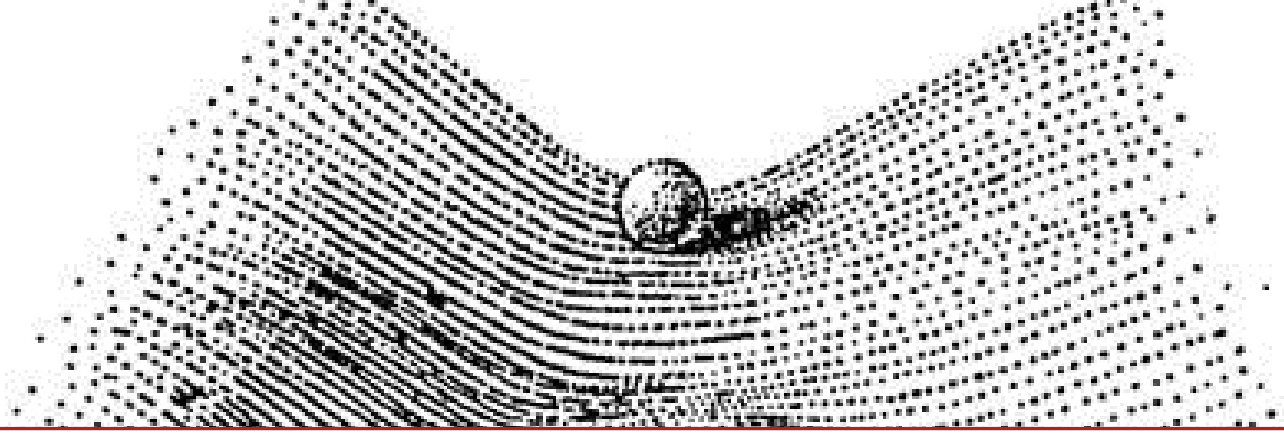

Endocrine Disrupting Chemicals and Epigenetic Regulation in the Placenta

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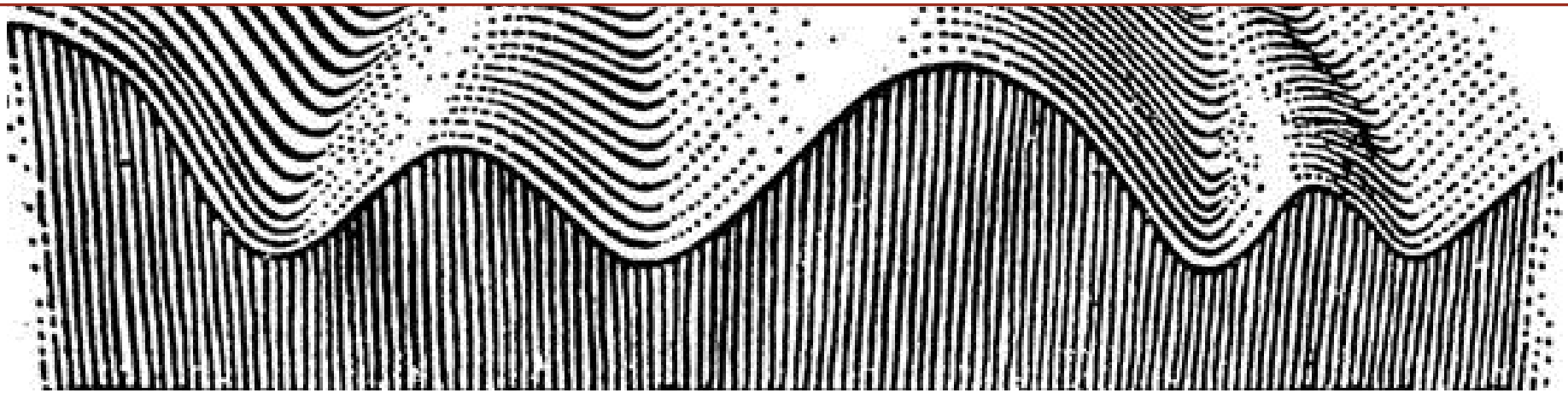


Endocrine Disrupting Chemicals

- EDCs are exogenous chemicals that can antagonize or mimic the effects of the body's endogenous hormones

- Phthalates and phenols are two classes of EDCs of significant concern:
  - Widespread human exposure
  - Suspected detrimental health effects

- EDCs measured in amniotic fluid, placental tissue, and cord blood indicates that the developing fetus is exposed to these compounds




Endocrine Disrupting Chemicals

	Phthalates	Phenols
Epidemiologic studies of prenatal exposure	• Increased risk of prematurity • Impaired mental & psychomotor development • Behavioral & emotional problems • Altered reproductive tract development in males	• Increased risk of prematurity • Sexually dimorphic influences on childhood behavior • Changes in metabolic profile




Endocrine Disrupting Chemicals

	Phthalates	Phenols

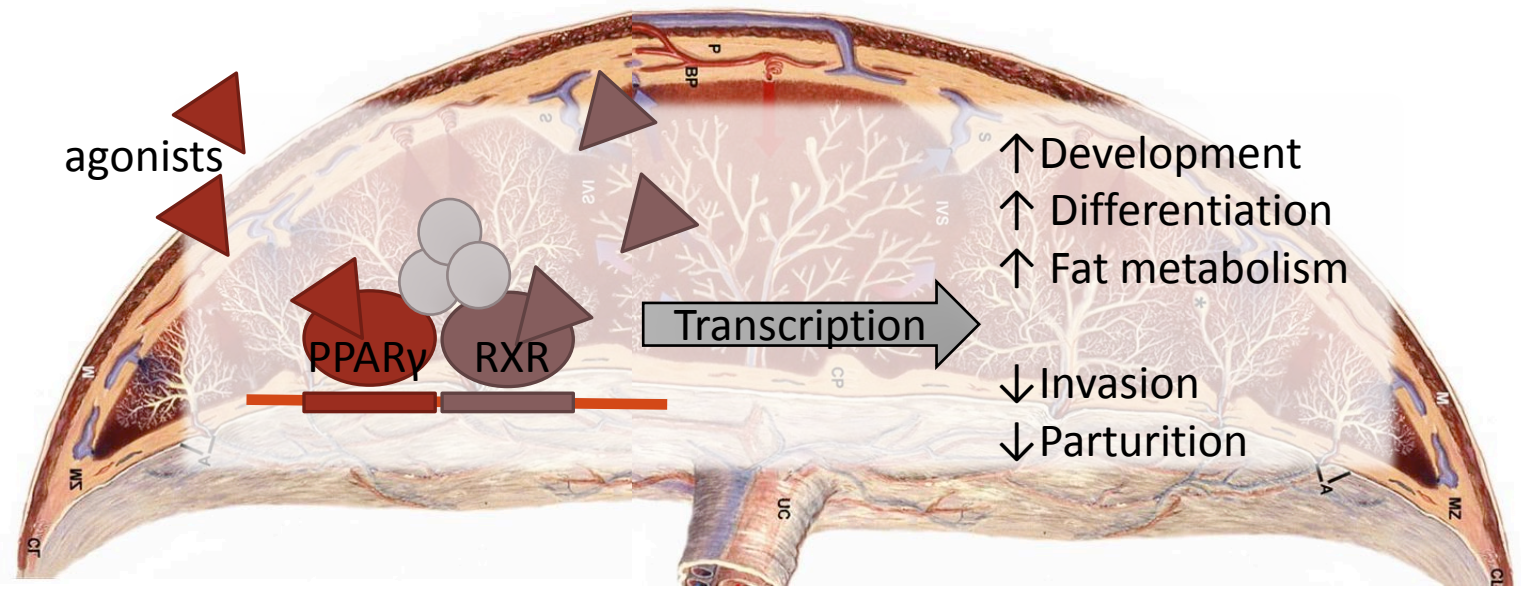
Applications	• Low molecular weight phthalates
	  • Solvents: lotion, nail polish
	• High molecular weight phthalates
	  • Plasticizers: flooring, wall coverings
		• Parabens
		  • Frequently in cosmetics
		• Non-parabens
		  • Sunscreen, antimicrobial preservatives,
		  • Bisphenol A: polycarbonate plastic, lining of food cans, receipt paper




EDCs and the Placenta

Associations between prenatal EDC exposure and pediatric outcomes may be mediated by alterations in the placenta

- EDCs suggested to alter placenta development and function
- Placental dysfunction can modify the supply of nutrients to the fetus and impact systems development



Study Population

A majority of the mothers in our study population were:

- Over the age of 30
- Normal/over-weight
- Caucasian
- Non-smokers
- C-section
- Nulliparous or one prior successful pregnancy

Characteristics	
Maternal Age	32.91 (5.01)
Pre-pregnancy BMI‡	25.45 (5.74)
Infant Sex‡ (N (%))	
Female	94 (51.93)
Male	85 (46.96)
Ethnicity (N (%))	
White non-Hispanic	126 (70.39)
Hispanic or Latino	25 (14.00)
Asian/Pacific-Islander	5 (2.79)
Black/African-American	23 (12.85)
Smoke During Pregnancy (N (%))	
No	174 (97.21)
Yes	5 (2.79)
Method of Delivery‡ (nmiss=6; N (%))	
Spontaneous	36 (20.81)
Induced	27 (15.61)
C-section	110 (63.58)
Parity (N (%))	
Nulliparous	64 (36.16)
1	66 (37.29)
2	32 (18.08)
≥3	15 (8.47)

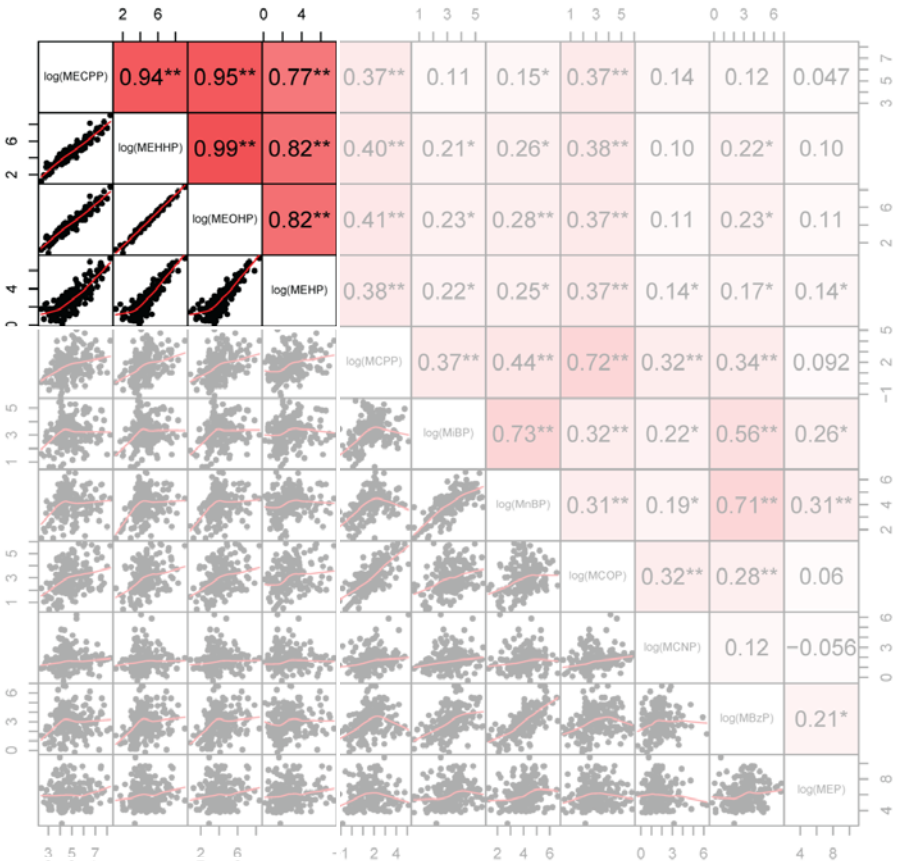
Phthalate Measurements

Phthalate	Abbrev.	High/ Low MW	LOD (mol/L)	%> LOD	GM (mol/L)
Mono-2-ethyl-5-carboxypentyl phthalate	MECPP	High	1.95	100	130.20
Mono-2-ethyl-5-hydroxyhexyl phthalate	MEHHP	High	2.38	99	98.07
Mono-2-ethyl-5-oxohexyl phthalate	MEOHP	High	2.39	98	60.62
Mono-2-ethylhexyl phthalate	MEHP	High	4.31	68	15.25
Mono-3-carboxypropyl phthalate	MCPP	High	0.79	84	5.34
Mono-isobutyl phthalate	MiBP	Low	2.70	95	24.98
Mono-n-butyl phthalate	MnBP	Low	2.70	97	58.44
Monocarboxyoctyl phthalate	MCOP	High	2.17	94	20.13
Monocarboxynonyl phthalate	MCNP	High	1.78	80	5.79
Monobenzyl phthalate	MBzP	High	1.17	97	21.05
Monoethyl phthalate	MEP	Low	4.12	100	445.19

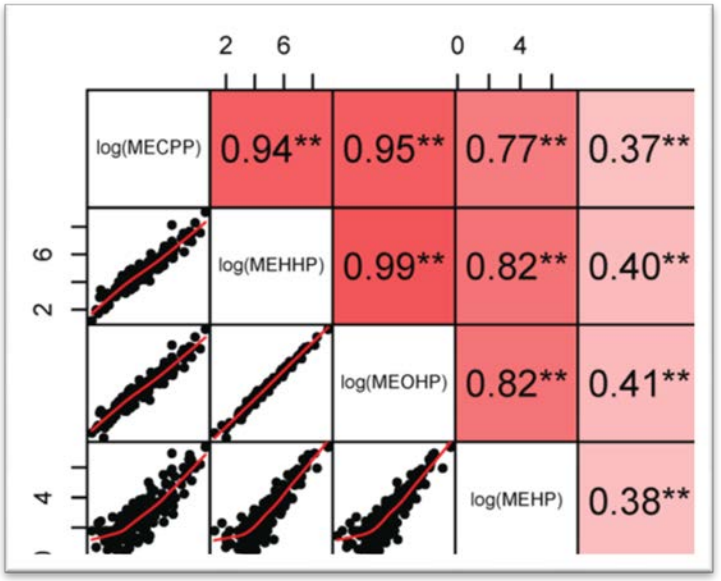
Phenol Measurements

Phenol	Abbrev.	Paraben Yes/No	LOD (mol/L)	%>LOD	GM (mol/L)
2,4-dichlorophenol	DCP	No	1.23	80	3.45
2,5-dichlorophenol	2,5 DCP	No	1.23	96	21.76
Benzophenone-3	BP-3	No	1.75	100	436.64
Bisphenol A	BPA	No	1.75	86	5.97
Butyl Paraben	BuPB	Yes	1.03	78	10.34
Methyl Paraben	MePB	Yes	6.57	100	1257.19
Propyl Paraben	PrPB	Yes	1.11	98	253.58
Triclosan	TCS	No	7.94	78	59.20

Spearman Correlations between Individual Phthalates

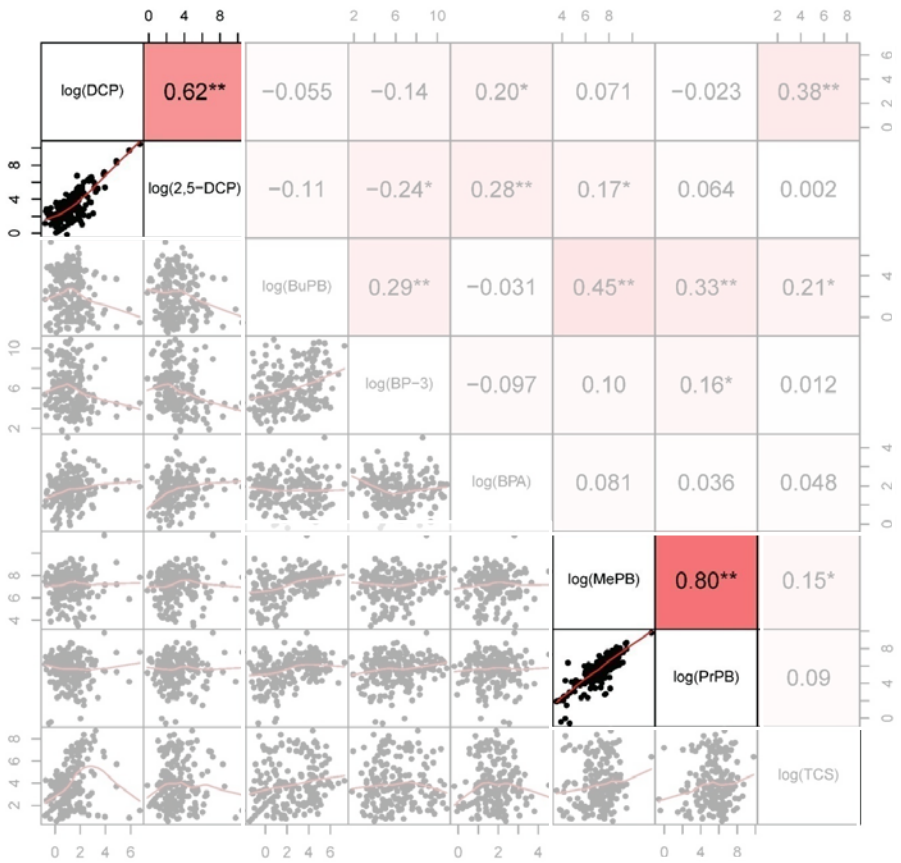


DEHP Metabolites



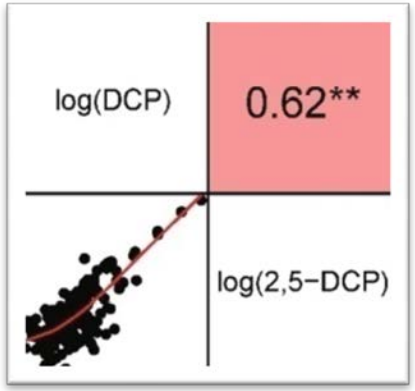
*p<0.05; **p<0.001 LaRocca and Binder et al (2014) Env Res

Spearman Correlations between Individual Phenols

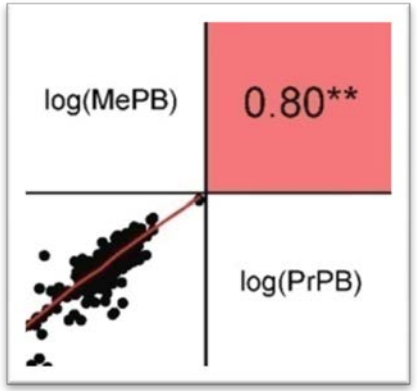


- Weaker correlations between individual phenols

Dichlorophenols



Parabens



*p<0.05; **p<0.001

LaRocca and Binder et al (2014) Env Res

Assessment of Epigenetic Mechanisms

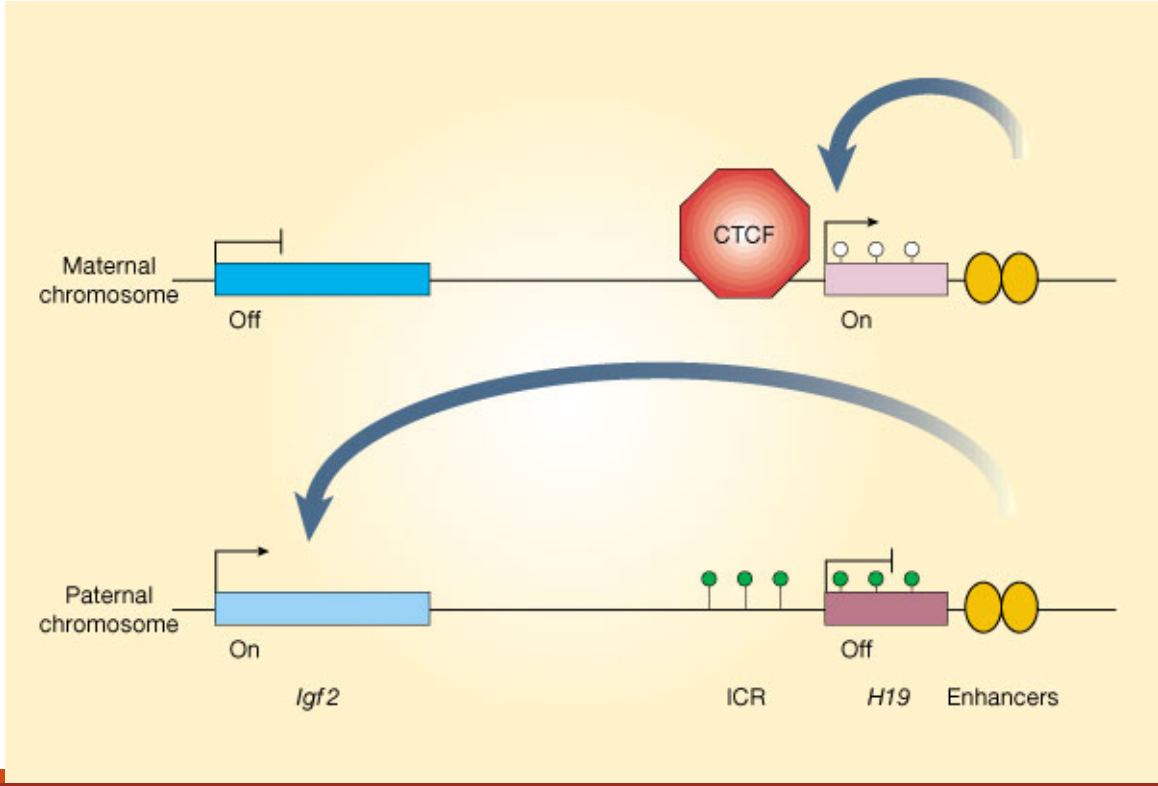
- Investigated the association between EDC levels and the regulation of two reciprocally imprinted genes implicated in fetal and embryonic growth (*IGF2* and *H19*)
  - Pyrosequenced methylation of differentially methylated regions (DMRs) of *H19, IGF2*DMR0, and *IGF2*DMR2
  - Assessed overall expression and allele-specific expression of *H19* and *IGF2*

Imprinting

•Genomic imprinting refers to the epigenetic mechanism through which a subset of genes are monoallelically expressed in a parent-of-origin specific manner

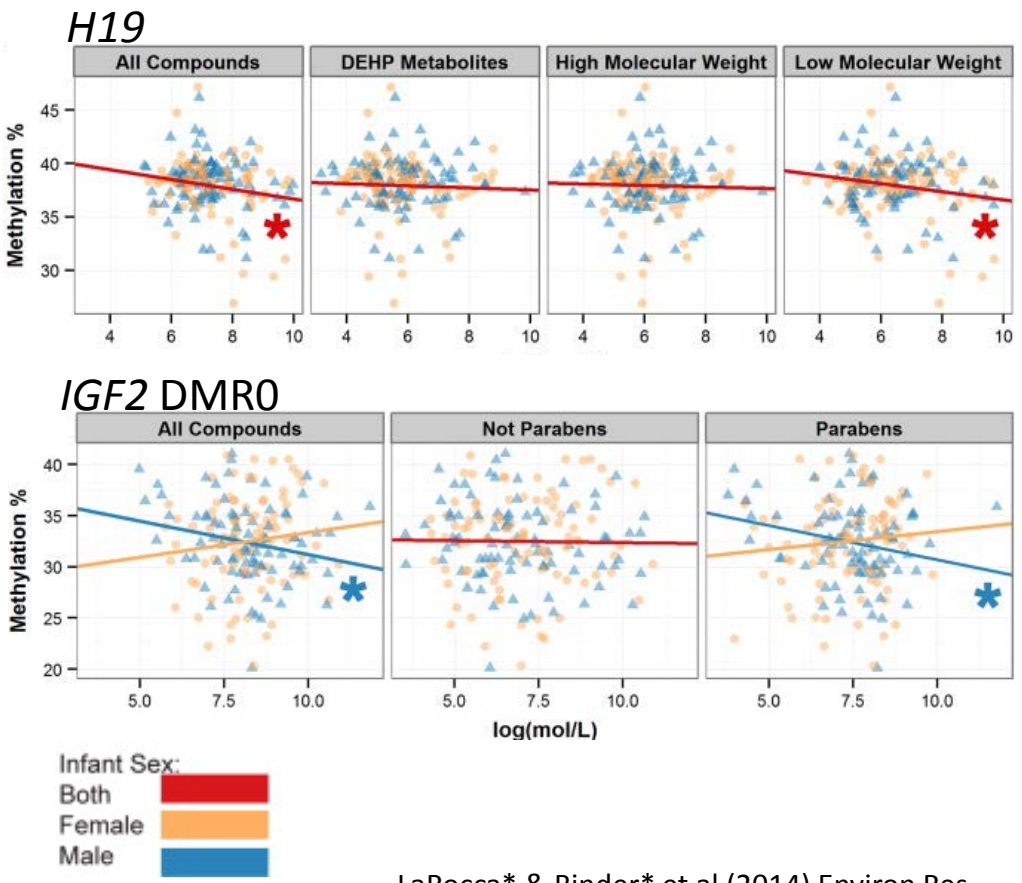
•Important to placental and fetal growth and development

•Possess differentially methylated regions (DMRs) whereby allelic methylation depends on the parent of origin



Assessment of Epigenetic Mechanisms

- Change in DMR methylation
  - Decrease in *H19* methylation was associated with increased phthalate burden
  - Decrease in *IGF2* DMR0 methylation with increased phenol burden
  - Effect modification by infant sex
- Variation in methylation was not associated with changes in allele-specific expression
- Increased deviation from allele-specific expression of *H19* was associated with DEHP metabolites and HMW phthalates

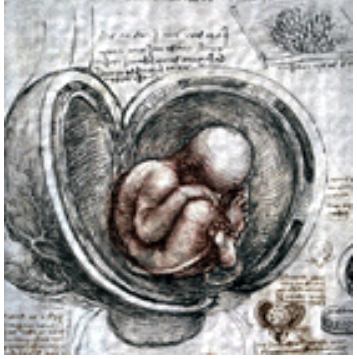


LaRocca* & Binder* et al (2014) Environ Res

Allele-Specific Expression *H19*

H19						
	Male Coeff	**Male CI**	**Female Coeff**	**Female CI**	**P value Compound**	**P value Sex Interaction**
Phthalates						
HMW	1.11*	(1.015, 1.207)	-0.05	(0.89, 1.03)	0.26	0.01*
LMW	0.97	(0.92, 1.03)	0.97	(0.92, 1.03)	0.37	0.78
DEHP	1.10*	(1.011, 1.188)	-0.03	(0.90, 1.03)	0.32	0.02*
ΣPhthalates	1.00	(0.93, 1.07)	1.00	(0.93, 1.07)	0.93	0.09
Phenols						
Parabens	0.96	(0.92, 1.01)	0.96	(0.92, 1.01)	0.14	0.70
Non-Parabens	1.01	(0.97, 1.05)	1.01	(0.97, 1.05)	0.65	0.37
ΣPhenols	0.99	(0.94, 1.04)	0.99	(0.94, 1.04)	0.74	0.27

Conclusions



First trimester additive phthalate and phenol biomarker measurements are associated with altered *H19* and *IGF2* methylation in placenta samples

Currently exploring epigenome-wide associations.

Epigenetic and transcriptional changes associated with prenatal EDC burden may reflect physiological changes in the placenta

- Critical period of development that may program later phenotypes

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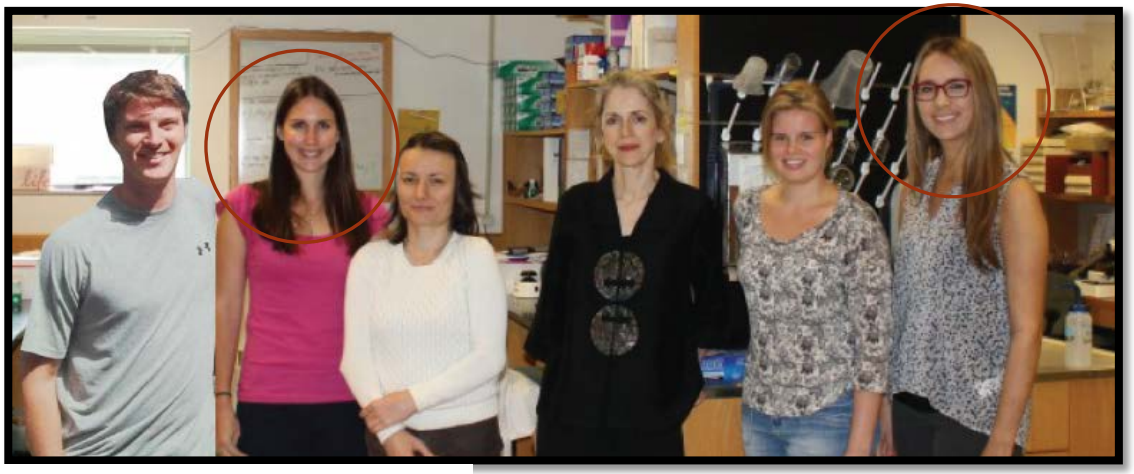
Rafael Irizarry



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Thank you!

QUESTIONS?