Biomonitoring and Temporality in Environmental Epidemiology: The data we collect versus the data we need

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EPA Temporality Workshop/28 January 2016

Workshop goal:

Explore state-of-the-science regarding the influence of duration and time-dependent concentrations or doses on a range of endpoints (health effects) and best practices for estimating risk.

Biomarkers – Ideal Properties

- Exposure and biological relevance
- Specificity
- Method sensitivity
- Stability
- No contamination
- Ability to adjust for matrix issues
- Ability to use data to estimate exposure over window of interest
- Ability to establish that exposure precedes effect

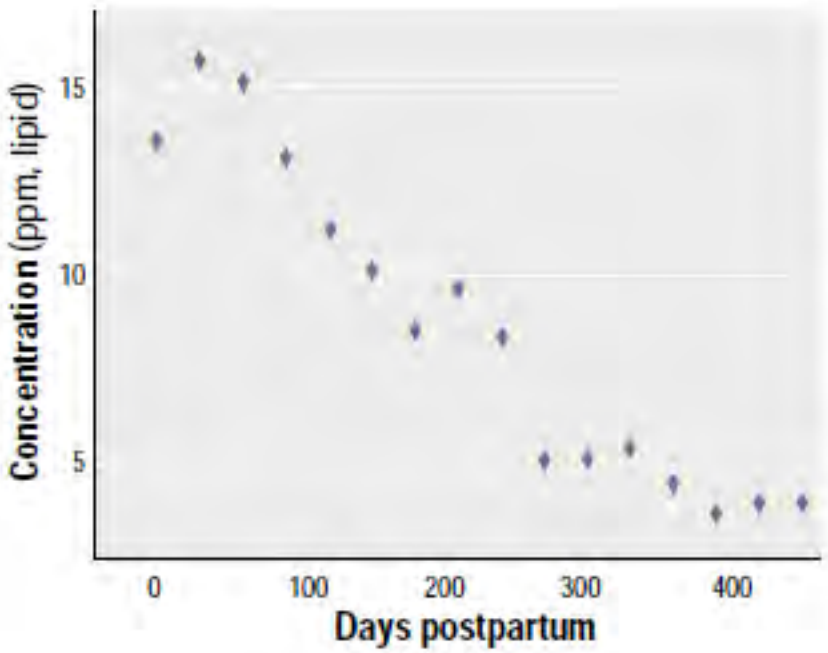
LaKind JS, Sobus JR, Goodman M, Barr DB, Fürst P, Albertini RJ, Arbuckle TE, Schoeters G, Tan Y-M, Teeguarden J, Tornero-Velez R, Weisel CP. 2014. A proposal for assessing study quality: Biomonitoring, Environmental Epidemiology, and Short-Lived Chemicals (BEES-C) Instrument. Environment International 73C:195-207.

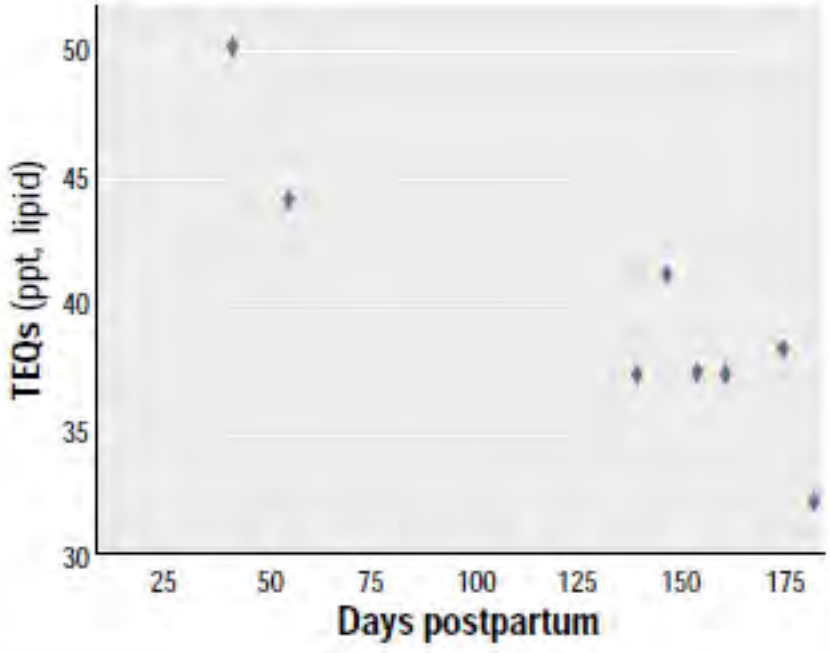
What is the problem?

Most epidemiology studies use 1 measurement to capture exposure

Persistent chemicals

Dioxins
Furans
PCBs
PBDEs
OC pesticides

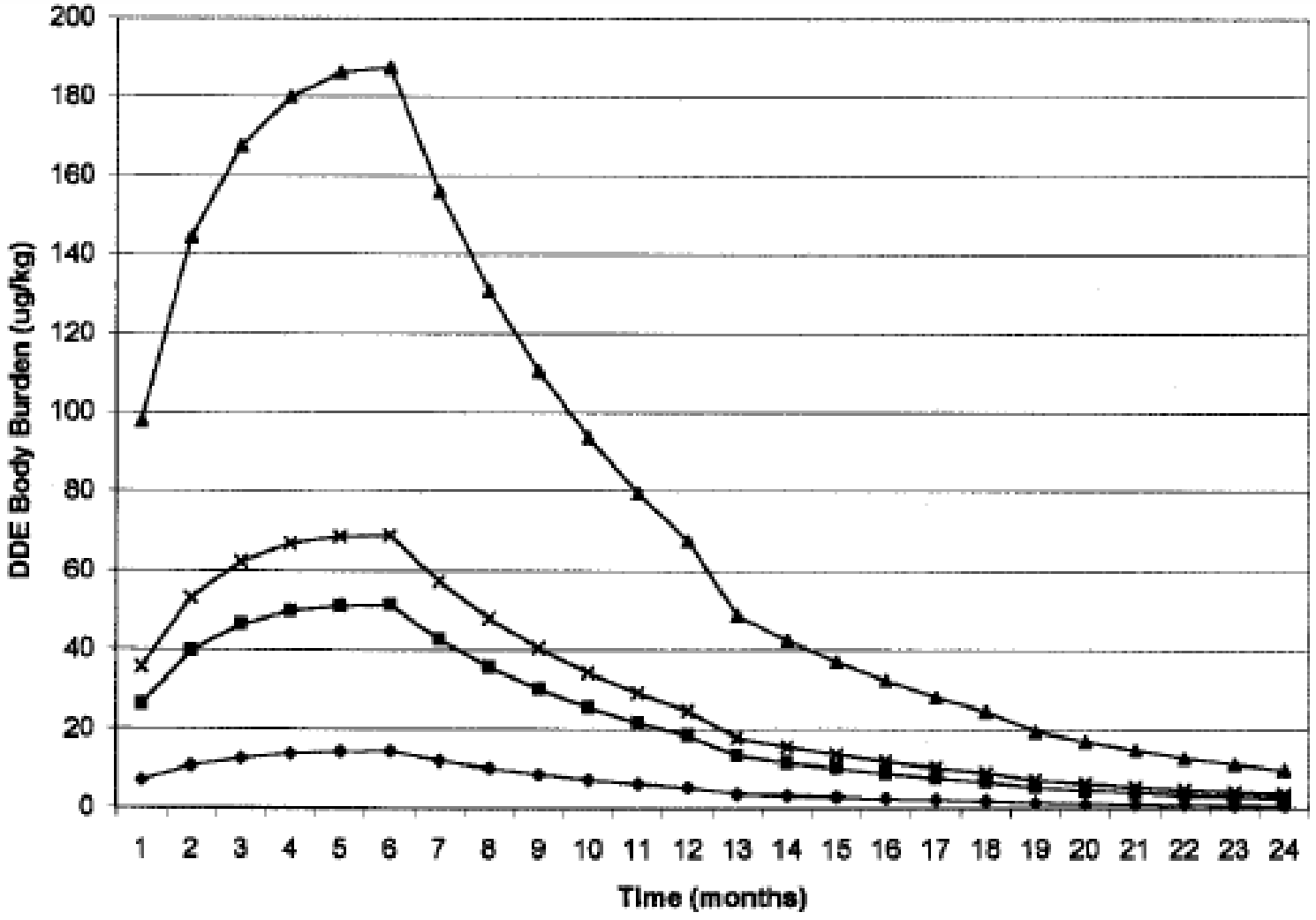




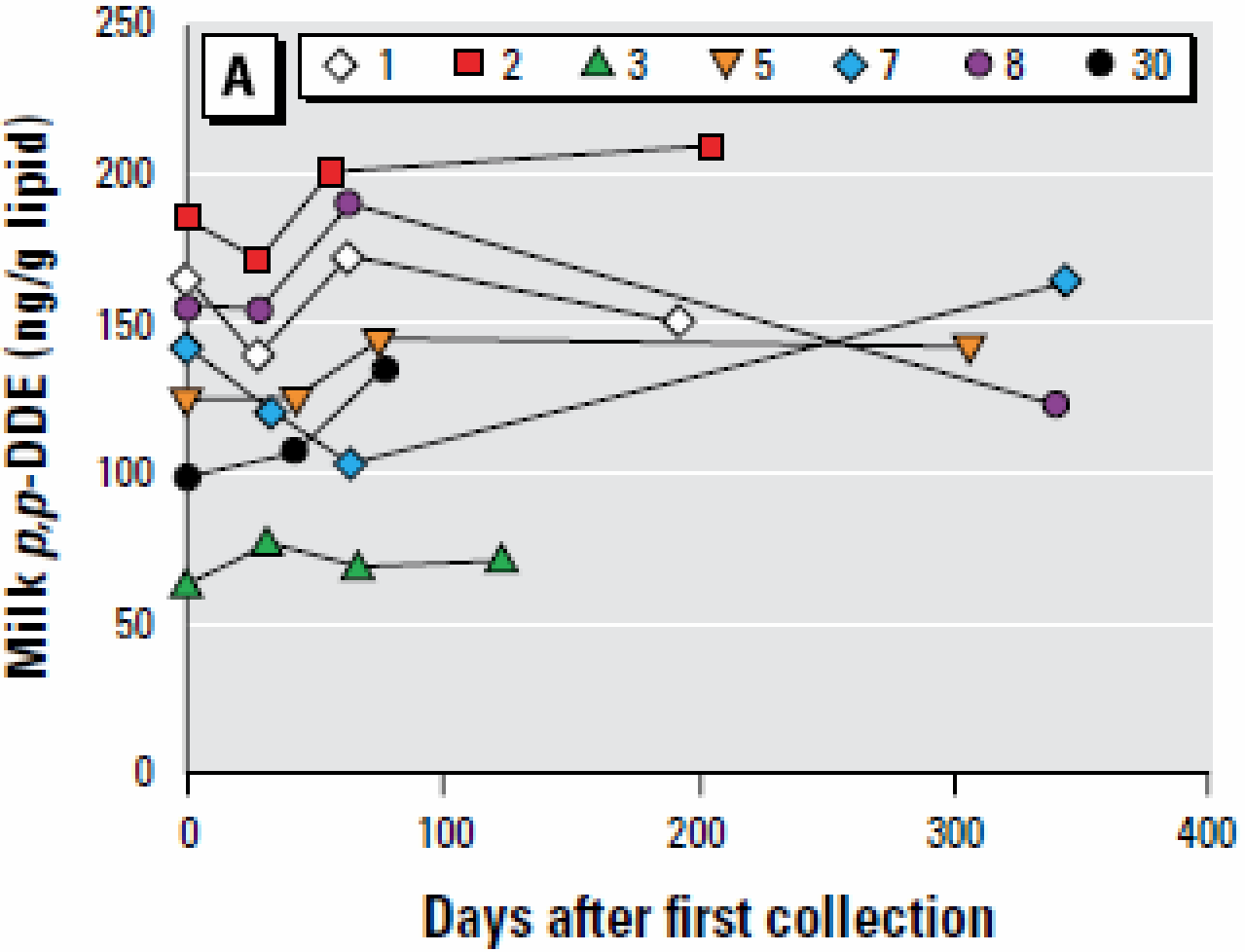
PCBs N = 1

Dioxins N = 1

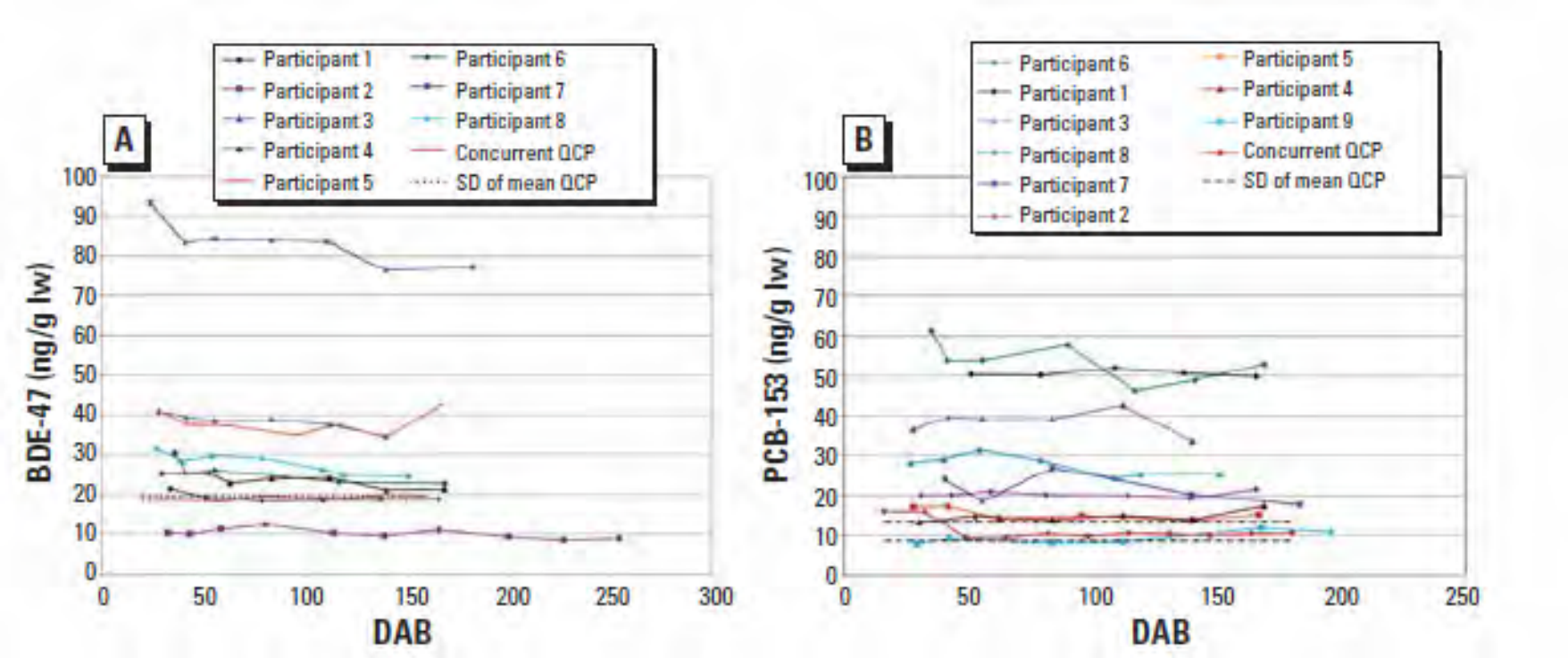
Hori, Organohalogen Compounds 13:65–67 (1993) and Yakushiji et al, Arch Environ Contam Toxicol 7(4):493–504 (1978). In: LaKind et al. 2001. Environ Health Perspect 109:75-88.



LaKind et al. 2000. J Toxicol Environ Health, Part A 59:605-639.



LaKind et al. Environ Health Perspect 117:1625–1631 (2009)



Even for well-studied chemicals, conventional wisdom can be wrong

Cautionary note about data collection and interpretation

Hooper et al. Environ Health Perspect 115:1271–1275 (2007)

Associations between infant exposures to environmental chemicals in breast milk and health outcomes: How many measures?

	1 measure	>1 measure	# studies
Flame retardants	4	0	5
PFCs	1	0	1
OCs	20	3	51

LaKind JS, Davis M, Lehmann GM, Hines E, Marchitti SA, Alcala C, Lorber M. Environmental chemicals in breast milk and infant formula and the relationship to infant/child health: A critical assessment of the literature

What about short-lived chemicals?

Exposure assessment should represent exposures that occurred prior to the development of the outcome - *key feature of study design*

Office of Health Assessment and Translation - Risk of Bias Rating Tool for Human and Animal Studies. https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf

How do exposure estimates that do not consider temporality impact our ability to interpret epidemiology results?

Critical Reviews in Toxicology

http://informahealthcare.com/txc
ISSN: 1040-8444 (print), 1547-6898 (electronic)

Crit Rev Toxicol, 2014; 44(2): 121–150
 DOI: 10.3109/10408444.2013.860075

informa
healthcare

REVIEW ARTICLE

Bisphenol A and indicators of obesity, glucose metabolism/type 2 diabetes and cardiovascular disease: A systematic review of epidemiologic research

Judy S. LaKind[1,2,3], Michael Goodman[4], and Donald R. Mattison[5,6]

31 studies:
1 sample

3 studies:
> 1 sample

Most cross-sectional

Data source	Obesity	BMI	WC	BW	Other
NHANES 03/04, US					Obesity II
Pooled NHANES 03/06, US					
Pooled NHANES 03/08, US					
IVF, US					
CHAMACOS, US*					BF
					BF
					BF
Fertility study, US					
Pregnant women study, US					
BCERC, US					
CEHS, US					
HOME study, US					
Mother/infant study, Taiwan					
Cryptorchidism study, France					
InCHIANTI study, Italy					Obesity II
PCOS study, Greece					
PIVUS study, Sweden					
National Biomon. Survey, Korea					
Osteoporosis study, Korea					
Korea					
BMEH, Korea					
Meningioma study, China					
Songnan study, China					
Changning study, China					
Shanghai school study, China**					WHtR, SFT
Women's study, China					HC, FM, FFM, WHR
PCOS study, Japan					
PCOS study, Japan					

LaKind et al. Crit Rev Toxicol. 2014 44(2):121-50

"Cross-sectional studies of … exposure and prevalent health complaints often do little to advance our understanding of any causal associations and create a body of literature that has the potential to distract both researchers and the public from pressing public health concerns. Prudent attention to the principles of causal inference with attention to issues of exposure assessment will assist in focusing scientific attention toward associations of public health importance"

Engel and Wolf 2013. Annu. Rev. Public Health 2013. 34:139–58

Issues with Single Biomarker Measurement:

Temporal stability?

Attenuation?

Bias?

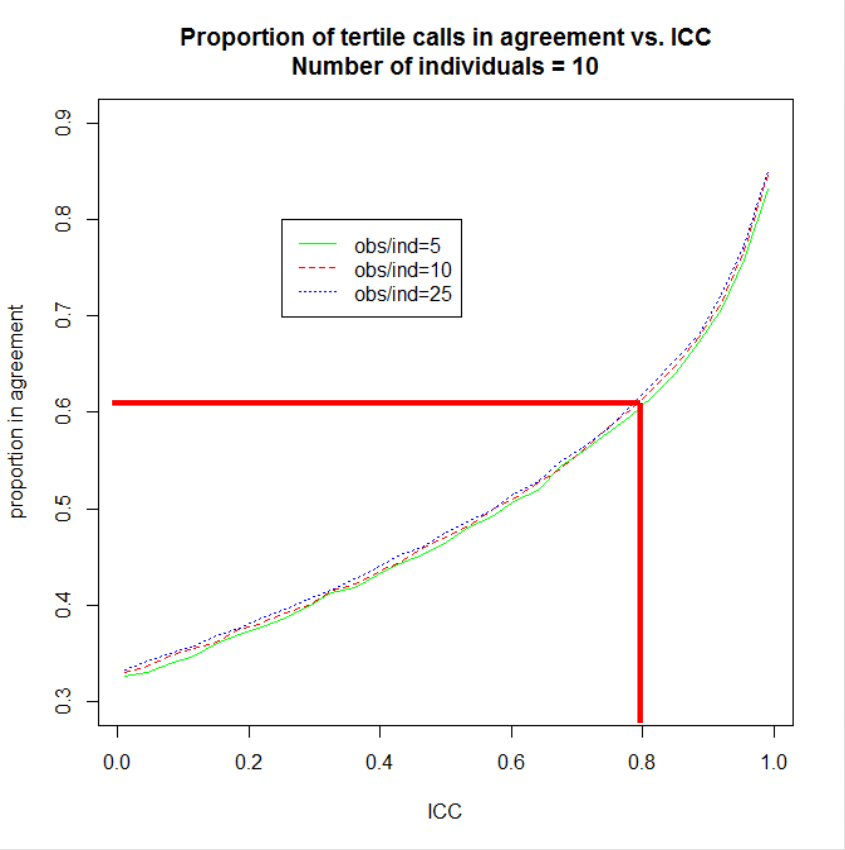
Single Sample: Temporal stability?

ICC = intraclass correlation coefficient = proportion of variability explained by between subject variation

$$ICC = \frac{\text{between-person variance}}{(\text{within-person variance} + \text{between-person variance})}$$

ICC > 0.40 - fair to good reproducibility

ICC ≥ 0.75 excellent



Rosner B. 2000. Fundamentals of Biostatistics. 5th edn. Duxbury, Pacific Grove, CA

Single Sample: Attenuation?

High within-person variability

↘

Increased measurement error

↘

Attenuation of associations between exposure and outcome

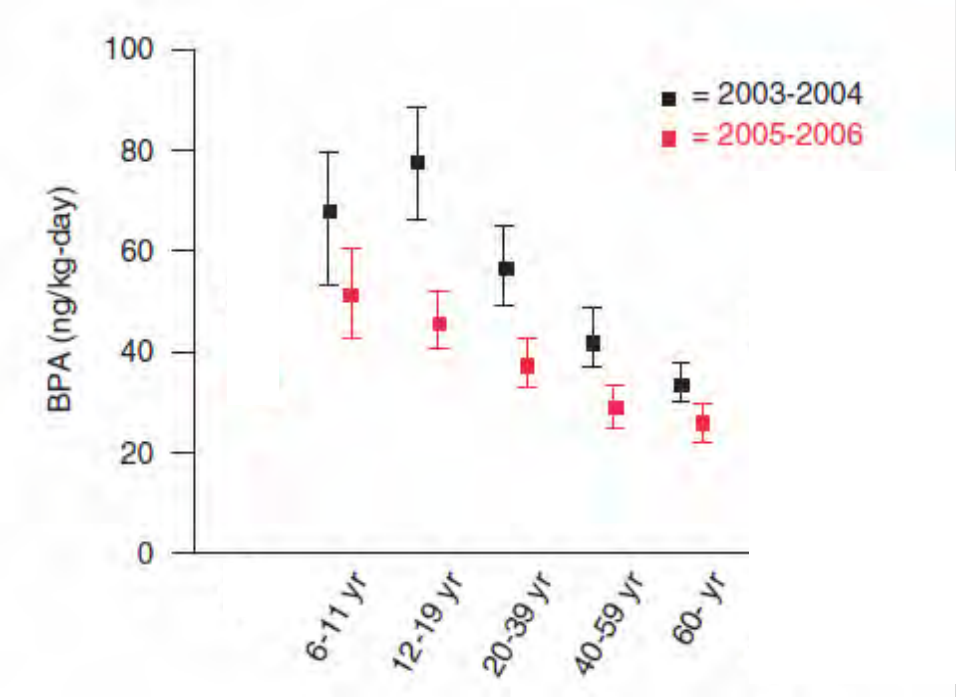
↘

More measurements will reveal associations

If null is true, more data won't translate to movement towards significant results

Single Sample: Bias?

measure may be affected by fasting interval, sampling time



Shorter fasting time, higher BPA

Longer fasting time, lower BPA

LaKind and Naiman. 2011. J Exp Sci Environ Epidemiol 21:272–279

"If you always do what you've always done, you'll always get what you've always got."

Biomarkers Workshop
Baltimore, MD 2013

"Best Practices for Obtaining, Interpreting and Using Human Biomonitoring Data in Epidemiology and Risk Assessment: Chemicals with Short Biological Half-Lives"

- Attendees: government, academia, and private institutions; US, Canada, Europe

- Expertise: analytical chemistry, exposure and risk assessment, epidemiology, medicine, PBPK modeling, and clinical biomarkers

Aim: Produce a set of systematic guidelines for:

- ✓ designing, implementing and interpreting studies of short-lived chemicals that use biomonitoring as the exposure metric
- ✓ evaluating study quality for WOE assessments
- ✓ evaluating quality during peer review:
  grants, publications

Environment International 73 (2014) 195–207

Contents lists available at ScienceDirect

Environment International

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

A proposal for assessing study quality: Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C) instrument

Judy S. LaKind [a,b,c,*], Jon R. Sobus [d], Michael Goodman [e], Dana Boyd Barr [f], Peter Fürst [g], Richard J. Albertini [h], Tye E. Arbuckle [i], Greet Schoeters [j,k], Yu-Mei Tan [d], Justin Teeguarden [l], Rogelio Tornero-Velez [d], Clifford P. Weisel [m]

The Workshop was sponsored by ACC, which was not involved in the design, management, or development of the Workshop or in the preparation or approval of the manuscript.

BEES-C

STUDY ASSESSMENT COMPONENTS	TIER 1	TIER 2	TIER 3
Biomarker Selection and Measurement			
Biological relevance Exposure biomarker			
Effect biomarker			
Specificity			
Method sensitivity			
Biomarker stability			
Sample contamination			
Method requirements			
Matrix adjustment			
Study Design and Implementation			
Temporality			
Exposure variability and misclassification			
General Epidemiological Study Design Considerations			
Study rationale			
Study participants			
Reporting			
Data analysis			

BPA and neurodevelopment

Exposure-Related Study Design and Execution					
Temporality	Hypothesis that early exposures are related to neurodevelopmental outcomes. Study is prospective birth cohort with both pre- and postnatal exposures assessed.	Maternal sample not routinely collected at same time-point. Prospectively collected samples with 1 maternal and 1 child sample.	Considered prenatal exposure and post natal exposure.	Exposure assessed prenatally outcomes ascertained at 3-5 years of age.	One time point prenatal 24-40 weeks and one time point for child 3-4 year.
Exposure variability and misclassification	Single sample from pregnant women and single sample from children.	Single sample in pregnancy.	Only single spot urinary sample per individual.	One sample.	Single spot urine can lead to misclassification. No explicit evaluation of error.

Exposure-Related Study Design and Execution					
Temporality	Hypothesis that early exposures are related to neurodevelopmental outcomes. Study is prospective birth cohort with both pre- and postnatal exposures assessed.	Prospectively collected samples over the course of study in mothers and children.	Samples are collected prior to health outcome measurements during the period that is assumed to be critical.	Exposure assessed prenatally and early in life, outcomes ascertained at 2 years of age.	Multiple time points were taken, 16 weeks and 26 weeks of pregnancy and at birth.
Exposure variability and misclassification	Reported correlations for concentrations cross three sampling times; Pearson r values; authors recognize potential for exposure misclassification based on only one sample at 16 weeks gestation; authors also noted moderate intra-individual correlation in BPA levels.	More than one sample collected but variability through pregnancy still not appropriately evaluated.	Reported correlations for concentrations cross three sampling times; Pearson r values were calculated but showed weak relationships; authors recognize potential for exposure misclassification based on only one sample at 16 weeks gestation.	Spot sample results converted to mean values. This is better that single spot values, but still inadequate for a chemicals with short half-life. A repeated measures analysis and a formal assessment of exposure misclassification would be helpful.	Multiple spot samples at different points in pregnancy, though appears to have been analyzed separately, possible misclassification of exposure for identifying short time sensitive windows of development is discussed.

Environ Int. 2015. 80:41–71

Summary/Conclusions

Growing recognition of the problem:

"The poor reproducibility of the measured urinary [haloacetic acid] concentrations indicate that a single measurement may not accurately reflect individual long-term exposure" (Wang et al. 2014)

"A consequence of the considerable variability in urinary excretion of BPA may be misclassification of individual BPA exposure level in epidemiological studies" (Lassen et al. 2013)

"These results indicate that a single measure of urinary 3-PBA [3-phenoxybenzoic acid - pyrethroid metabolite] was not sufficient to characterize average exposure" (Morgan et al. 2016)

Summary/Conclusions

- Difficult to do studies with more/better exposure data: increased burden on researchers, requires more funding, more participant cooperation

- May not be possible to get perfect studies funded, but we can still work towards ensuring that the exposure data capture actual exposures at relevant time(s)

- Funding agencies, journals – encouraging better exposure assessments – use of BEES-C or components of instrument
  (Office of Health Assessment and Translation - Systematic Review and Evidence Integration: quality of exposure assessment is being considered as a topic for future method/terminology refinement)

You can't always get what you want...

But if you try sometime you find you get what you need

Rolling Stones