

Prenatal Exposure to Phthalates is Significantly Associated with increased Language Delay in Children in Sweden and the U.S.

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Language disorders in early childhood are risk markers for language and other neurodevelopmental and neuropsychiatric problems later in life

Screening for speech and language delay in preschool children: systematic evidence review for the US Preventive Services Task Force (Nelson et al., 2006)

Systematic review of the literature on characteristics of late-talking toddlers (Desmarais et al., 2008)

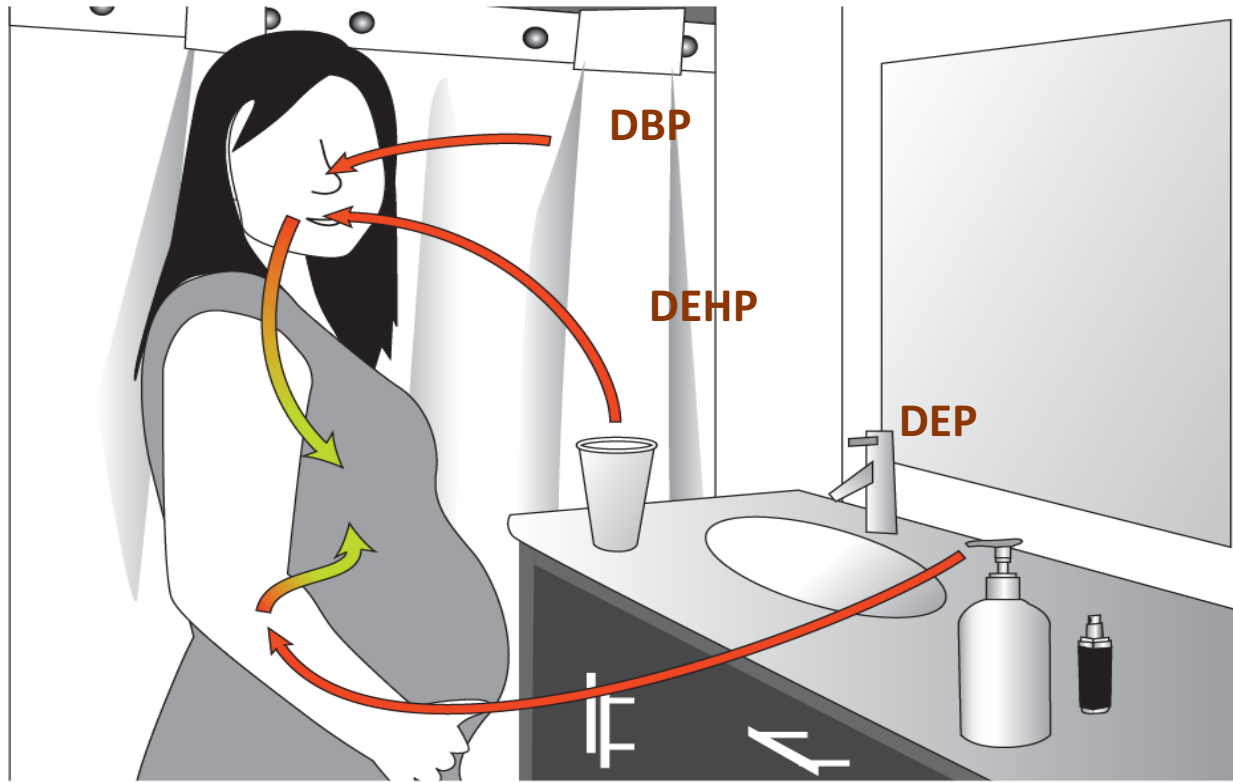
Neuropsychiatric and neurodevelopmental outcome of children at age 6 and 7 years who screened positive for language problems at 30 months (Miniscalco et al., 2006)

Language skills at age 6 years in Swedish children screened for language delay at 2½ years of age (Miniscalco et al., 2007)

How was language delay defined?

- **SELMA:** Miniscalco (2006) language questionnaire
 - Includes: “**How many words can your child say?** (The words need not be spoken correctly, but you should be able to understand what the child is saying)”.*
 - Maternally completed at 30-month clinic visit
 - Responses categorized: <25 words, 25 to 50 words, >50 words
- **TIDES:** English translation of Miniscalco (2006) language questionnaire
 - Mailed to mothers when child was 37 months (median)

Language Delay (LD) was defined as ≤ 50 words in both studies

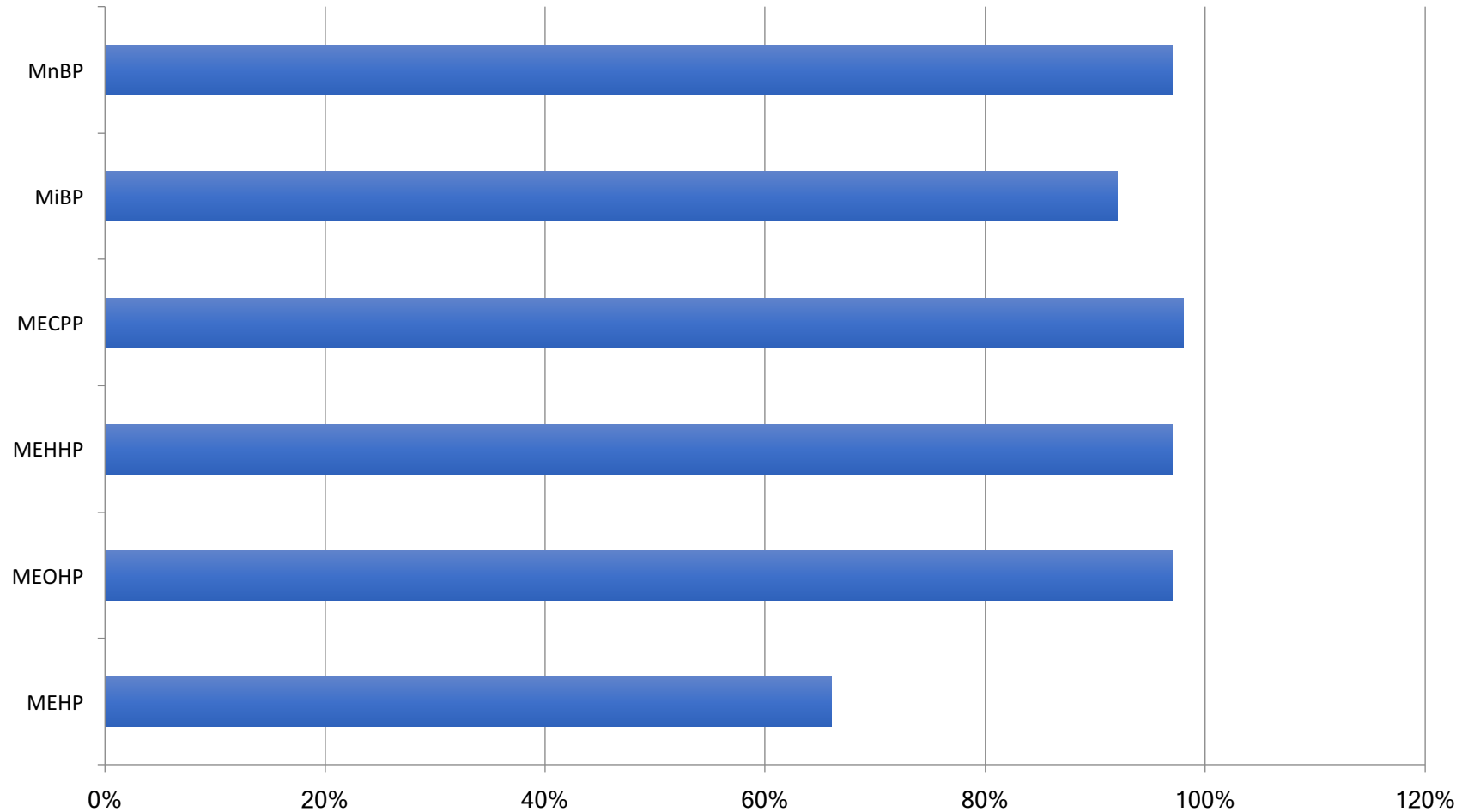


Phthalates: Exposure in pregnancy

Some phthalates and their metabolites

<i>Parent compound</i>	<i>Metabolites</i>
<i>Diethylhexyl phthalate (DEHP)</i>	<i>MEHP</i>
	<i>MEOHP</i>
	<i>MEHHP</i>
	<i>MECCP</i>
<i>Di-n-butyl phthalate (DBP)</i>	<i>MnBP</i>
	<i>MiBP</i>
<i>Benzyl butyl phthalate (BBzP)</i>	<i>MBzP</i>
Diethyl phthalate (DEP)	MEP

Phthalates are ubiquitous



Percent above LOD in first trimester urine (TIDES)

Comparing phthalates in SELMA and TIDES

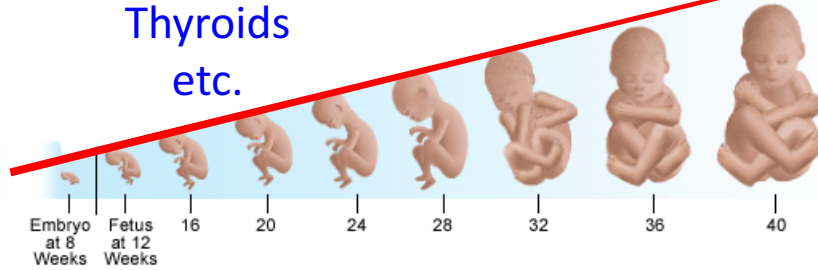
	SELMA (N=963)	TIDES (N=370)
Metabolite (ng/mL) (GM, 95% CI)		
MBP	69.4 (66.0, 74.6)	10.5 (9.0 11.9) ¹
MBzP	16.1 (15.1, 17.2)	3.4 (3.0, 4.0)

¹ Includes MnBP + MiBP in TIDES



Natural hormones

Estrogen
Testosterone
Thyroids
etc.



1st trimester Phthalates

- DEP
- DBP
- BBzP
- DEHP

Neurodevelopment



Language Delay

(2.5 years)
(N=1,103)

Number of words used by the child

Psychological tests (WISC)

at 7 years
(N=1,006)

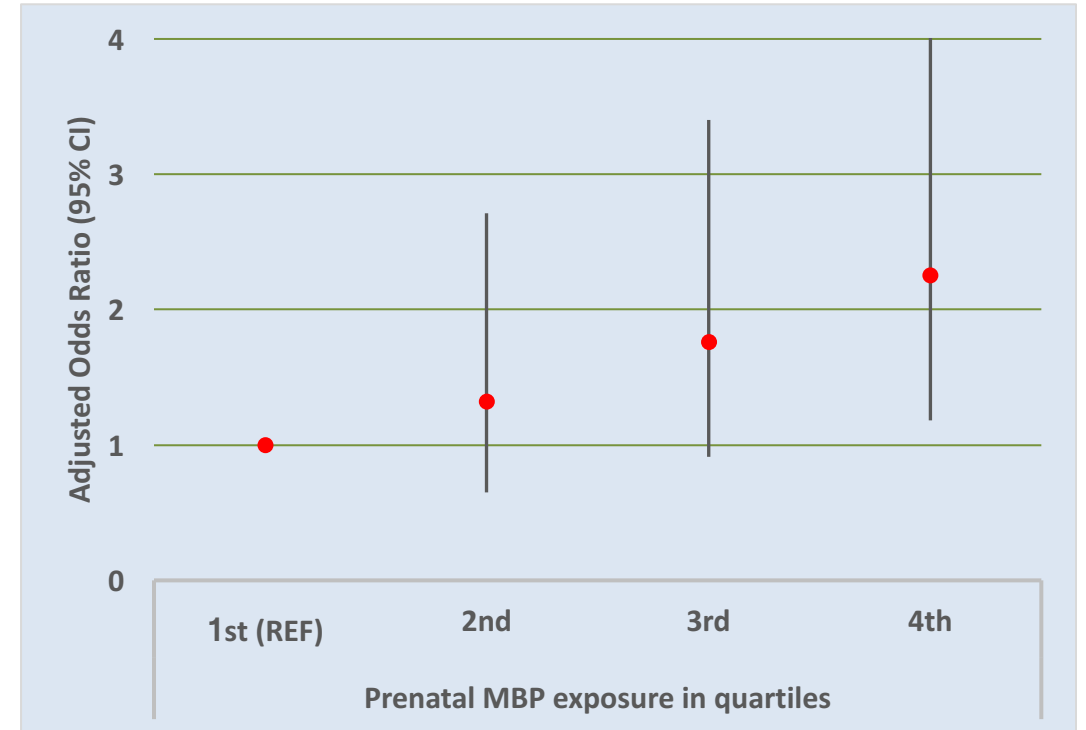
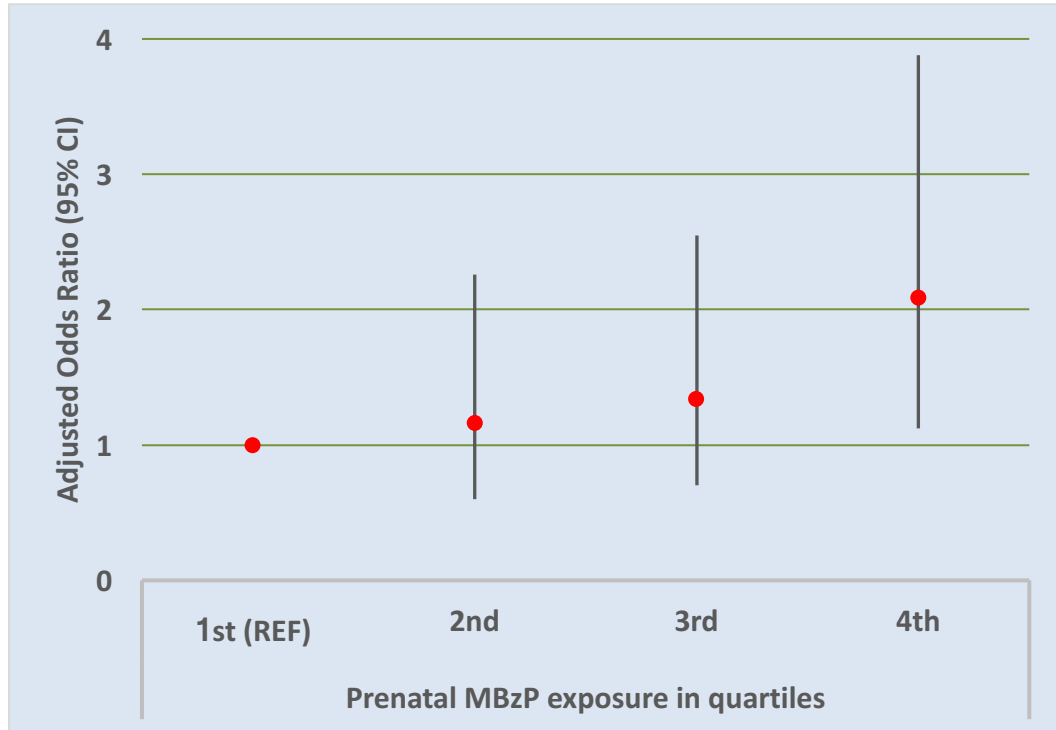
Motor
Cognition
Behavior

Association between prenatal phthalate exposure and language delay in 963 SELMA children at 30mos

Compound	OR (95% CI)		Adjusted for All Covariates and Interaction Term ^c	P Value for Interaction Term	Boys (n = 508) ^d	Girls (n = 455) ^d
	Crude ^a	Adjusted ^b				
MEP	1.16 (1.02-1.33)	1.14 (1.00-1.31)	1.28 (1.04-1.64)	.29	1.09 (0.93-1.29)	1.29 (1.00-1.66)
MBP	1.33 (1.07-1.67)	1.29 (1.03-1.63)	1.30 (0.85-2.01)	.99	1.31 (1.00-1.71)	1.23 (0.79-1.92)
MBzP	1.29 (1.10-1.51)	1.26 (1.07-1.49)	1.08 (0.81-1.45)	.59	1.39 (1.13-1.71)	1.04 (0.76-1.41)
MEHP	0.91 (0.77-1.09)	0.90 (0.75-1.09)	0.80 (0.58-1.10)	.34	0.99 (0.78-1.24)	0.78 (0.56-1.08)
MEHHP	0.91 (0.76-1.10)	0.89 (0.73-1.09)	0.79 (0.55-1.13)	.41	0.97 (0.76-1.23)	0.76 (0.51-1.10)
MEOHP	0.97 (0.89-1.18)	0.95 (0.77-1.18)	0.78 (0.53-1.15)	.21	1.07 (0.83-1.38)	0.74 (0.50-1.12)
MECPP	0.91 (0.76-1.10)	0.89 (0.73-1.09)	0.81 (0.58-1.15)	.50	0.95 (0.75-1.21)	0.77 (0.53-1.12)
MCMHP	0.86 (0.70-1.06)	0.86 (0.69-1.08)	0.79 (0.52-1.19)	.60	0.90 (0.69-1.18)	0.76 (0.49-1.17)

LD associated with MBP and MBzP overall and in boys but not significantly in girls

LD by quartile of phthalate exposure



Adjusted for creatinine, sex, premature birth, mother's education. smoking status and weight at study enrollment. First quartile is the reference category

The Infant Development and the Environment Study (TIDES)



- Women enrolled by 13 weeks gestation (2010-2012) (N=869)
- Subjects enrolled in
 - Minneapolis MN
 - San Francisco CA
 - Rochester NY
 - Seattle WA
- Data Coordinating Center
 - Mount Sinai NY

TIDES I: Exposure Assessment

- Biological specimens during pregnancy
 - Urine phthalates in 1st, 2nd, 3rd trimester
- Questionnaire data during pregnancy
 - Collected in 1st, 2nd, 3rd trimester
 - Possible sources of phthalates (diet, personal care products, occupation, etc.)
 - Other exposures: Including stress and medications
- Interim questionnaire when children were (average) 37 months
 - Included Swedish questions on language development

Prenatal phthalate exposure and language delay in TIDES

Table 4. Associations Between Prenatal Urinary Phthalate Metabolite Levels and Language Delay in Children in TIDES

Compound	OR (95 % CI)		Adjusted for all Covariates and Sex × Exposure		Stratification and Adjustment ^d	
	Crude ^a	Adjusted ^b	Adjusted for All Covariates and Interaction Term ^c	P Value for Interaction Term	Boys (n = 185) ^d	Girls (n = 185) ^d
MEP	1.05 (0.88-1.25)	0.98 (0.79-1.23)	0.73 (0.38-1.41)	.34	0.85 (0.66-1.11)	1.07 (0.76-1.50)
MBP	1.40 (1.08-1.80)	1.26 (0.93-1.71)	1.87 (0.73-4.81)	.38	1.15 (1.00-2.10)	1.15 (0.72-1.84)
MiBP	1.48 (1.12-1.96)	1.41 (0.99-2.01)	1.90 (0.63-5.77)	.57	1.45 (0.95-2.21)	0.95 (0.57-1.56)
Sum DBP	1.43 (1.08-1.88)	1.29 (0.91-1.84)	1.97 (0.67-5.79)	.42	1.47 (0.96-2.24)	1.06 (0.63-1.78)
MBzP	1.28 (1.04-1.58)	1.16 (0.90-1.48)	1.02 (0.49-2.11)	.72	1.16 (0.88-1.53)	1.17 (0.80-1.71)
MEHP	1.10 (0.88-1.39)	1.07 (0.81-1.41)	1.95 (0.89-4.26)	.12	1.25 (0.93-1.69)	0.85 (0.55-1.30)
MEHHP	1.14 (0.91-1.43)	1.15 (0.87-1.51)	1.56 (0.70-3.48)	.43	1.23 (0.92-1.63)	1.11 (0.72-1.71)
MEOHP	1.08 (0.84-1.37)	1.10 (0.82-1.46)	1.51 (0.66-3.48)	.33	1.19 (0.88-1.61)	1.12 (0.72-1.74)
MECPP	1.24 (0.97-1.58)	1.19 (0.89-1.60)	1.32 (0.81-2.14)	.63	1.19 (0.86-1.65)	1.16 (0.72-1.86)

LD associated with MBP and MBzP overall, but not significantly in adjusted models

Comparing SELMA and TIDES populations

	SELMA	TIDES
Caucasian/ non-Hispanic (%)	100	74.1
Premature birth (%)	4.6	10.4
Mother completed college (%)	65.3	76.5
Mother smoked (%)	5.3	6.2

Language use in SELMA and TIDES

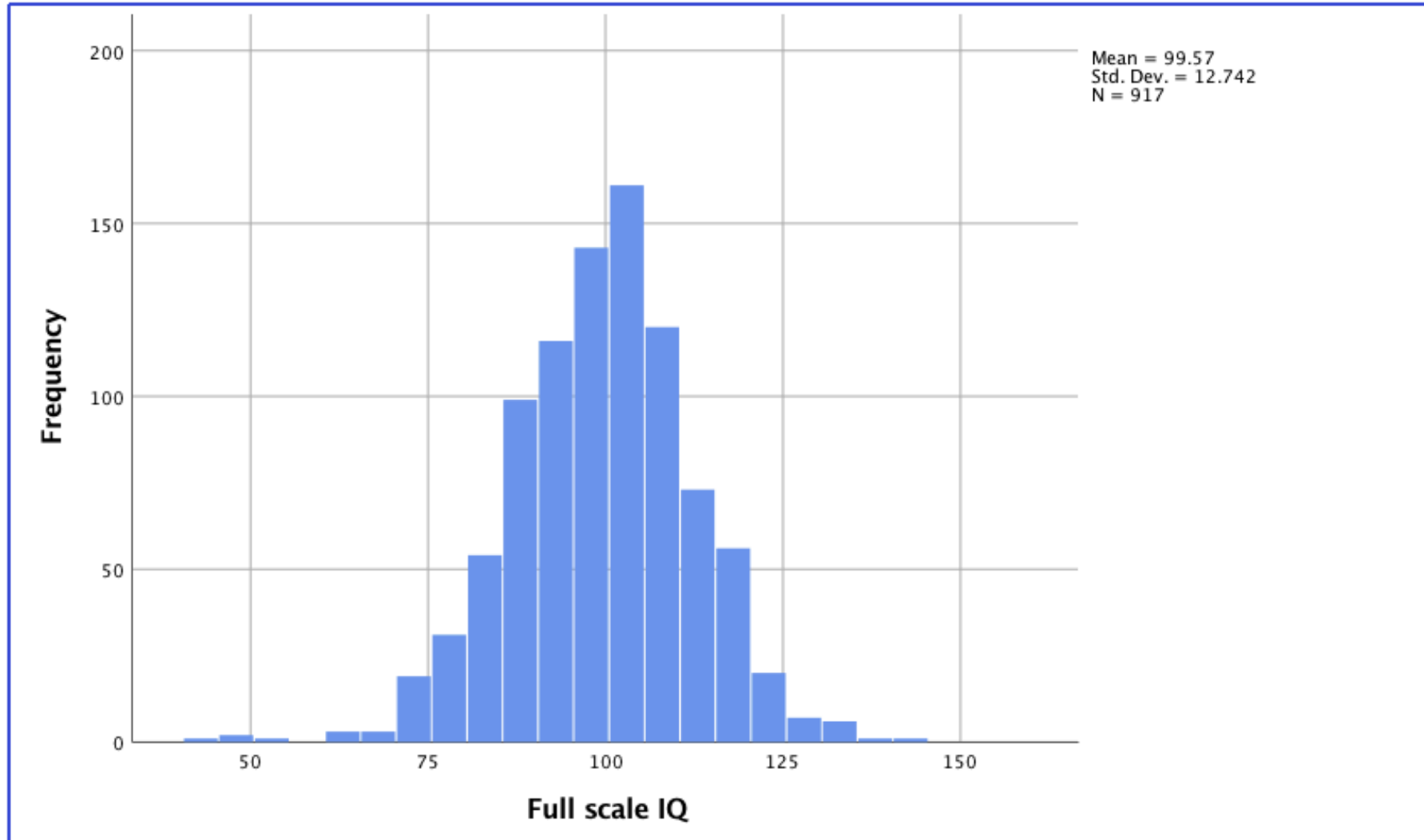
	Girls		Boys	
	Selma	TIDES	Selma	TIDES
<25	1.1	1.1	4.1	4.3
25-50	4.9	6.5	9.4	8.1
<50 (LD)	6.0	7.6	13.5	12.4

Overall, the rates of LD was 10% in both studies!

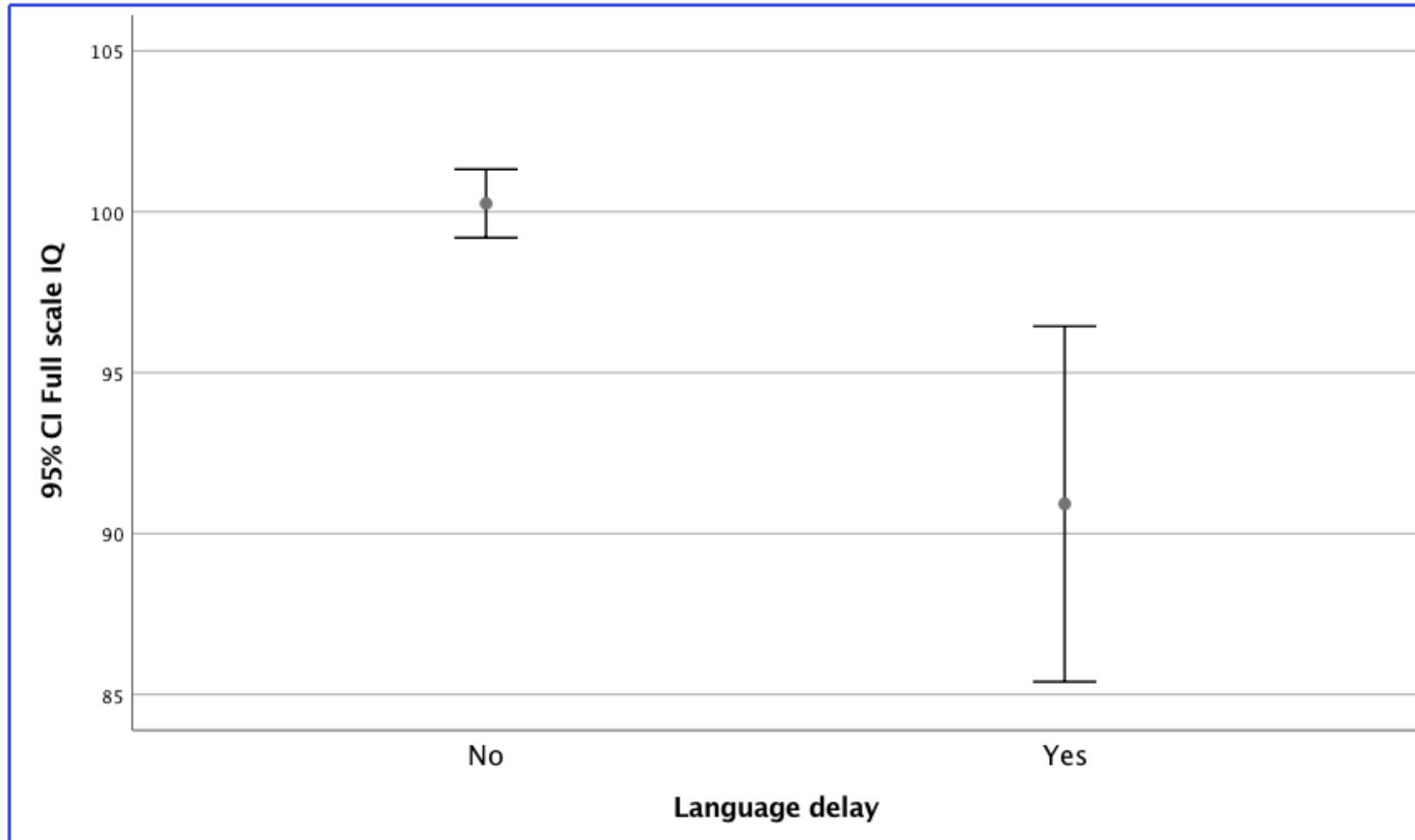
Literature on prenatal phthalates and cognition

- Ten prior studies on prenatal phthalates and cognitive outcomes
- Most measured exposure in third (or unspecified) trimester
- Variety of instruments and age at assessment examined
- Associations in all ten, most negative, but some varied by sex
- Associated phthalates varied across studies
 - DEHP in 5 studies (not ours)
 - ***DBP in 5 studies (and ours)***
 - DEP in 3 studies (not ours)
 - ***BBzP in 2 studies (and ours)***

Full scale IQ at 7y in SELMA



Language delay at 30m vs Full scale IQ at 7y



Adjusted association btw language delay at 30m and cognitive skills at 7y

		Coefficients ^a						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	89.834	4.851		18.517	.000	80.303	99.366
	Language delay	-6.353	2.158	-.126	-2.944	.003	-10.592	-2.114
	IQ_PL	.119	.035	.151	3.408	.001	.051	.188
	Mother_education_01	3.240	1.239	.118	2.616	.009	.807	5.674
	SMOKEcot	-2.413	1.230	-.084	-1.963	.050	-4.830	.003
	MVIKT	-.073	.038	-.082	-1.920	.055	-.149	.002
	Prematurity	-3.577	2.703	-.056	-1.324	.186	-8.887	1.733

a. Dependent Variable: Full scale IQ

DBP and BBP

- DBP is used as a plasticizer in personal care products (***nail polish and fragrances***) and building materials (***paints and coatings***).
 - Developmental and Reproductive Toxicant on CA's Prop 65 list.
- BBzP is used as a plasticizer for ***polyvinyl chloride*** (PVC)
 - Developmental Toxicant on CA's Prop 65 list
- DBP and BBzP permanently banned in children's toys and child care products in Europe and USA
- DBP and BBzP deemed "substances of very high concern" in REACH and cannot be used in Europe without permission since 2015

*Source: Silent Spring Institute

Conclusions

Key Points

Question Is prenatal phthalate exposure associated with language development in children at 30 to 37 months of age?

Findings In this cohort study of 2 independent studies that included a total of 1333 mother-child pairs, exposure to dibutyl phthalate and butyl benzyl phthalates during pregnancy was significantly associated with language delay in preschool-aged children.

Meaning These findings suggest that additional examination of the association of phthalates with language delay is warranted.