

Update from CDC: Phthalates and Phthalate Alternatives

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Outline

- ❑ **Phthalates exposure generalities**
- ❑ **Changes in exposures**
 - Use of NHANES
 - Archived samples: DINCH example
 - German Environmental Specimen Bank
- ❑ **Selection of phthalate biomarkers**
 - DiNP
 - DBP and DiBP
- ❑ **Toxicology vs exposures**
 - DPP
- ❑ **Future work**

What are Phthalates?

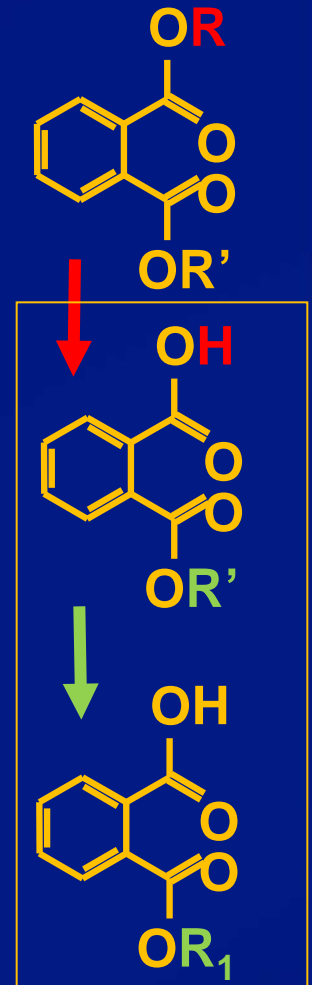
❑ Widely used industrial chemicals

- As plasticizers of PVC
 - Miscellaneous products
 - Medical devices, tubing and blood bags
- In consumer & personal care products
 - Fragranced products, cosmetics
 - Paints, ink & lacquers
 - Medications

❑ Adverse health outcomes in experimental animals exposed to high doses of phthalates

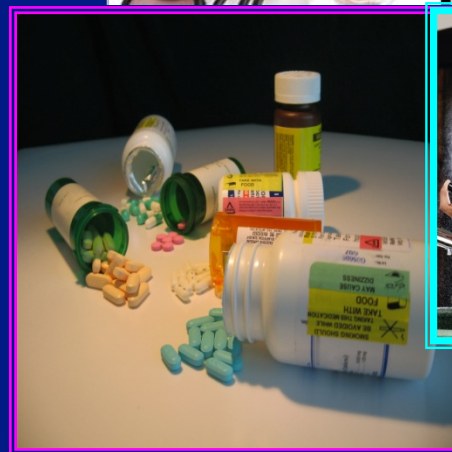
❑ Emerging data on potential human effects at background exposure levels

❑ Metabolites as biomarkers of exposure



The Human Exposure Scenario

- ❑ Controlled conditions, as in animal studies, do not apply
- ❑ Numerous and even unknown exposure routes and sources
- ❑ Unknown dose, duration, frequency and timing
- ❑ People exposed to chemical “cocktails” (multiple/mixtures)
- ❑ Biomonitoring to assess exposures



CDC's Phthalates Biomonitoring Program Areas

- ❑ **Assess exposure to phthalates & alternatives**
- ❑ **Assess associations between exposure & health**
- ❑ **R&D to improve Biomonitoring practices**
 - ❑ Develop analytical methods
 - ❑ Identify & validate biomarkers
 - ❑ Replacement chemicals
 - ❑ Develop Standard Reference Materials
- ❑ **Capacity building**
 - ❑ Public Health Laboratories: Performance testing

Biomonitoring Methods

General requirements

- ❑ Sensitive
- ❑ Specific/Selective
- ❑ Accurate
- ❑ Precise

Biomonitoring-specific

- ❑ Minimum sample volume
 - ❑ Reduce solvent use & waste
- ❑ Multianalyte & high-throughput
 - ❑ Increase efficiency
- ❑ Reproducible
- ❑ Include QA/QC program
 - ❑ Accountability
- ❑ Automated
 - ❑ Cost effective

Best compromise

Accuracy: The Importance of Quantification

- ❑ Analytical standards
 - Custom synthesis
- ❑ Analytical method
- ❑ Well-maintained instrumentation
- ❑ Trained personnel
- ❑ External Quality Assessment Programs
 - G-EQUAS (<http://www.g-equas.de/>)
 - Four DEHP metabolites, MnBP, MiBP, MBzP
 - Accuracy of standards (neat vs solution)

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Article

Accuracy Investigation of Phthalate Metabolite Standards

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Standard Reference Materials

□ NIST SRMs

- Urine from smokers (3672)
- Urine from non-smokers (3673)
- First frozen urine reference materials characterized for organic environmental contaminants
 - 11 phthalate metabolites



Table 2. Reference Mass Fraction Values for Selected Phthalate Metabolites in SRM 3672

Phthalate Metabolites	Mass Fraction ^(a,b) ($\mu\text{g}/\text{kg}$)	
Mono-carboxynonyl phthalate isomers ^(c)	1.92 \pm	0.06
Mono-carboxyoctyl phthalate isomers ^(d)	21.3 \pm	1.1
Mono-(2-ethyl-5-carboxypentyl) phthalate	35.2 \pm	1.7
Mono-(2-ethyl-5-hydroxyhexyl) phthalate	24.8 \pm	0.4
Mono-(2-ethyl-5-oxohexyl) phthalate	14.9 \pm	0.4
Mono-(2-ethylhexyl) phthalate	4.13 \pm	0.15
Mono-(3-carboxypropyl) phthalate	2.99 \pm	0.20
Monobenzyl phthalate	8.37 \pm	0.18
Monoethyl phthalate	94.5 \pm	3.0
Mono-isobutyl phthalate	6.40 \pm	0.28
Mono- <i>n</i> -butyl phthalate	10.6 \pm	0.5

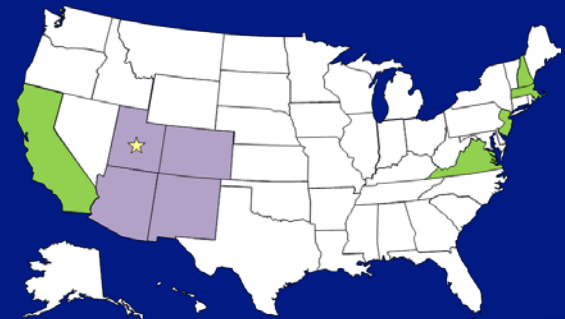
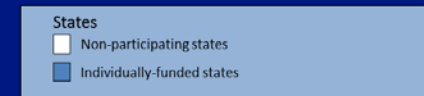
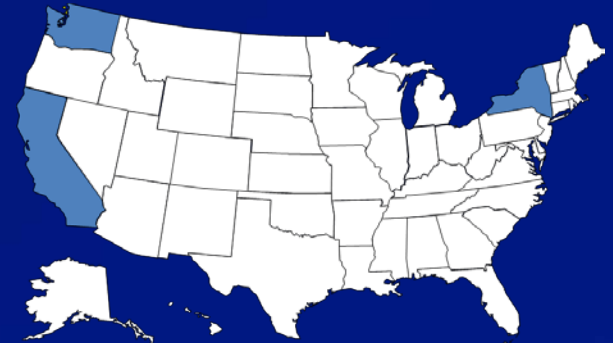
State Biomonitoring Cooperative Agreements

□ Technical support (2009+)

- Training
- Site visits
- Advisory services

□ Quality assurance programs (2012+)

- In-kind performance testing
 - Phthalates & other plasticizers
 - PAHs
 - Environmental Phenols & PCPs
 - Pesticides
 - Universal Pesticides
 - Dialkyl Phosphates
 - PFCs



Exposure to Phthalates in the United States

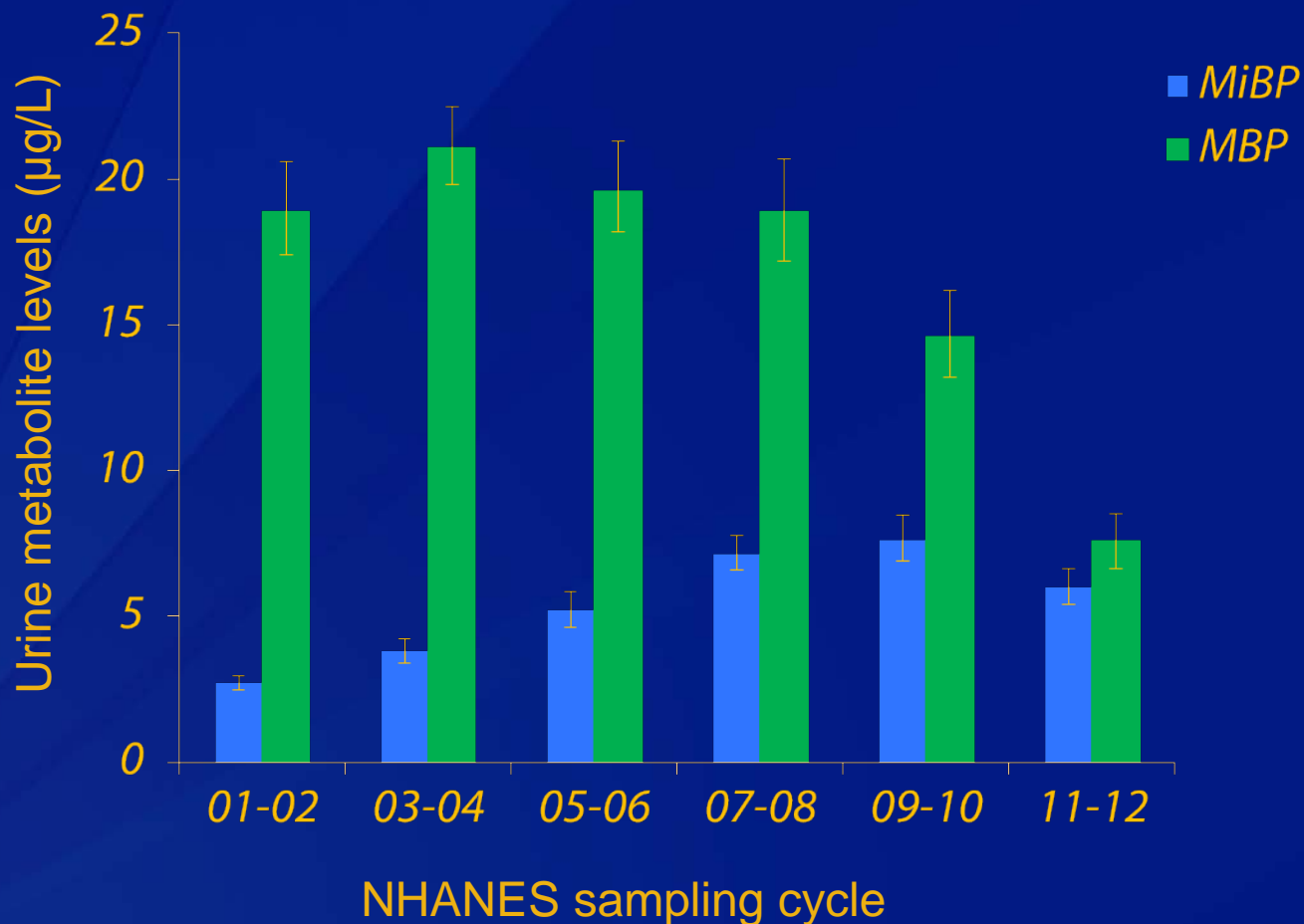
- Most Americans (6+ years) are exposed

NHANES 2011-2012	
<i>Compound</i>	<i>Detection frequency (%)</i>
<i>DEHP</i>	100
<i>DiNP</i>	100
<i>DiDP</i>	99
<i>BBzP</i>	98
<i>DnBP</i>	94
<i>DiBP</i>	99
<i>DEP</i>	100

n=2,489

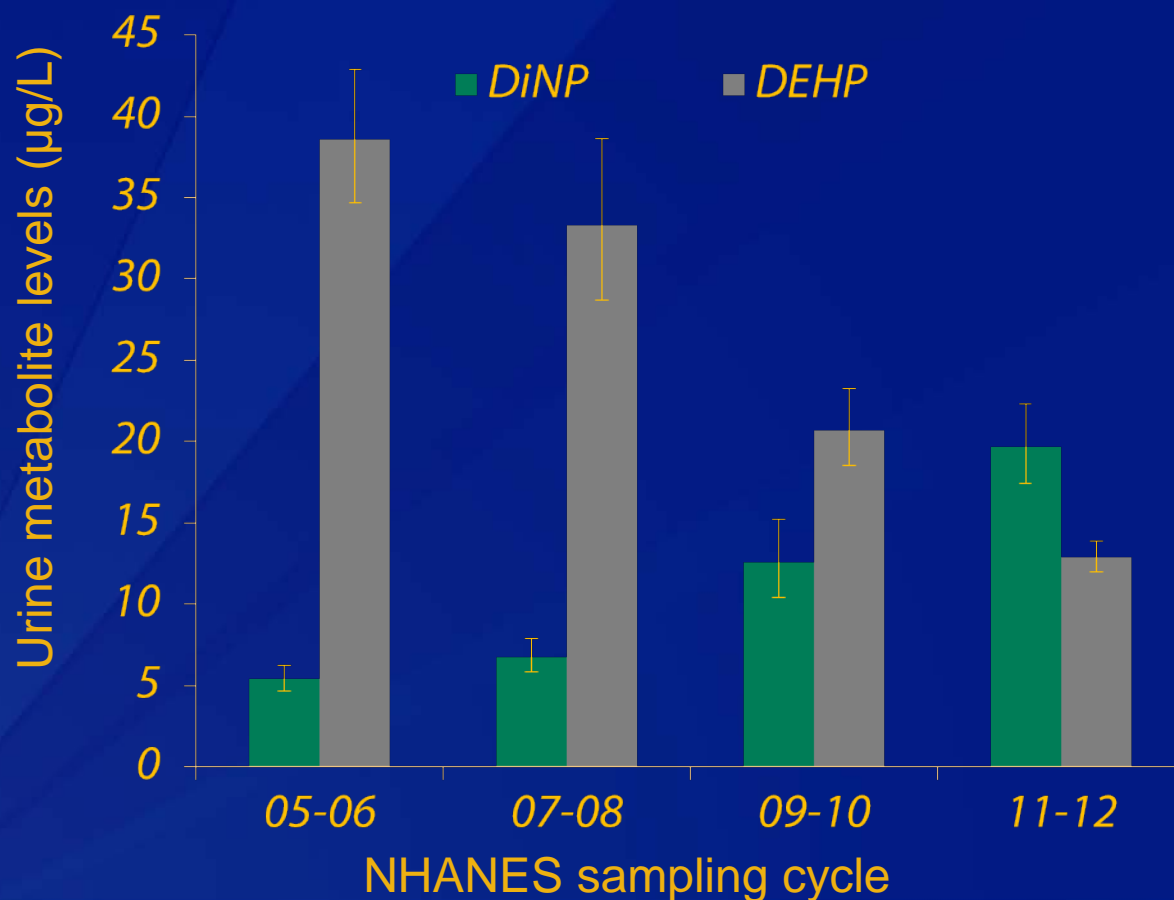
Is Americans' Exposure to Phthalates Changing?

- Some exposures increased: DiBP (↑ 121%)
- Other exposures decreased: DBP (↓ -60%)



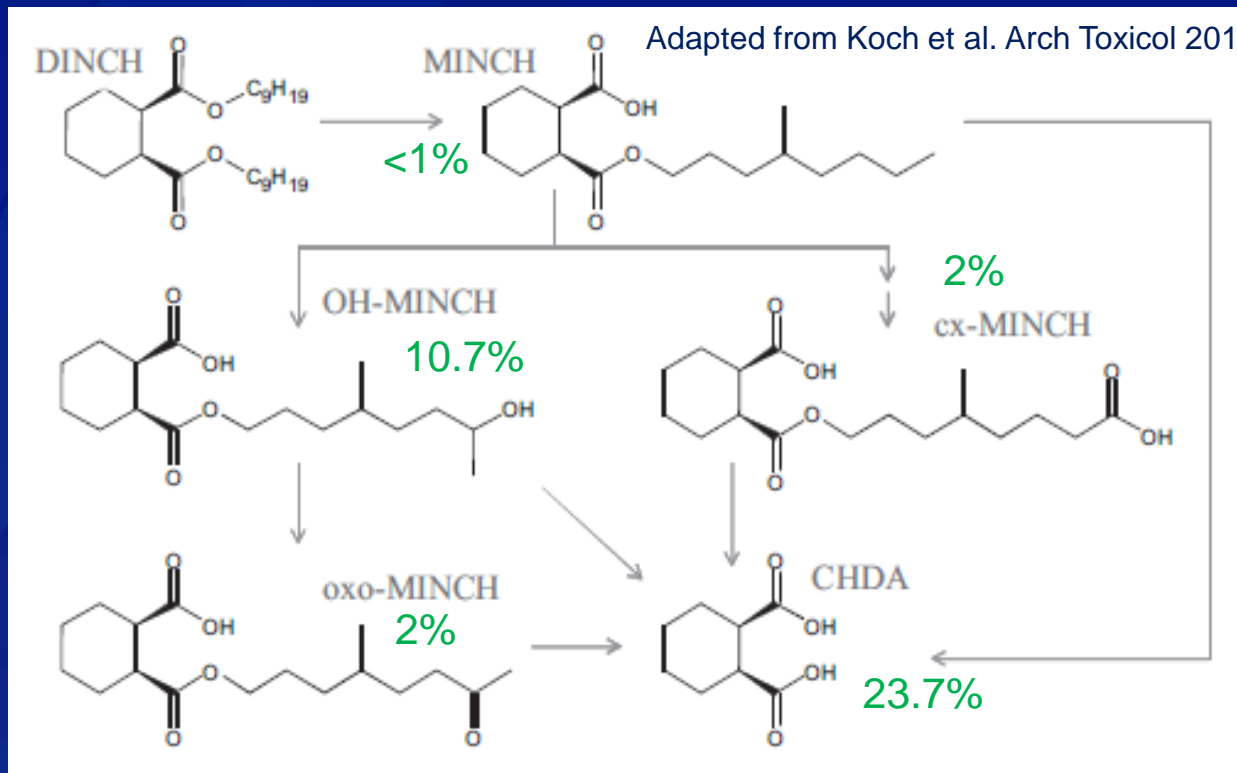
Americans' Exposures Change across Phthalates

- Some exposures increased: DiNP (↑ 265%)
- Other exposures decreased: DEHP (↓ -67%)
- Legislative actions and public scrutiny



Other Plasticizers: DINCH

- ❑ Phthalate alternative introduced in Europe in 2002
- ❑ DEHP replacement
 - Toys, medical devices, food packaging
- ❑ Metabolites as exposure biomarkers



Are Exposures to DINCH Changing?

- ❑ **Convenience U.S. adult sampling (2000-2012)**
 - DINCH metabolites
 - Undetected in 2000-1
 - Increasing detection frequency after 2001
 - Increasing concentrations
- ❑ **Similar results observed in Germany**

DINCH metabolite (OH-MINCH) urinary concentrations				
<i>Year</i>	<i>N</i>	<i>Detection frequency (%)</i>	<i>50th (µg/L)</i>	<i>95th (µg/L)</i>
2000	114	0	<LOD	<LOD
2001	57	0	<LOD	<LOD
2007	23	4	<LOD	<LOD
2009	118	8	<LOD	0.5
2011	94	13	<LOD	1.5
2012	121	19	<LOD	1.4

LOD: 0.4 µg/L

DINCH General Population Data

Germany

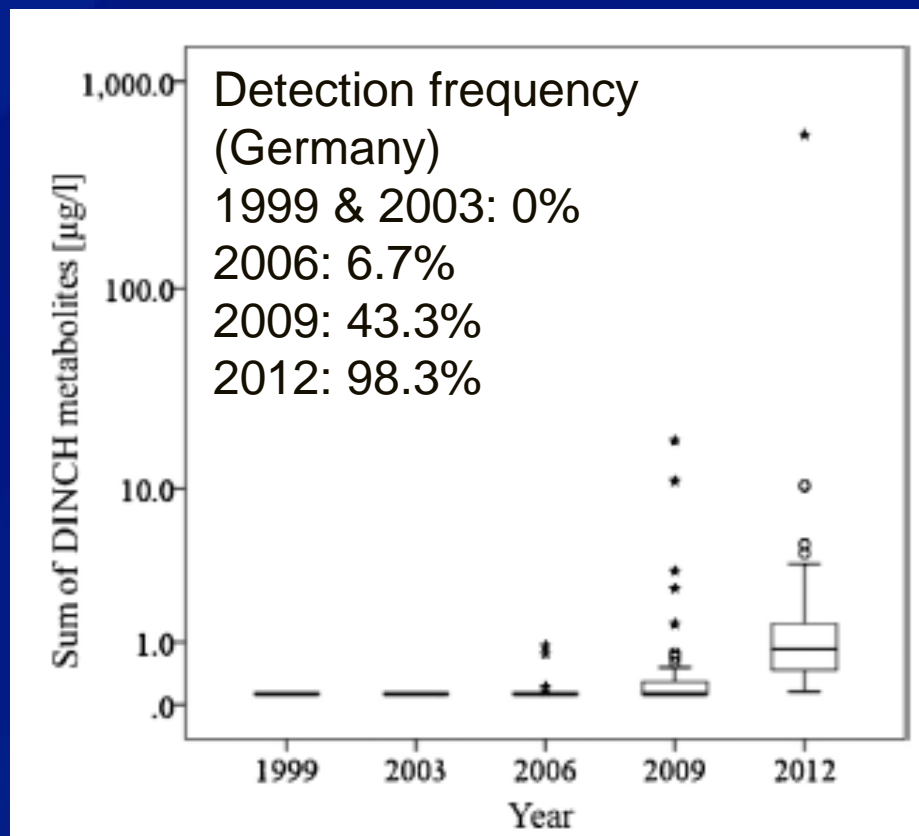
□ ESB

- 24-h urine samples
- College students
- 60 samples/year
- 4 metabolites

USA

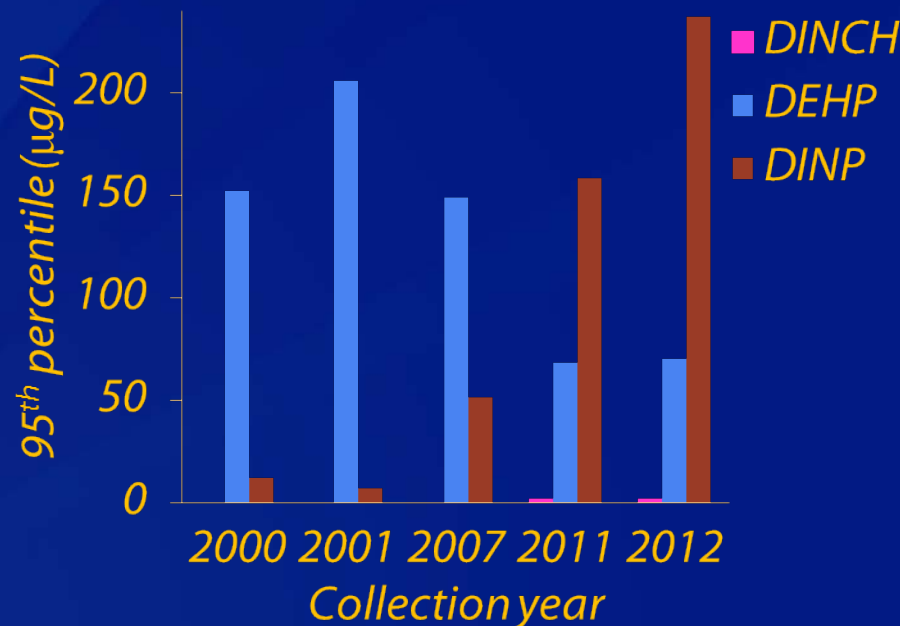
□ NHANES 2011-2

- Spot sample
- 6+ years old
- One metabolite (OH-MINCH)
- Detection frequency: 24% (605/2489)
- Range: <LOD (0.4 µg/L) to 168 µg/L



Are DINCH and Other Phthalates Replacing DEHP?

- **DINP/DEHP trends in convenience samples**
 - US & German general population
- **DINCH & DINP may be replacing DEHP**
 - Isomeric compounds
 - Starting with NHANES 2013-4, CDC will include another DINCH isomer



Monitoring Changes in Phthalates Exposures

- ❑ **Constantly evolving**
- ❑ **Identification of biomarkers**
 - In-vitro metabolism
 - In-vivo animal studies
 - Human studies
 - University of Bochum, Germany
- ❑ **Biomarkers choice**
- ❑ **Access to archived urine**
 - Convenience samples
 - General population samples

Analyte vs Exposure Biomarker

Many analytes can be measured simultaneously, but additional information is needed to demonstrate the utility of these analytes as exposure biomarkers

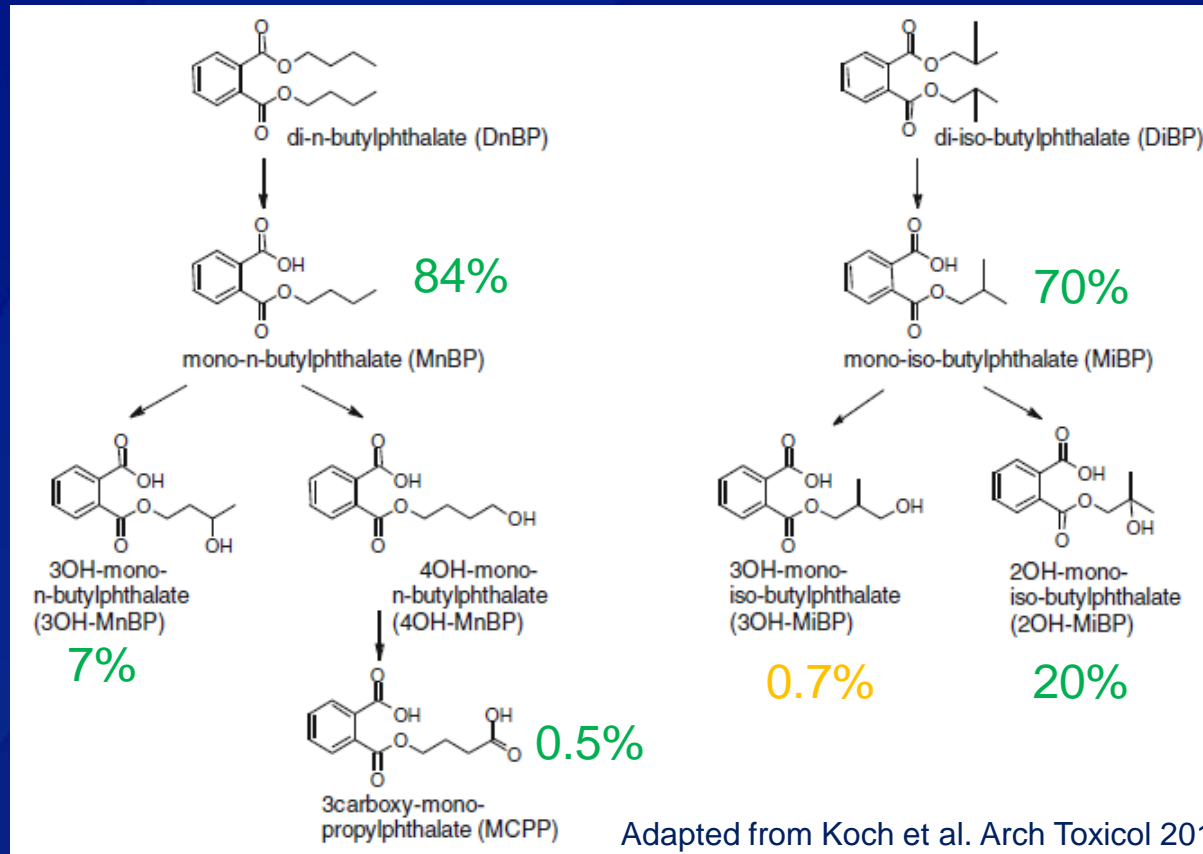
Selection of Exposure Biomarkers: DINP Example

- ❑ DINP metabolites: MNP (~2%) and MCOP (~11%)
- ❑ MNP (minor metabolite): insensitive biomarker of DINP background exposures

Unweighted number of participants (weighted percentage)	MCOP urinary concentrations			
	<i>Detectable</i>	<i>Non-detectable</i>	<i>Total</i>	
MNP urinary concentrations	<i>Detectable</i>	347 (12.9%)	2 (0.02%)	349 (12.9%)
	<i>Non-detectable</i>	2100 (82.4%)	99 (4.7%)	2199 (87.1%)
	<i>Total</i>	2447 (95%)	101 (5%)	

- ❑ Select most abundant/relevant biomarker to minimize exposure misclassification
 - 82.4% of persons classified as exposed to DINP are misclassified based on urinary concentrations of MNP only

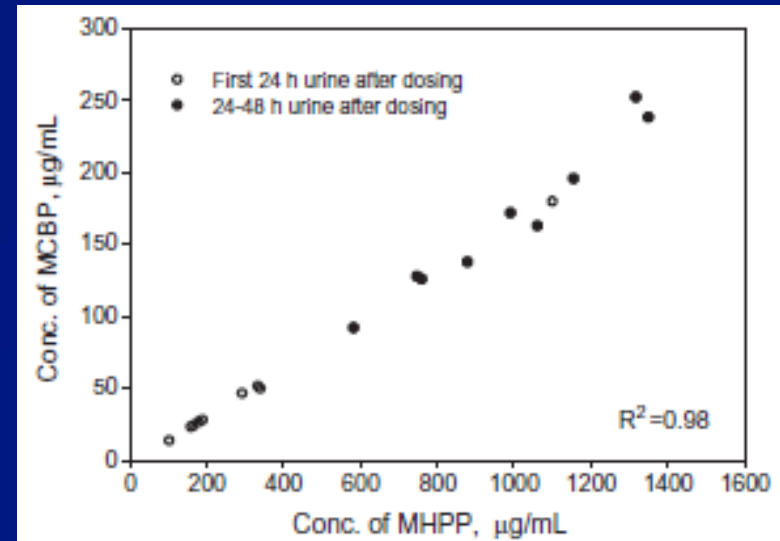
Dibutyl Phthalates in NHANES



- ❑ NHANES 1999-2000: MBP (MnBP + MiBP)
- ❑ NHANES 2001-12: MnBP & MiBP
- ❑ NHANES 2013+: MnBP, MiBP, 3OH-MnBP, 2OH-MiBP

Toxicology vs Exposure: Dipentyl Phthalate (DPP)

- ❑ Nitrocellulose plasticizer
 - Plastic film, inks & wood coatings
- ❑ Testicular toxicant in rats
- ❑ In-vivo metabolism in rats
 - Nine rats
 - Single oral dose (500 mg/Kg)
 - Urine collected 24-h & 48-h after dose



DPP metabolite median urinary concentrations (µg/mL)

Metabolite	24-h post dose	48-h post dose
MPP	222	75
MHPP	993	191
MCBP	168	29

Human Exposure to Dipentyl Phthalate (DPP)

- **Forty-five spot samples**
- **Anonymously collected in 2009 from adults**
 - Relatively low detection frequency for MHPP (specific)
 - No correlation between MHPP & MCBP/MCPP
- **Limited exposure to DPP in US adults**

DPP metabolite urinary concentrations			
<i>Metabolite</i>	<i>% Detection</i>	<i>Min (µg/L)</i>	<i>Max (µg/L)</i>
<i>MPP</i>	<i>0</i>	<i>NA</i>	<i>NA</i>
<i>MHPP</i>	<i>29</i>	<i><LOD</i>	<i>8</i>
<i>MCBP</i>	<i>4</i>	<i><LOD</i>	<i>221</i>
<i>MCPP</i>	<i>13</i>	<i><LOD</i>	<i>40</i>

What Exposure Biomarkers Should We Measure?

□ Analytical method

- Can we add more analytes?
- Instrumentation
 - DiDP vs Bis-(2-propylheptyl)phthalate (DHP)

□ Toxicokinetics

- Abundance
- Specificity

□ Target population

- Exposures can be population-specific
 - Age-dependent

□ Nature of exposure

- Background vs specific exposures

Take Home Messages

- ❑ **Americans are exposed to phthalates**
- ❑ **Market changes in commercial formulations**
 - Introduction of replacement chemicals
 - Phthalates (e.g., DiNP)
 - Non-phthalates (e.g., DINCH)
 - Changing exposures
- ❑ **Biomonitoring & biomarkers toxicokinetics**
 - Specificity
 - Abundance
- ❑ **Method adequate for intended purpose**
- ❑ **Banking of urine**
 - Trends evaluation

Future Work

- **Continue NHANES & studies on targeted populations**
 - Track exposures to “legacy” & replacement chemicals
 - Fill in data gaps to better understand temporal trends and underlying reasons
- **Identify & incorporate phthalate and phthalate replacement biomarkers**

Acknowledgements

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THANK YOU!

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