



Variability in excretion of urinary metabolites of toxicants with short half-lives: Implications for results communication and interpretation

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Today's Talk

- Brief background on urinary metabolites as exposure biomarkers
- Examples of within and between subject variability
- Introduce discussion on
 - Implications for communicating results to study participants
 - Implications for results interpretation





Common Exposure Biomarkers

Measurements in:

- Urine
- Blood
- Breast milk
- Saliva
- Hair
- Meconium

- Urine is easy to collect, non-invasive, readily available, laboratory methods are commonly available. Especially useful for children.





What is a Metabolite?

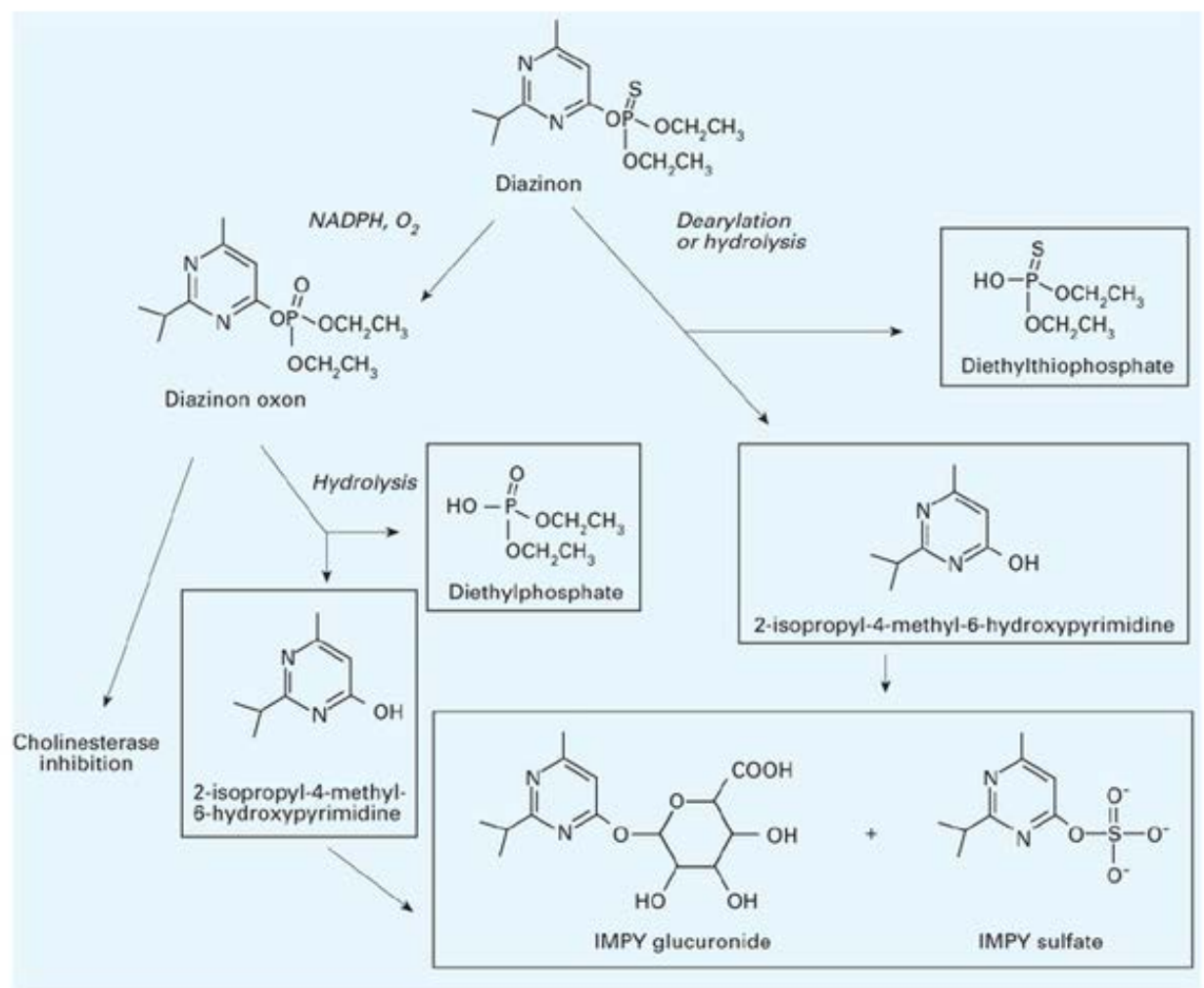


Figure 1. The general metabolism of *O,O*-diethyl OP pesticides using diazinon as a model. The metabolites enclosed in boxes are excreted in urine.

Barr et al 2004



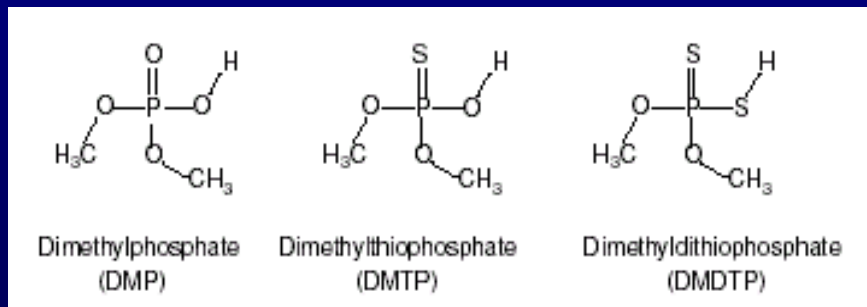
Example: Organophosphate (OP) Pesticides



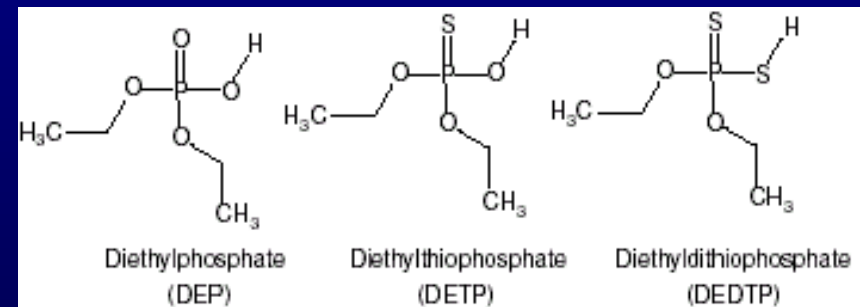
- Account for about ½ of all insecticides used in U.S.
- Widely used in agriculture
- Some banned for home use
- Short half-lives in body (hrs-days)
- Excreted in urine as dialkyl phosphate (DAP) metabolites
- Acute neurotoxins

Urinary Biomarkers of Exposure

- **Dialkylphosphates (DAPs): excretory products of OPs**
 - DAPS = 3 dimethyls & 3 diethyls
 - ~75% of registered OPs metabolize to DAPs in urine
 - **CLASS-specific NOT** pesticide-specific

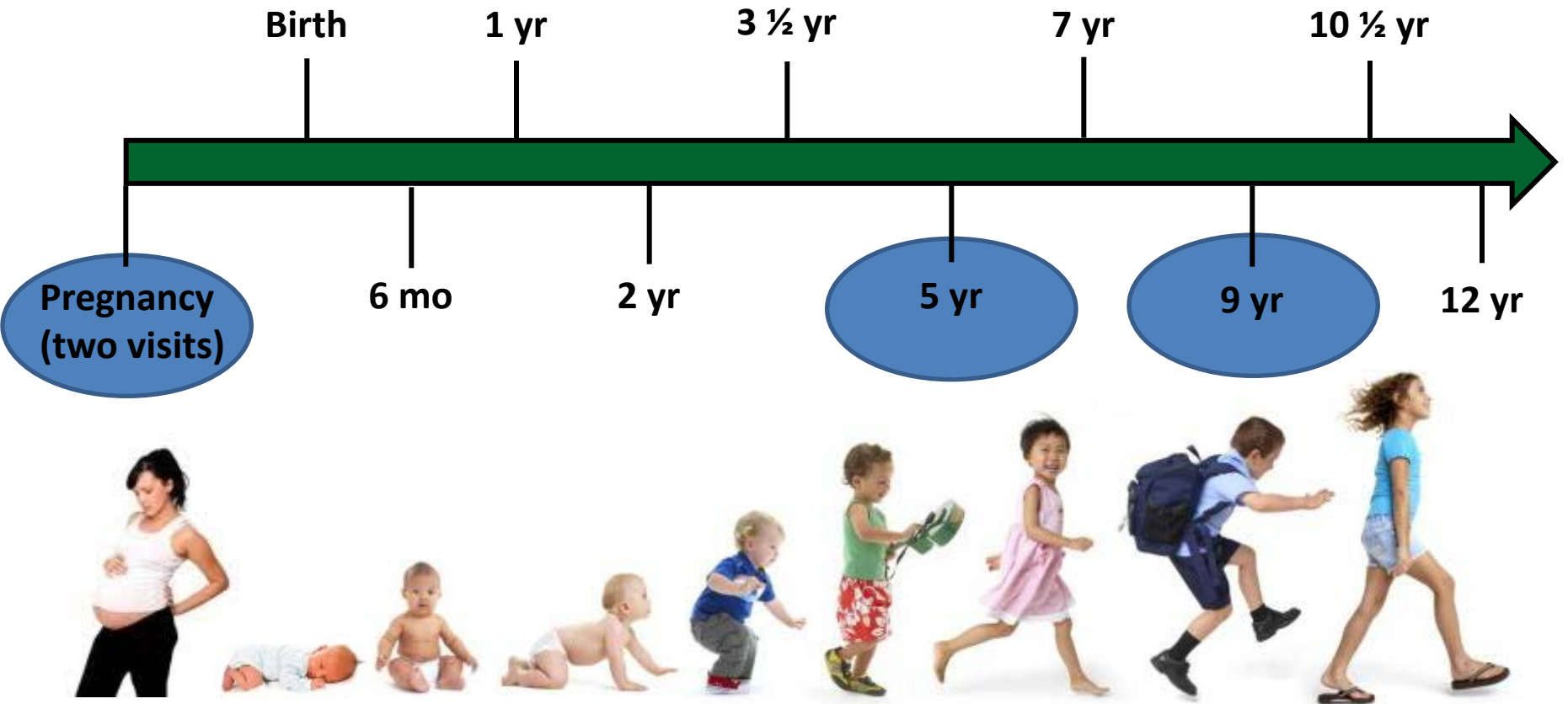


Dimethyls



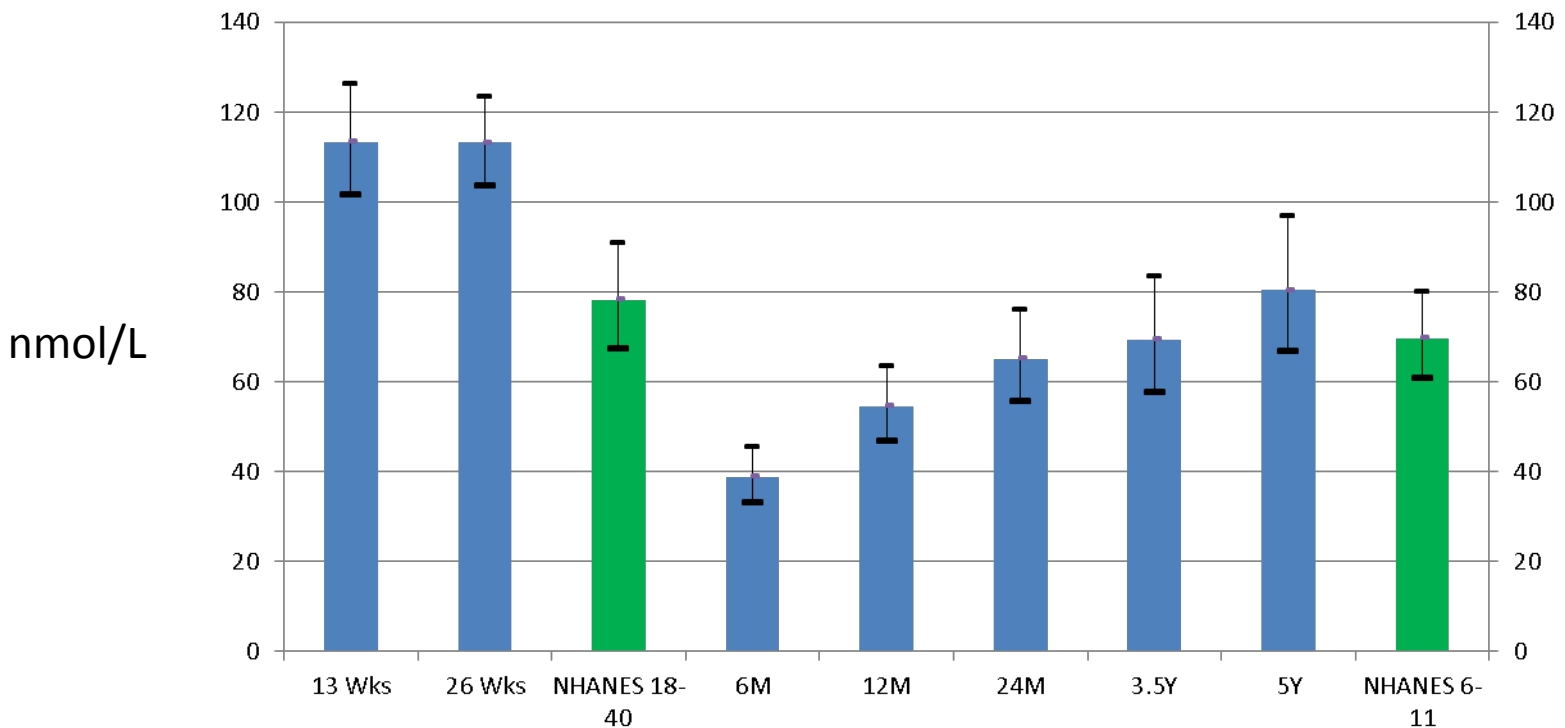
Diethyls

CHAMACOS Cohort Study





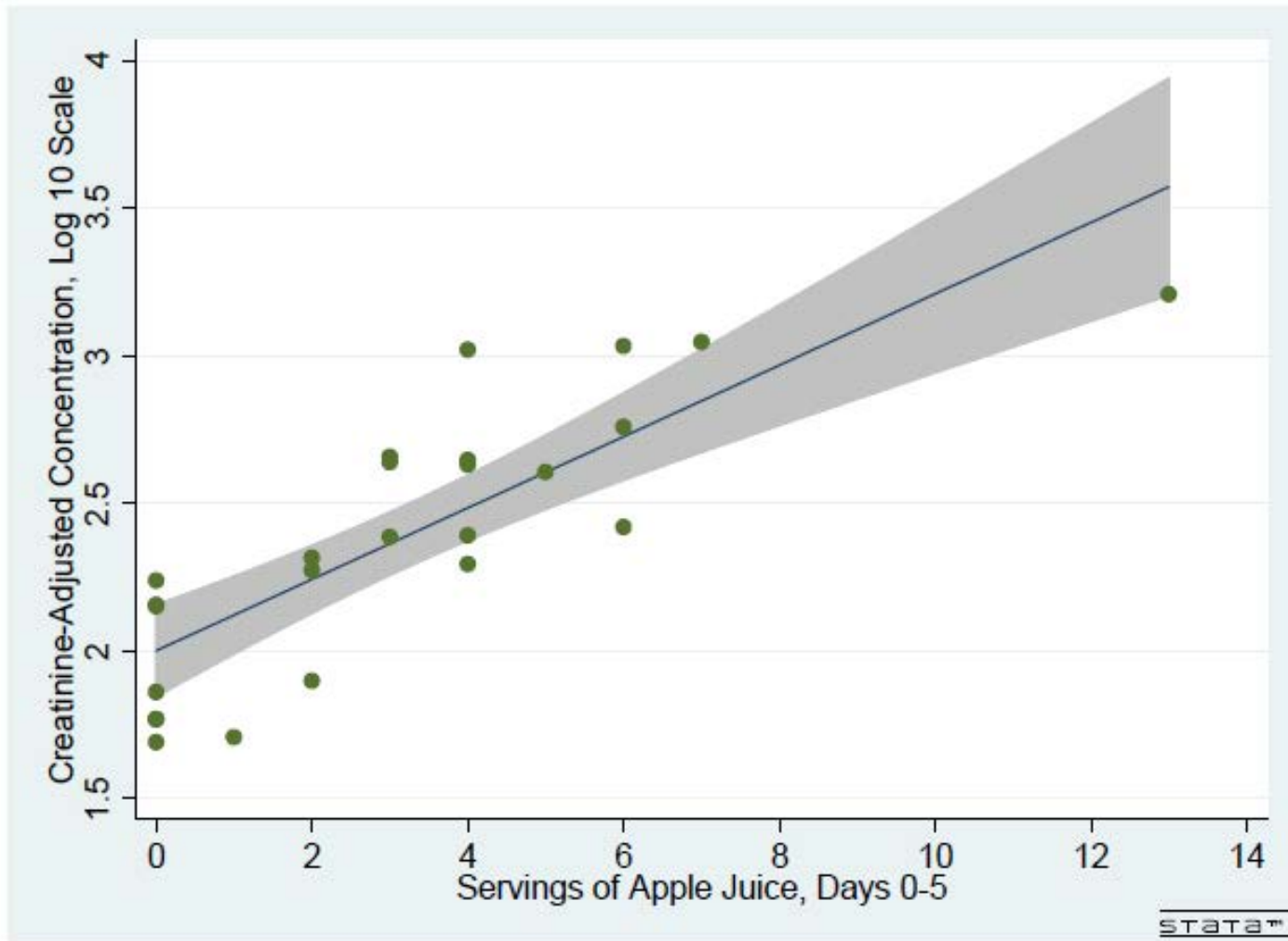
Prenatal and child OP metabolites in CHAMACOS and National Reference



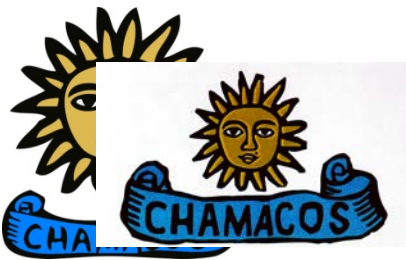
* National Health and Nutrition Examination Survey



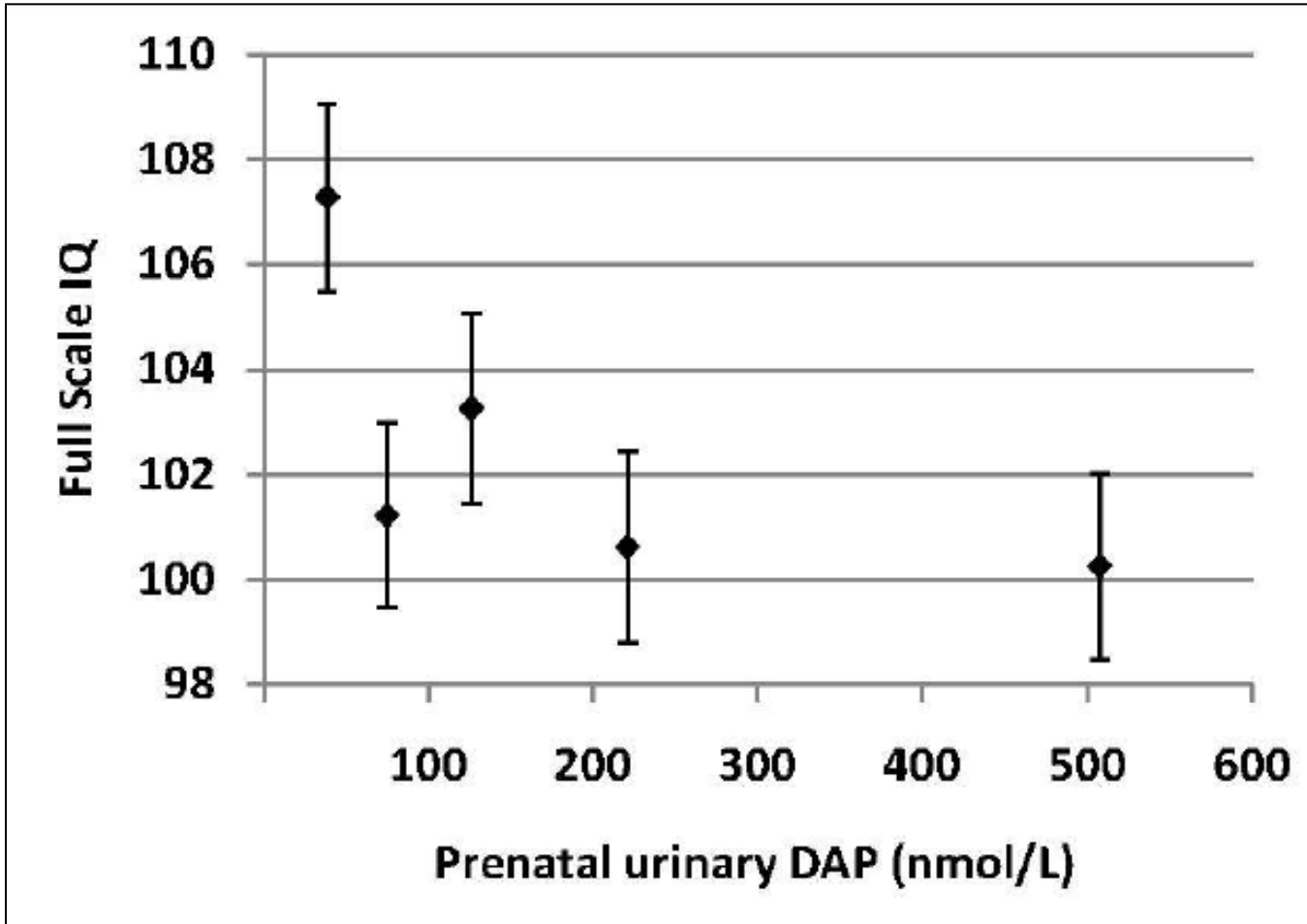
Fruit juice consumption could explain some variability in OP levels



Bradman and Kogut, et. al. in preparation



Prenatal DAPS related to WISC IQ at age 7



Adjusted for HOME score (6 months), maternal education and IQ, and language of testing

Bouchard et al. ,EHP, 2011



For OPs, urinary metabolites can provide valuable information about exposure and health effects.

However, there are limitations.



Variability

Sources:

- Intermittent exposures
- Short half-life in body
- Differences in metabolic capacity
- Differences in pharmacokinetic characteristics



Correlation of 24 hr samples collected three days apart (n=25, ages 3-6, Cr adj.)

Total DAPS 0.35

Dimethyls 0.36

Diethyls 0.15

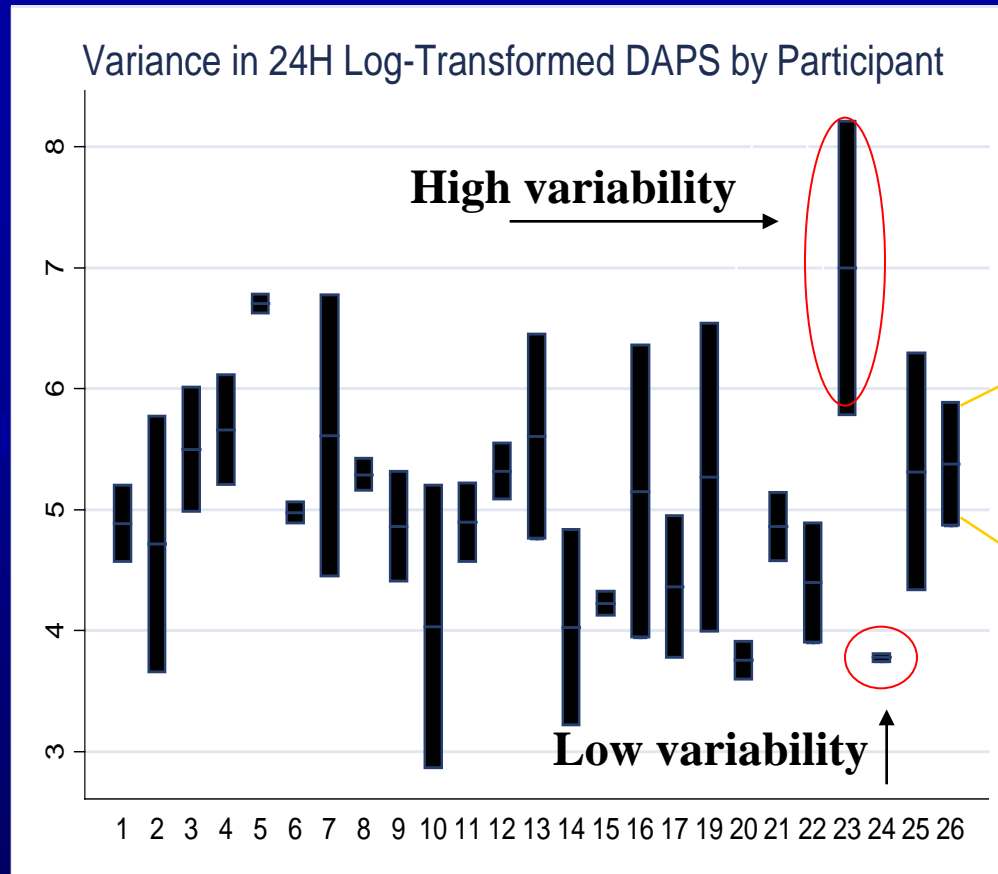
p>0.5

Bradman and Kogut et al, in final review.
Do not cite.



Metabolites in 24 hr urine samples collected 3 days apart (n=25 pairs).

Log [DAPS]



Estimated within and between variability (SD)

Between

35%

Within

65%

Do not cite.

Bradman and Kogut et al, in final review



Correlation of DAP metabolites in spot urine samples collected 1-6 days apart

Days Elapsed Between Paired Samples

0 (Same Day)	1	2	3	4	5	6
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Spot Samples

	(N=92 ^a)	(303)	(248)	(203)	(154)	(77)	(25)
Total DAPs	0.46*	0.45*	0.25*	0.23*	0.17*	0.16	0.16
Total DMs	0.49*	0.48*	0.35*	0.30*	0.21*	0.18	0.13
Total DEs	0.25*	0.22*	-0.15	0.08	0.02	0.11	-0.27



Variance apportionment for OP, BPA, and phthalate metabolites

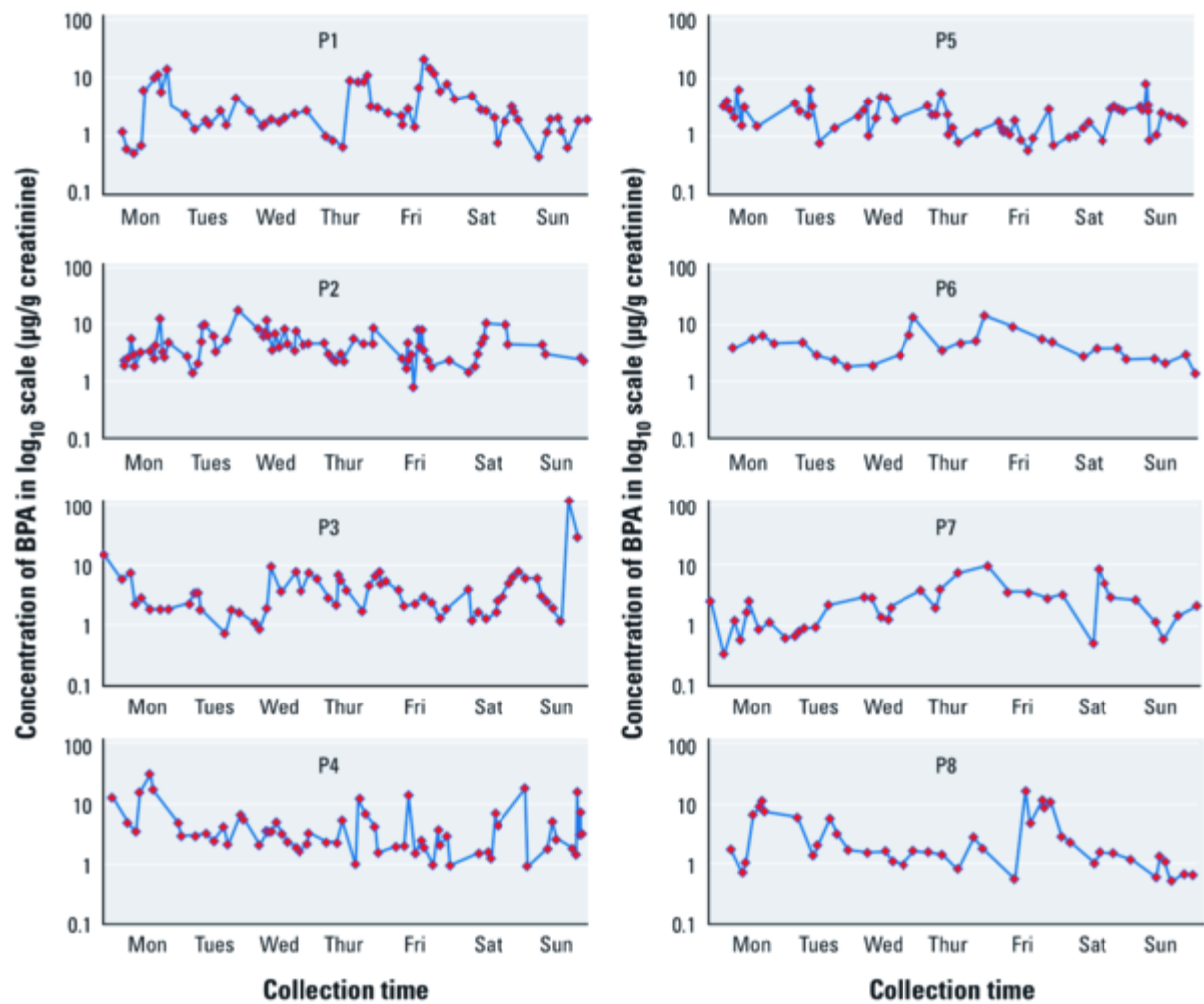
Variance	OP (%)	BPA (%)	Ph- DEHP (%)	Ph- DEP (%)
Between subject	31	9	17	77
Within-subject between-day	20	21	32	2
Within-subject within-day	49	70	51	21

Source: Bradman et al submitted (OP - children)

Source: Preau et al 2010; Ye et al 2010 (BPA and phthalates - adults)



BPA in adult urine over one week



Ye et al 2010



OP Exposure Classification in Children: Sensitivity and Specificity of Spot Samples vs One Week of Exposure

	High (Top 20%)		Elevated (Top 40%)	
	Sensitivity	Specificity	Sensitivity	Specificity
One Sample	0.46	0.87	0.63	0.75
Two Samples ^c	0.60	0.90	0.76	0.84
Three Samples ^c	0.64	0.91	0.73	0.82

Bradman and Kogut, in final review.
Do not cite.



Implications for Returning Results

- Some metabolites show little intra-individual variability in spot samples.
- For others, high within-subject variability raises challenges:
 - providing exposure information to participants (acute, vs. chronic)
 - comparing to larger group or other populations



CHAMACOS:

Approaches for Results Return

- Begins with consent
 - Purpose of study
 - Medical or non-medical utility of measurements
 - Informed that results available
 - Return results at each visit if requested
 - One on one meeting
 - Offer repeat testing – usually some tests low
 - Provide education on reducing exposures
- To date: No problems or other concerns among participants.



Technical Challenges

- Urinary metabolites are a valuable tool to assess exposure to non-persistent pesticides:
 - Ease of collection, especially important for children
 - Laboratory methods often available
 - Potential for exposure missclassification



Implications for epidemiology and risk assessment

- High intra-individual variability.
 - Cross sectional sampling *may* give range of population exposure, but not indicator of individual chronic exposure.
 - Single measurements may be relevant to acute exposures, but not chronic.
 - Studies need to consider these factors to be adequately powered



Research Needs

- More research is needed to evaluate intra- and inter-person variability of exposure biomarkers;



Thanks to our funders



and Katie Kogut



Questions/Discussion