Case Study on Phthalates

Phthalate exposures during pregnancy

Results from a birth cohort study of NYC inner-city mothers and newborns

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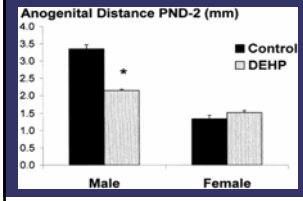
Why are we concerned about prenatal exposures?

Exposures are ubiquitous: 78 – 99% of U.S. population exposed.
A number are endocrine disruptors; including as antiandrogens.
Experimental and preliminary epidemiology evidence indicates

- A number are reproductive toxicants associated with:
- Malformations of developing male reproductive tract
- Increased intrauterine/postnatal death;
- Decreased fetal growth
- Modulation of gestational age (?)



(www.Nottoopretty.org)

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Specific aims of our research

Aim 1: Characterize phthalate exposures during pregnancy among NYC African American and Dominican women (n=350).

Aim 2: Examine effects of prenatal phthalate exposures on modulation of gene expression in placental tissue.

Aim 3: Examine effects of prenatal phthalate exposure on gestational age and fetal growth.

NIEHS RO1 ES013543 (Whyatt R., P.I.)

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Pregnancy (N=725) . . . . . child age 9-11

Exposure Assessment | **Biomarkers of Exposure Effect/Susceptibility** | **Outcome**

Environmental Exposures	Biomarkers	Clinical Outcomes
Air Pollutants		
PAH, PM	PAH-DNA Adducts	Fetal Growth
ETS	Cotinine	Child Neurodevelopment
Allergens	Immune changes	Wheeze/Asthma
Metals	Lead, Mercury	
Pesticides	Pesticides	
Phthalate diesters	Phthalate monoesters	
Susceptibility Factors		

Funded by U.S. EPA and NIEHS

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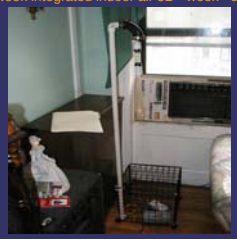
Cohort

Number: 300 mother/newborn pairs from CCCEH cohort
Race/Ethnicity: African American and Dominican
Residence: Northern Manhattan and South Bronx
Exclusion: Smokers, Illicit Drug, HIV, Hypertension, Diabetes

48 hour personal air 3rd trimester

2 week integrated indoor air 32nd week - delivery



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Biologic Samples

- Maternal prenatal urine
- Maternal postnatal urine
- Newborn postnatal urine
- Meconium
- Placental tissue

Medical record data: gestational age, gender, birth weight, length, head circumference, maternal height, pre-pregnancy weight and weight gain, medications

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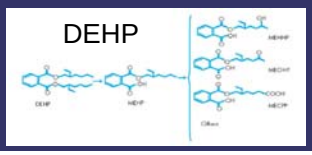
Phthalate Diesters In Air	Monoester Metabolites In Urine
Di (2-ethylhexyl) phthalate (DEHP)	Mono(2-ethylhexyl) phthalate (MEHP) Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) Mono(2-ethy-5-oxolhexyl) phthalate (MEOHP) Mono(2-ethy-5-carboxypentyl) phthalate (MECPP)
Di-n-butyl phthalate (DBP)	Mono-n-butyl phthalate (MBP)
Butylbenzyl phthalate (BBzP)	Monobenzyl phthalate (MBzP) Mono-n-butyl phthalate (MBP, minor metabolite)
Diethyl phthalate (DEP)	Monoethyl phthalate (MEP)

Once inside the body:
- Rapidly hydrolyzed to monoester & other oxidative metabolites
- Glucuronidated and excreted
- Half-life: 12 to 48 hours

DEHP



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Placental gene expression

Pathways	Genes
Steroid synthesis and metabolism	peroxisome proliferator activated receptor (PPARγ) aromatase (CYP19) aryl hydrocarbon receptor (AhR) cholesterol side chain cleavage enzyme (P450scc) 17β-hydroxysteroid dehydrogenase (17β-HSD 1)
Xenobiotic metabolism	CYP1B1, AhR, CYP19
Oxidative stress	Epoxide hydrolase (EH)
Fatty acid transport	PPARγ, fatty acid transport protein (FATP)
Trophoblast differentiation	PPARγ, human chorionic gonadotropin (hCG)

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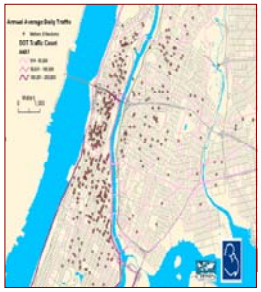
Demographics (n = 246)

Maternal age (years)	25.6 ± 4.6
Ethnicity	
Latina	74%
African American	26%
Marital Status	
Never married	62%
Education	
< High School	37%
Annual Household Income	
<$10,000	44%
Gestational age	39.2 ± 1.9



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Research Results

Aim 1: Characterize phthalate exposures during pregnancy among NYC African American and Dominican women.

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Phthalate levels in personal air samples and maternal urine samples during pregnancy

Air levels (µg/m3) (N=96)			Urine levels (ng/ml) (N=246)		
Diester	%>LOD	GM (95% CI)	Monoester	%>LOD	GM (95% CI)
DEHP	100%	0.18 (0.16, 0.21)	MEHP	85%	4.8 (4.0, 5.8)
			MEOHP	100%	18.2 (15.6, 21.3)
			MEHHP	100%	20.2 (17.2, 23.6)
DnBP	100%	0.45 (0.41, 0.51)	MnBP	100%	37.5 (33.3, 42.2)
BBzP	100%	0.05 (0.04, 0.06)	MBzP	100%	17.5 (14.8, 20.7)
DEP	100%	2.15 (1.92, 2.41)	MEP	100%	232 (199, 272)

- Correlations: BBzP to MBzP (r=0.51, p<0.0001); DEP to MEP (r=.22, p = 0.04)
- Urinary levels of MBP significantly higher than in US. women 18-40 years sampled in NHANES 2001-02
- Personal and indoor air levels similar and except for DEHP were highly correlated (r=0.51-67, p<0.01)

Adibi et al., submitted, 2007

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Intraclass correlation coefficients for phthalates in repeat indoor air samples (N=32 homes) and maternal urine samples (N=28) during pregnancy (2-4 samples per subject)

Indoor air		Maternal urine	
DEHP	0.48	MEHP	0.35
		MEOHP	0.34
		MEHHP	0.36
DnBP	0.59	MnBP	0.62
BBzP	0.83	MBzP	0.66
DEP	0.54	MEP	0.30

Adibi et al., submitted, 2007

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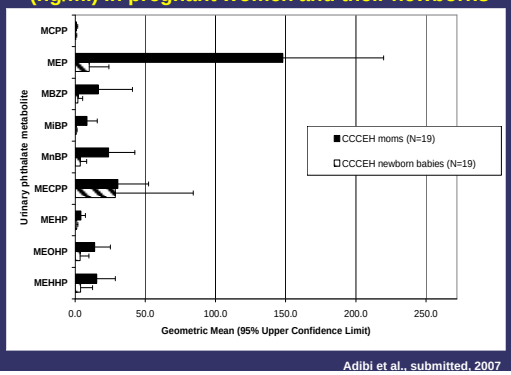
Urinary profile of phthalate metabolite concentrations (ng/ml) in pregnant women and their newborns



Adibi et al., submitted, 2007

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Research Results

Aim 2: Examine effects of prenatal phthalate exposures on modulation of gene expression in placental tissue.

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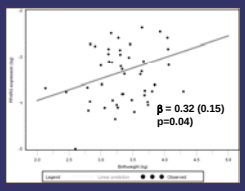
Gene expression ⇒ Placental function ⇒ Clinical outcomes (n=55)

Gene	PPARγ	CYP19	Ahr	FATP
Median mRNA molecules/sample	3.0 X 10^3	2.0 X 10^4	4.4 X 10^2	8.6 X 10^2

(ln)PPARγ expression/cyclophilin ⇒ Birthweight



Regression model adjusted for sampling characteristics, maternal weight, health conditions in current pregnancy, previous pregnancy outcomes, and demographic factors

Adibi et al., in preparation

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Research Results

Aim 3: Examine effects of prenatal phthalate exposure on gestational age and fetal growth.

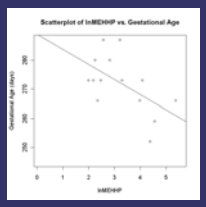
1. Latini et al.: cord blood MEHP inverse with gestational age (EHP, 2003)
2. Our pilot: gestatiional age inverse with maternal oxidative metabolites

Gestational Age

(ln)MEOHP -5.3 days, p=0.01

(ln)MEHHP -5.4 days, p<0.01

3. Two recent epidemiologic study show positive associations between maternal prenatal urinary levels and gestational age.



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Conclusions

- **Phthalate exposures are widespread among NYC African Americans and Dominicans during pregnancy**
- **Phthalates are detected in 85%-100% of indoor air, personal air and maternal urine samples**
- **Indoor air levels appear stable over time and are significantly correlated with personal air levels in most cases.**
- **A significant correlation between air and urine levels was seen for two phthalates**
- **DEHP exposures may be modulating gestational age**

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Acknowlegements

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