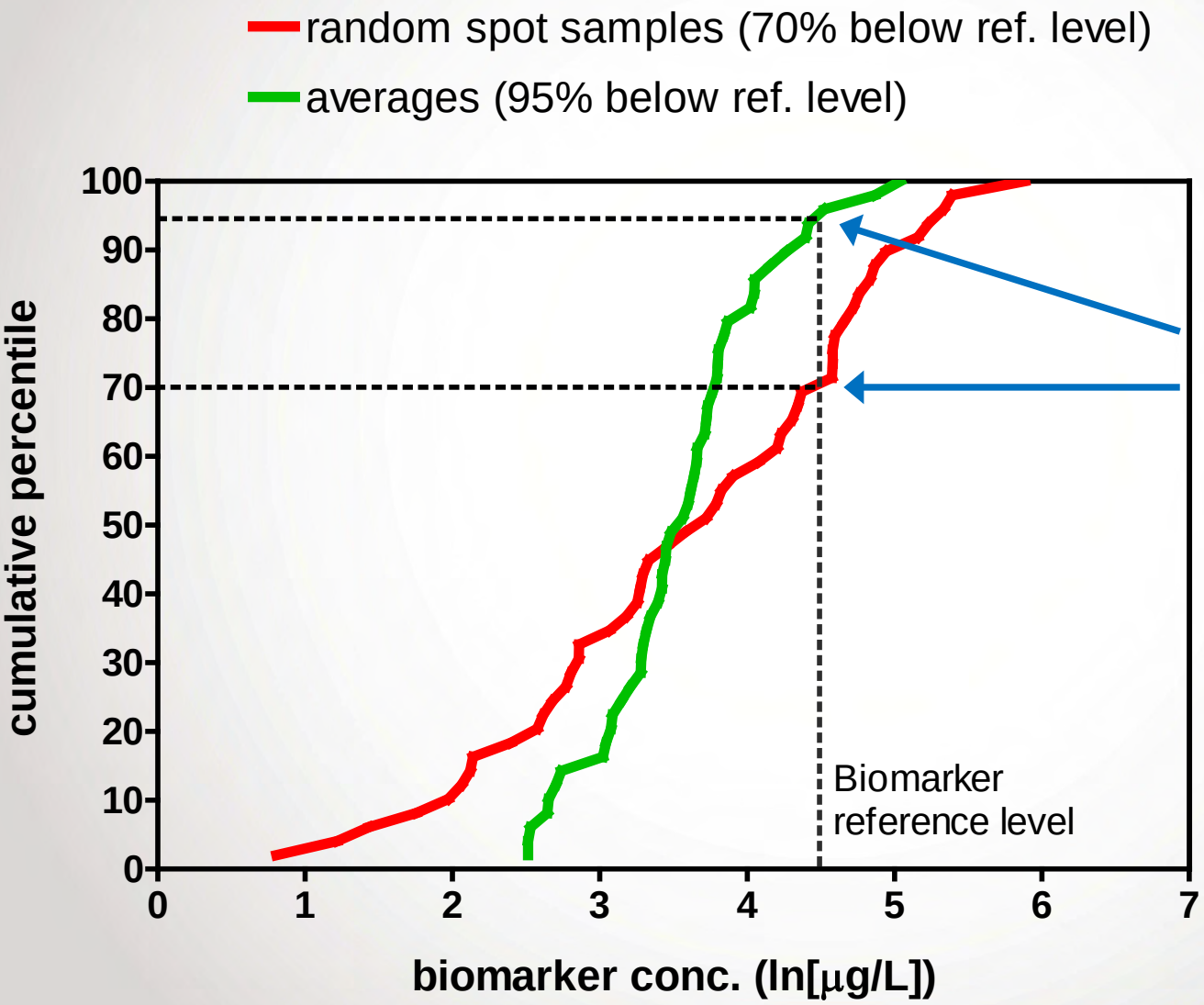


Do biomarker measurements exceed the BE?



Aylward et al. *Environ Health Perspect.* 2013 Mar;121(3):287-94.

Visualizing the Challenge



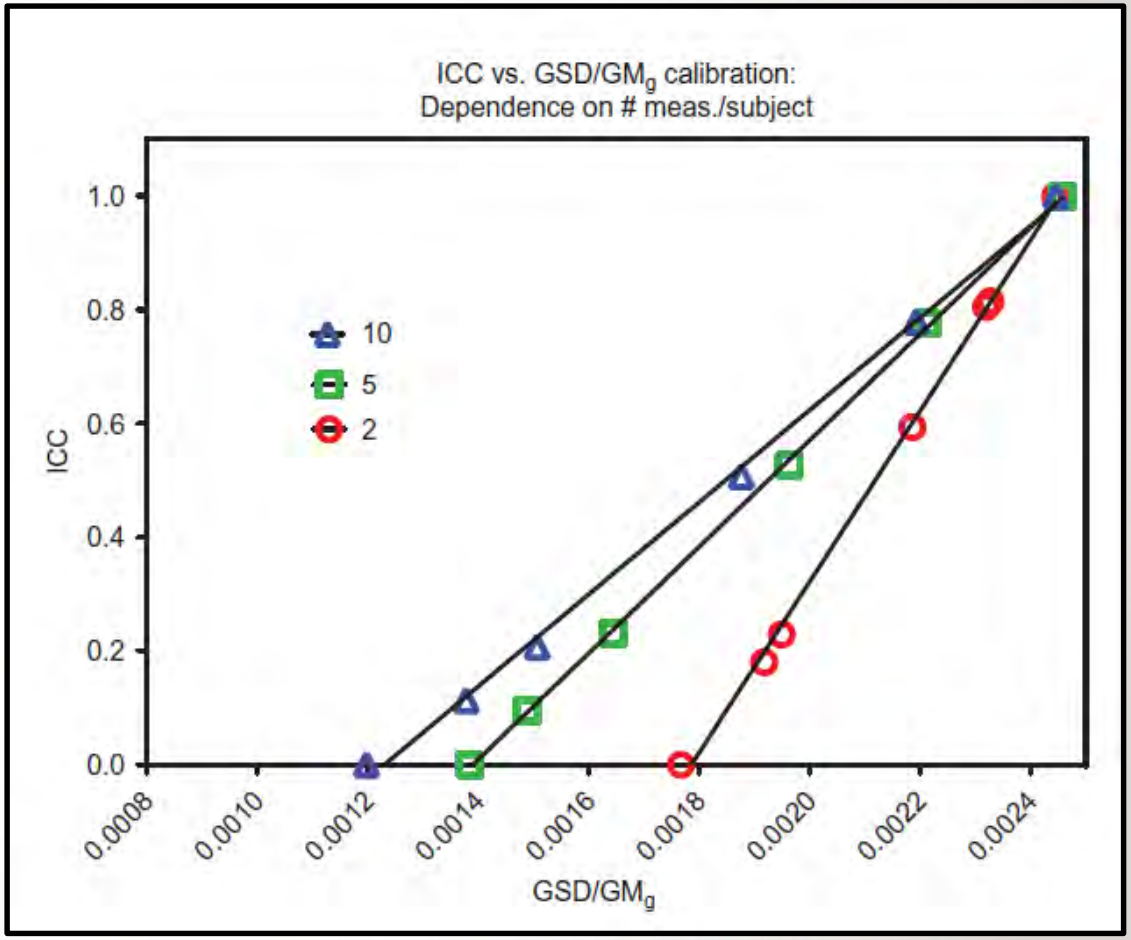
Can we estimate the magnitude of this shift for existing biomarker data?

Published Distribution Conversion Method

Known: $\mathbf{GM_{means}} = \mathbf{GM_{spot}}$

Solve for $\mathbf{GSD_{means}}$ given:
- $\mathbf{GM_{spot}}$
- $\mathbf{GSD_{spot}}$
- **ICC**
- ***m*** *(# repeats)*

Where **ICC** = *between-person measurement variance / total measurement variance*



Pleil and Sobus., *JTEH A*. 2013.

Case-Study Example

- Parent Chemical: di(2-ethylhexyl)phthalate (DEHP)
  - Plasticizer
    - Cosmetics, food packaging, medical devices

- Urinary Metabolites:
  - Mono-2-ethylhexyl phthalate (MEHP) (7.3% MEF)
  - Mono-(2-ethyl-5-hydroxyhexyl)phthalate (MEHHP) (24.7%)
  - Mono-(2-ethyl-5-oxohexyl)phthalate (MEOHP) (14.9%)
  - Mono-(2-ethyl-5-carboxypentyl)phthalate (5cx-MEPP) (21.9%)
  - Mono-(2-carboxymethylhexyl)phthalate (2cx-MMHP) (5.4%)

Serial-Sampling Dataset

- U.S. CDC study (2005)
- 8 adult participants
  - 4 male, 4 female
  - Ages 25-58
  - Collect every urine void for 7 continuous days
- Urine samples analyzed for MEHHP
  - 56 possible person-days (8 participants × 7 days)
  - 44 complete person-days (avg 5.5 days/person)
  - 328 urine samples over 44 complete person-days
  - ~7.5 samples/person-day
  - ~41 samples/person

BE for MEHHP

- Exposure guidance value = 0.02 mg/kg-day (EPA RfD)
- BE = 400 µg/L (based on sum of 4 DEHP metabolites)
- Urine conc per µg DEHP/kg-day administered dose
  - MEHP = 2.1 µg/L
  - MEHHP = 7.3 µg/L
  - MEOHP = 4.4 µg/L
  - 5cx-MEPP = 7.1 µg/L

  Sum of 4 metabolites = 20.9 µg/L

  - Ratio of MEHHP (7.3) to sum (20.9) = 0.35
- BE_{MEHHP} = 140 µg/L

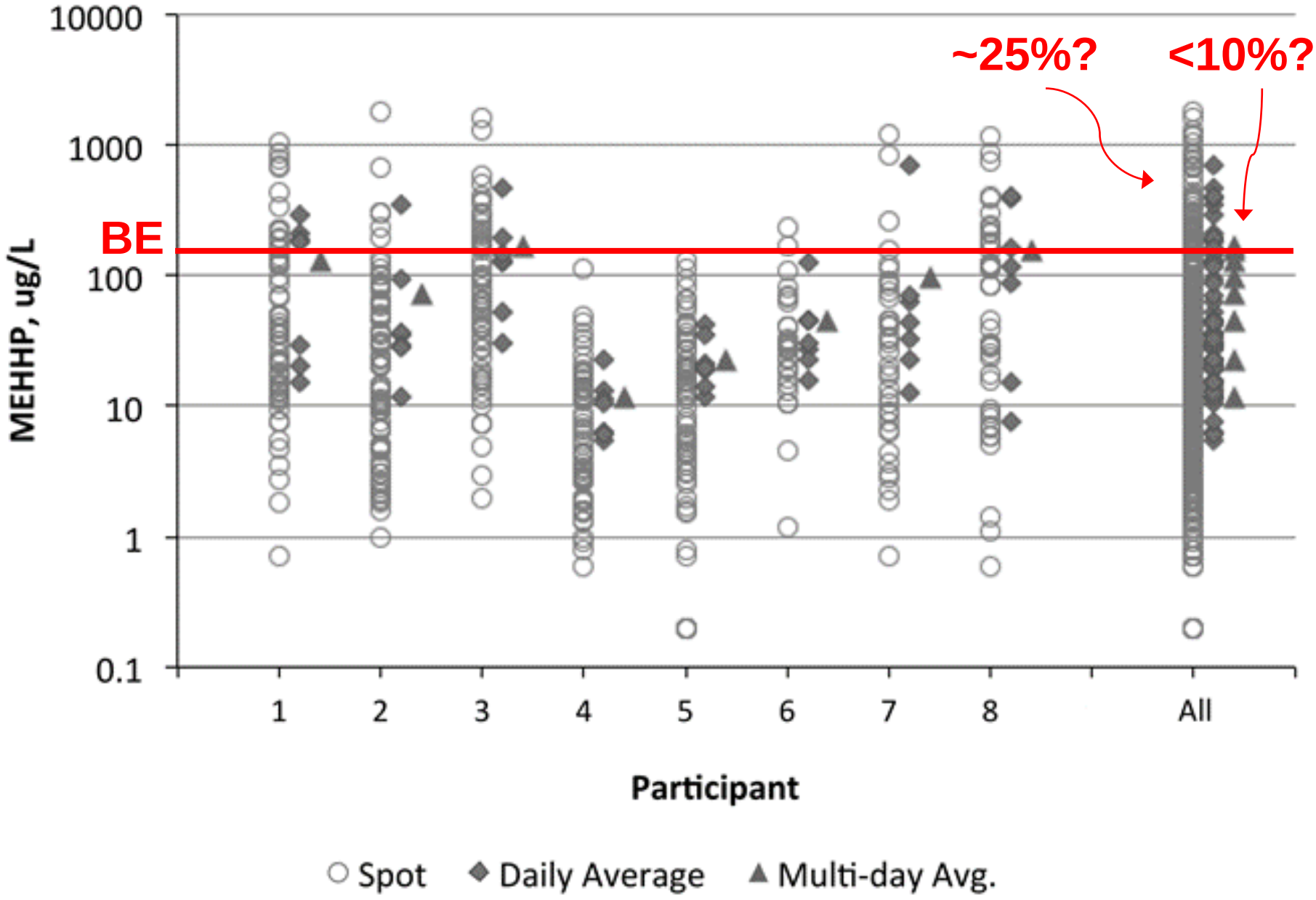
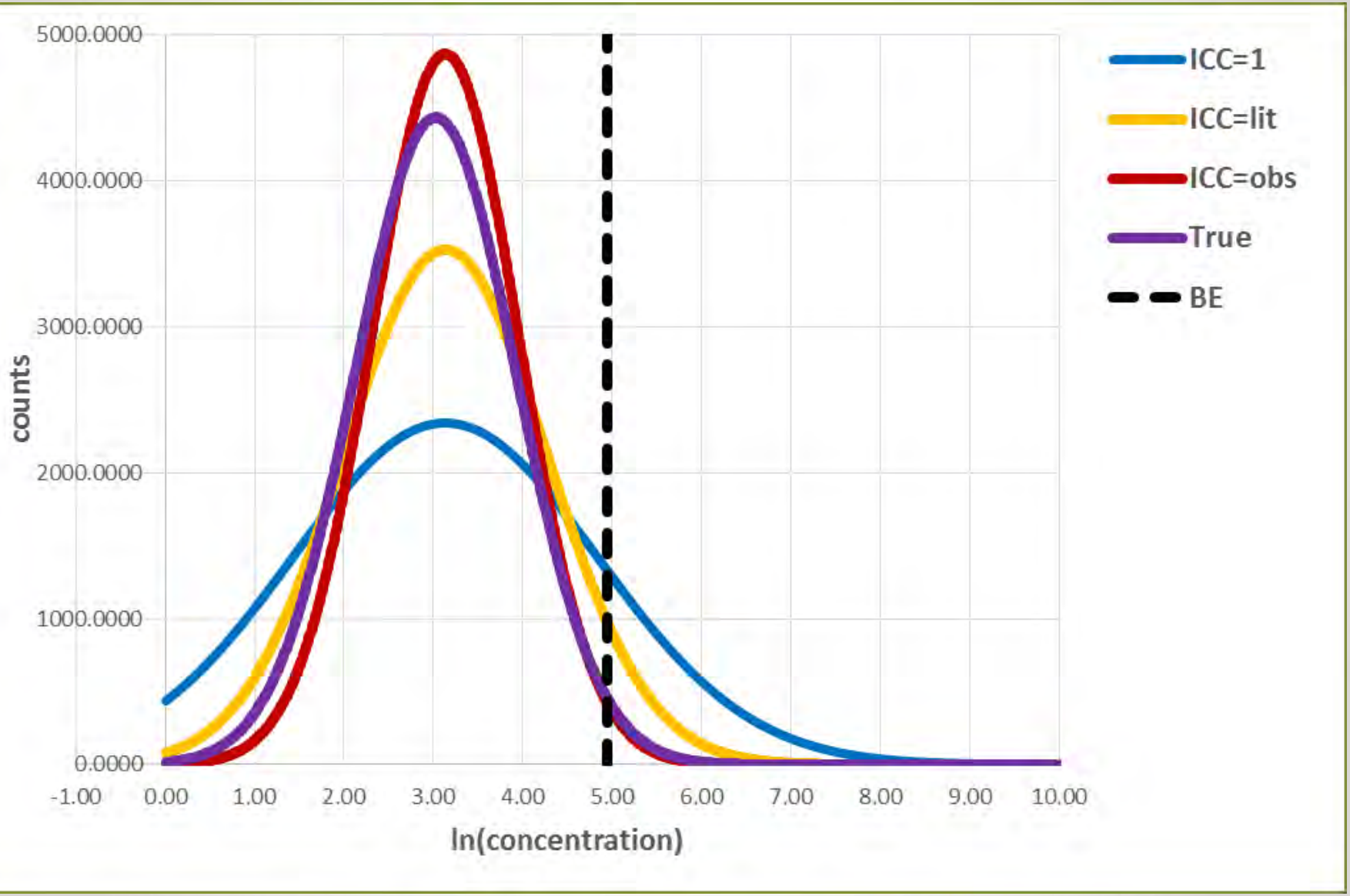


figure from L. Aylward

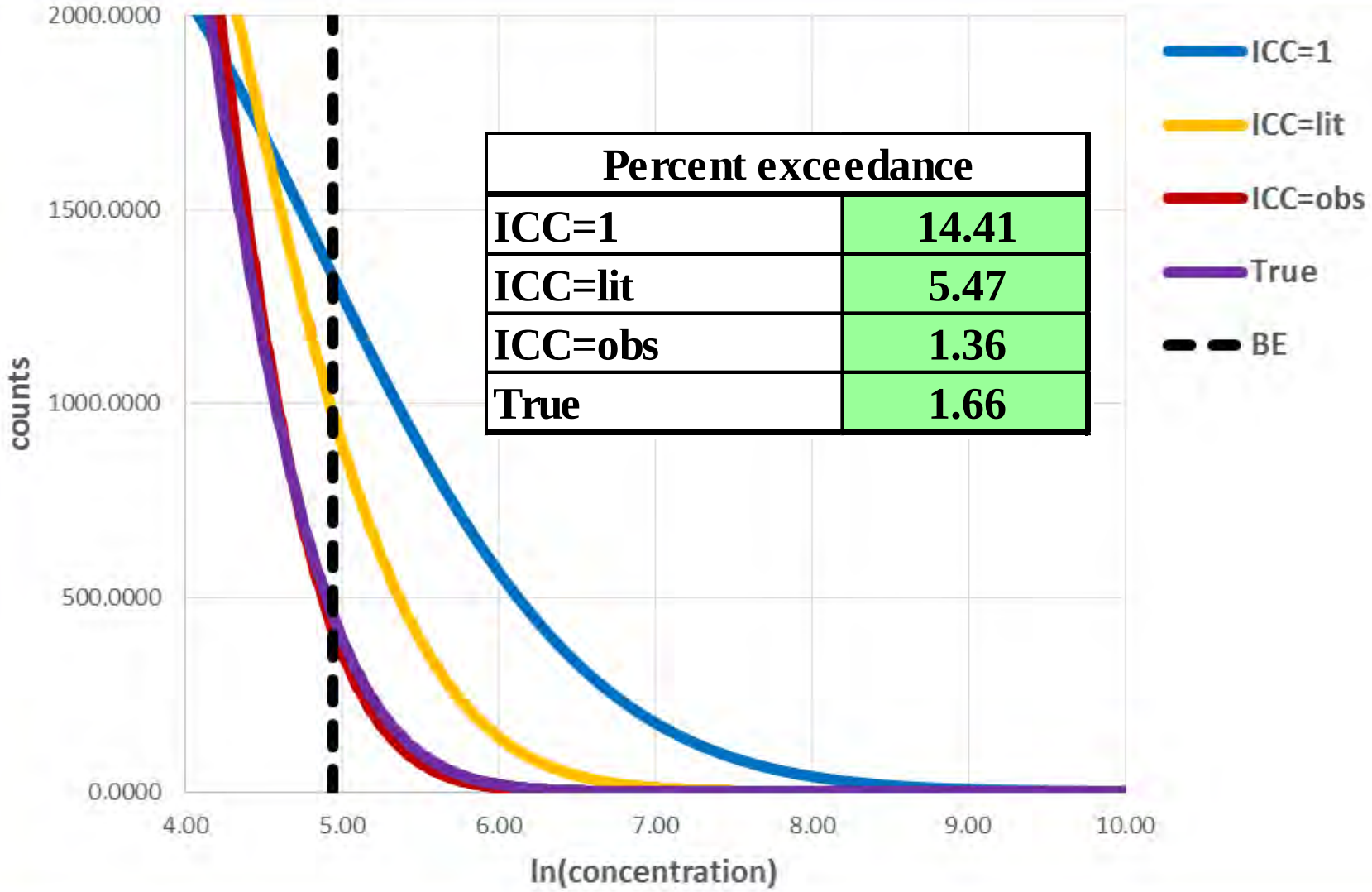
Exceedance Predictions

- Scenario #1: Worst case → ICC=1
  - Dist. of averages = Dist. of spots
  - Maximum exceedance
- Scenario #2: Use literature ICCs
  - Small m (# of repeated measures)
  - Small n (# of subjects)
  - Applicability to current study?
- Scenario #3: Use study ICCs
  - True ICCs (over 1 week)
  - Large m
- Scenario #4: Use global GM & GSD
  - Based on subject-specific mean values (ln-space)
  - Closest to “true” (unobservable) mean levels

MEHHP Results



MEHHP Results



Percent exceedance	
ICC=1	14.41
ICC=lit	5.47
ICC=obs	1.36
True	1.66

Case Study #2: Summary and Conclusions

- Tools exist for interpreting spot biomarker data against BEs
- Rigorous repeat-measures studies useful for evaluation
- MEHHP results summary:
  - Default “worst-case” approach overestimated exceedance (>10%)
  - Literature ICCs with small “m” led to slight overestimation
  - Study ICCs (m=41) led to accurate predictions
  - Limited exceedance (<2%) based on true averages
- ICC tool should be further evaluated using other chemicals with a range of ICCs.

Final Thoughts on Biomarker Interpretation

Spot Sampling

Exposure Assessment

nvironmental Epidemiology

Short Half-life

Intermittent Exposure

Acknowledgments

- Case Study #1:
  - Krista Christensen
  - Martin Phillips
  - Cecilia Tan
  - Matt Lorber
  - Todd Blessinger
- Case Study #2:
  - Joachim Pleil
  - Lesa Aylward & Sean Hays (Summit Toxicology)