

US EPA ARCHIVE DOCUMENT



# **Discussion of analyses of prenatal chlorpyrifos exposure and neurodevelopmental outcomes**

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# Outline

- Discussion of 2004 EHP paper
- Comparison of our results with data from other cohort studies
- Further discussion of mechanisms as described in the table

# Purpose of the 2006 Pediatrics paper

This paper looked at the relationship between prenatal chlorpyrifos exposure and neurodevelopmental outcomes in 228 children born in the cohort between 3/1998 and 7/2002



## Description of the Cohort

**Number:** 730 mother/newborn pairs

**Ethnicity:** African American and Dominican

**Residence:** Northern Manhattan & South Bronx

**Demographics:** largely low-income, unmarried

**Characteristics:**

- Non-smokers
- Non-illicit drug users
- No history of HIV, hypertension, diabetes

**Consent for:** Personal air monitoring, annual maternal interviews, blood samples (cord, maternal and child), home observation, annual child assessments



# Data Sources

- **Maternal interview (prenatal)**  
Age, education, race/ethnicity, income, employment
- **Biologic samples (delivery)**  
Umbilical cord blood, maternal blood
- **Medical records (delivery)**  
Gestational age, sex, birth weight, length, head circumference, medical complications
- **Observational measure of the home (2 years)**  
The HOME Inventory
- **Child and maternal testing (1, 2, 3 years)**  
Bayley Scales of Infant Development (BSID-II)  
Maternal IQ (TONI-3)
- **Maternal report (3 years)**  
Child Behavior Checklist



# Postnatal Measures

## Timeline

6 Month    12 Month    24 Month    36 Month    48 Month    60 Month    72 Month    84 Month



Bayley Scales of  
Infant Intelligence

X    X    X

HOME Scale

X

Childhood Behavior Checklist

X

Wechsler Pre-School & Primary  
Scale of Intelligence - R

X

Wechsler Intelligence  
Scale for Children IV4

X



## Means and Proportions on Measures of Development at 12, 24, and 36 Months of Age

Domain	Age of Assessment		
	12 mo.	24 mo.	36 mo.
	Mean (sd)	Mean (sd)	Mean (sd)
<b>Mental Development</b>	<b>94.03 ( 9.8)</b>	<b>85.10 (12.4)</b>	<b>89.58 (11.4)</b>
<b>Motor Development</b>	<b>96.22 (12.2)</b>	<b>97.04 (11.5)</b>	<b>100.46 (13.0)</b>
	%	%	%
<b>Mental Delay (&lt;85)</b>	<b>14.30</b>	<b>29.20</b>	<b>22.60</b>
<b>Motor Delay (&lt;85)</b>	<b>12.20</b>	<b>15.30</b>	<b>9.20</b>





# Logistic regression models testing effects of chlorpyrifos on adjusted odds of motor delay at 12, 24, and 36 months, adjusted for race, gender, gestational age, maternal education, maternal IQ, ETS, and home environment (N=228)

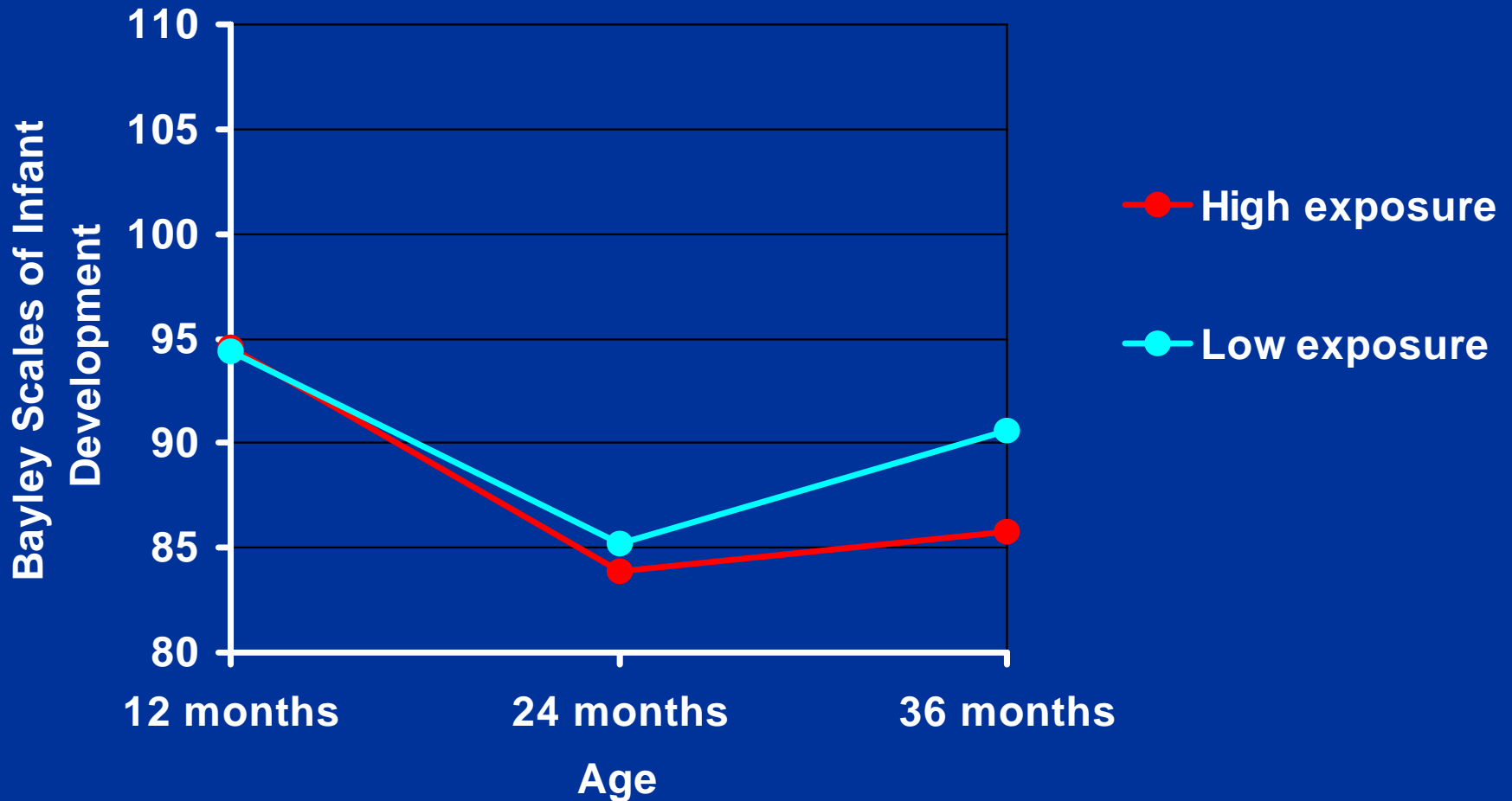
	Dependent Variable: Psychomotor Delay (PDI <85)					
	Model 1: 12 months		Model 2: 24 months		Model 3: 36 months	
Variable	OR	95% C.I.	OR	95% C.I.	OR	95% C.I.
<u>Prenatal Exposures:</u>						
ETS	0.945	0.42, 2.15	0.771	0.33, 1.80	1.689	0.65, 4.41
<b>Chlorpyrifos</b>	1.883	0.78, 4.53	1.010	0.37, 2.76	<b>4.934</b>	<b>1.78, 13.72</b>
<u>Covariates:</u>						
Race/Ethnicity	1.590	0.69, 3.67	0.864	0.36, 2.09	0.545	0.19, 1.53
Gender	0.908	0.42, 1.96	0.737	0.33, 1.63	2.058	0.82, 5.14
Gestational Age (wks)	0.997	0.78, 1.28	0.881	0.68, 1.14	1.005	0.73, 1.39
Maternal IQ	1.010	0.98, 1.04	0.982	0.95, 1.02	1.025	0.99, 1.06
No HS Degree	1.103	0.48, 2.50	1.235	0.54, 2.81	0.369	0.12, 1.13
Home Inventory	0.985	0.92, 1.06	1.010	0.94, 1.09	0.943	0.87, 1.02



# Multiple linear regression models testing effects of chlorpyrifos on Bayley mental development at 12, 24, and 36 months, adjusted for race, gender, gestational age, maternal education, maternal IQ, ETS, and home environment (N=228)

Variable	Model 1: 12 mo.			Model 2: 24 mo.			Model 3: 36 mo.		
	B	SE	P-val.	B	SE	P-val.	B	SE	P-val.
<u>Prenatal Exposure</u>									
<b>ETS</b>	.466	1.4	0.744	-3.032	1.66	0.069	-0.058	1.44	.968
<b>Chlorpyrifos</b>	-.344	1.7	0.836	-1.480	2.03	0.466	<b>-3.327</b>	<b>1.76</b>	<b>0.060</b>
<u>Covariates:</u>									
<b>Race/Ethnicity</b>	.229	1.4	0.874	6.176	1.73	<0.001	<b>6.286</b>	<b>1.47</b>	<b>&lt;.001</b>
<b>Gender</b>	-2.97	1.3	0.023	-3.760	1.58	0.018	<b>-3.680</b>	<b>1.34</b>	<b>0.006</b>
<b>Gestational Age</b>	.355	0.4	0.421	1.466	0.59	0.013	<b>1.287</b>	<b>0.47</b>	<b>0.007</b>
<b>No HS Degree</b>	-.29	0.4	0.843	-2.298	1.70	0.179	<b>-2.888</b>	<b>1.45</b>	<b>0.048</b>
<b>Maternal IQ</b>	-5.98	5.0	0.229	1.715	5.66	0.762	-6.751	4.89	0.169
<b>Home Inventory</b>	.173	0.1	0.150	0.200	0.14	0.165	<b>0.589</b>	<b>0.13</b>	<b>&lt;.001</b>
<b>R<sup>2</sup></b>	<b>.040</b>			<b>.139</b>			<b>.251</b>		

# Estimated Effects of Prenatal Chlorpyrifos Exposure on Cognitive Development in Children 12 through 36 months of Age, using General Linear Modeling (GLM)



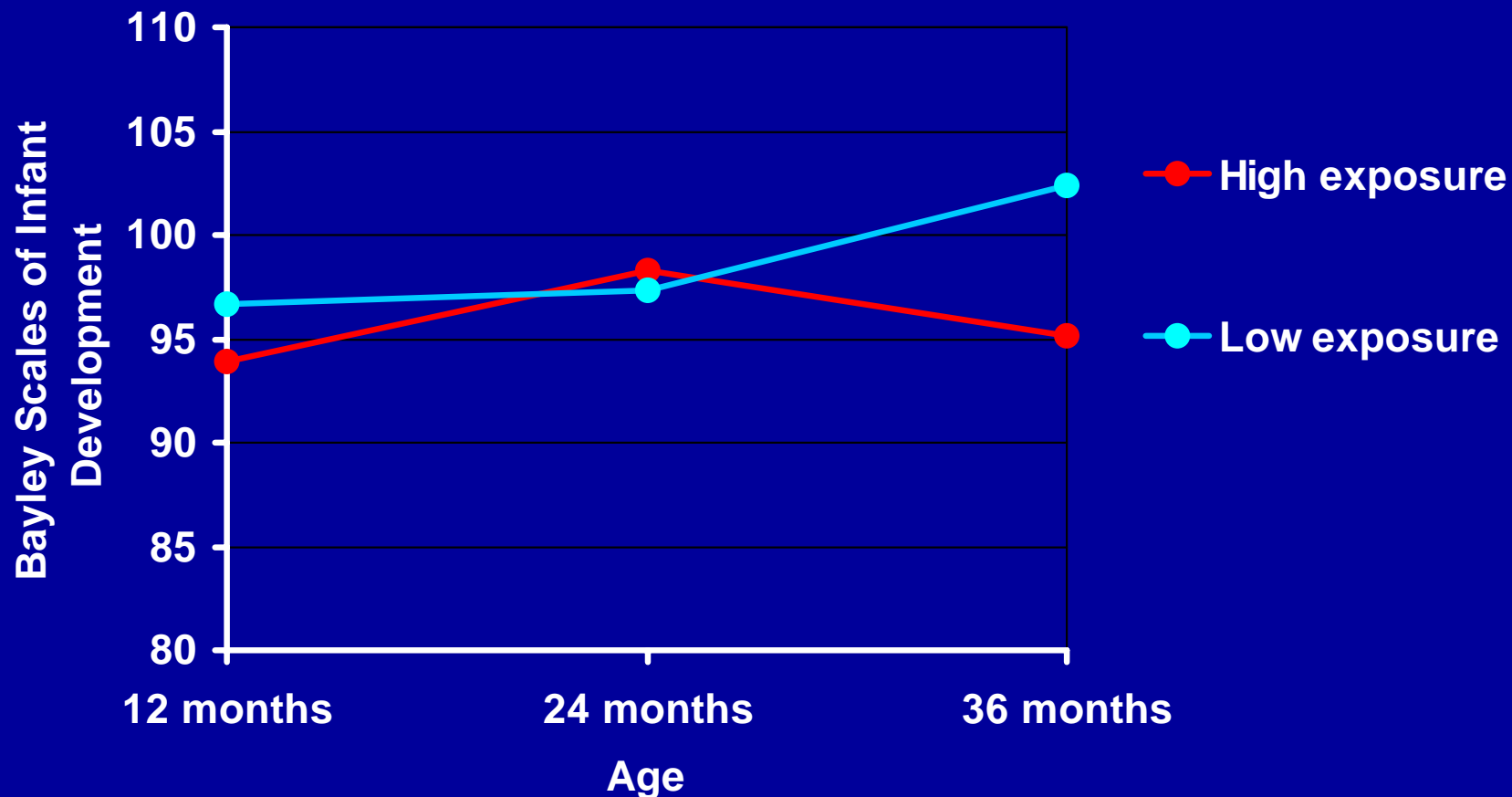
Models are adjusted for race/ethnicity, sex, gestational age, maternal education, maternal IQ, Home Inventory, ETS; High CPF (upper quartile) versus all other



# Multiple linear regression models testing effects of chlorpyrifos on Bayley psychomotor development at 12, 24, and 36 months, adjusted for race, gender, gestational age, maternal education, maternal IQ, ETS, and home environment (N=228)

	Model 1: 12 months			Model 2: 24 months			Model 3: 36 months		
Variable	B	SE	P-val.	B	SE	P-val.	B	SE	P-val.
<u>Prenatal Exposures:</u>									
ETS	0.312	1.76	0.859	2.826	1.63	0.084	-0.135	1.79	.940
<b>Chlorpyrifos</b>	<b>-3.304</b>	<b>2.11</b>	<b>0.118</b>	<b>1.171</b>	<b>1.98</b>	<b>0.555</b>	<b>-6.463</b>	<b>2.18</b>	<b>.003</b>
<u>Covariates:</u>									
<b>Race/Ethnicity</b>	<b>-2.004</b>	<b>1.81</b>	<b>0.270</b>	<b>2.149</b>	<b>1.70</b>	<b>0.207</b>	<b>3.876</b>	<b>1.82</b>	<b>.034</b>
Male Gender	0.112	1.64	0.947	0.079	1.54	0.959	-2.954	1.66	.077
<b>Gestational Age</b>	<b>-0.161</b>	<b>0.56</b>	<b>0.773</b>	<b>0.203</b>	<b>0.53</b>	<b>0.699</b>	<b>1.376</b>	<b>0.64</b>	<b>.033</b>
Maternal IQ	-0.807	1.77	0.650	-1.258	1.66	0.449	1.693	1.81	.350
No HS Degree	-0.711	6.26	0.910	0.092	5.56	0.987	-5.775	6.08	.343
Home Inventory	-0.077	0.15	0.611	0.089	0.14	0.527	0.298	0.16	.057
R <sup>2</sup>	.024			.035			.106		

# Estimated Effects of Prenatal Chlorpyrifos Exposure on Motor Development in Children 12 through 36 months of Age, using General Linear Modeling (GLM)



Models are adjusted for race/ethnicity, sex, gestational age, maternal education, maternal IQ, Home Inventory, ETS

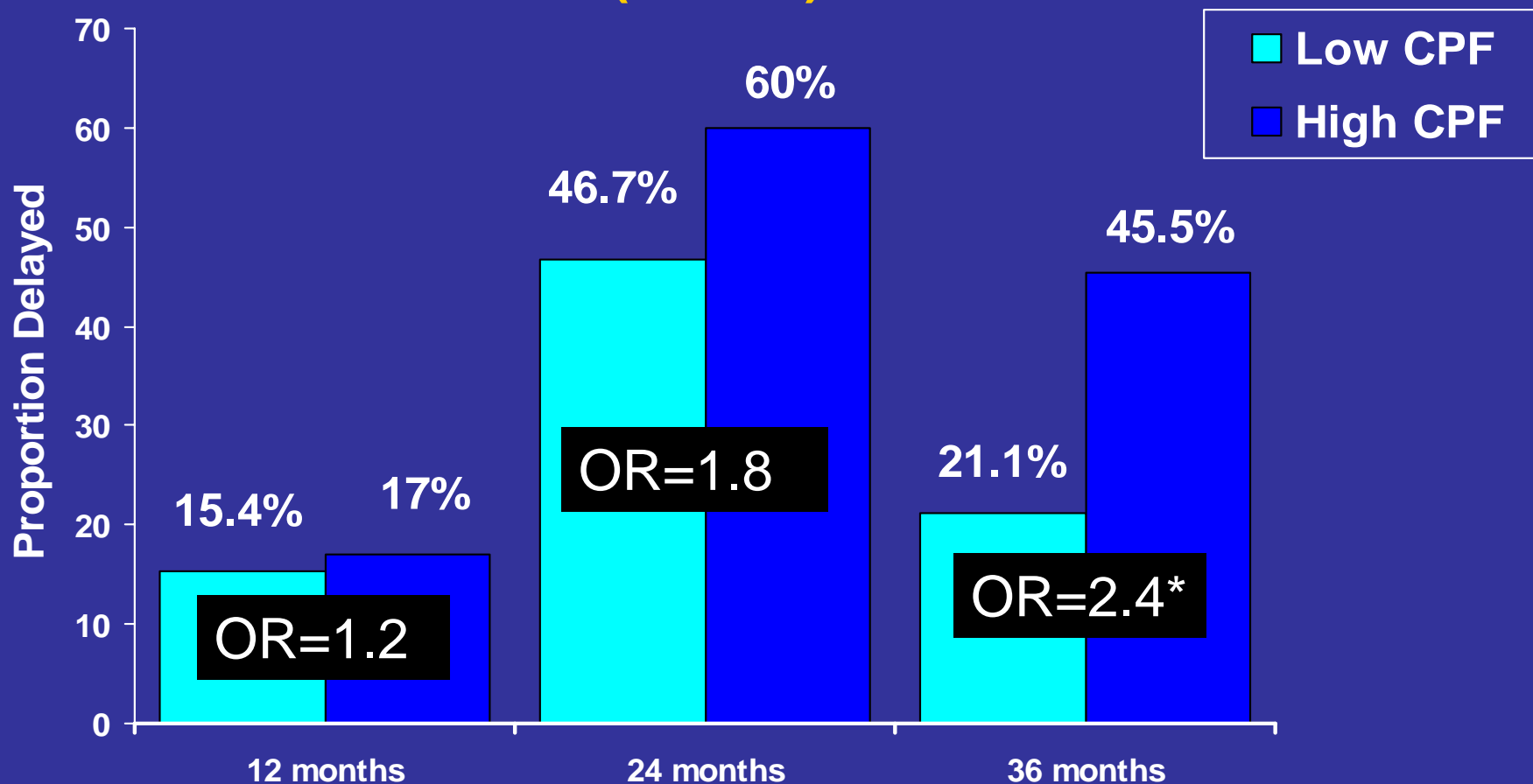
High chlorpyrifos (upper quartile) versus all other levels



**Logistic regression models testing effects of chlorpyrifos on adjusted odds of mental delay at 12, 24, and 36 months, adjusted for race, gender, gestational age, maternal education, maternal IQ, ETS, and home environment (N=228)**

Dependent Variable: Significant Delay (MDI <85)						
	Model 1: 12 months		Model 2: 24 months		Model 3: 36 months	
Variable	OR	95% CI	OR	95% CI	OR	95% CI
<u>Prenatal Exposures:</u>						
<b>ETS</b>	0.582	0.25, 1.33	1.258	0.70, 2.26	1.232	0.65, 2.32
<b>Chlorpyrifos</b>	1.219	0.49, 3.06	1.754	0.86, 3.60	<b>2.383</b>	<b>1.12, 5.08</b>
<u>Covariates:</u>						
<b>Race/Ethnicity</b>	1.064	0.48, 2.38	<b>0.473</b>	<b>0.26, 0.87</b>	<b>0.358</b>	<b>0.18, 0.72</b>
<b>Male Gender</b>	1.658	0.80, 3.44	1.678	0.96, 2.92	<b>1.950</b>	<b>1.08, 3.52</b>
<b>Gestational Age</b>	1.001	0.79, 1.27	0.890	0.72, 1.10	0.829	0.68, 1.02
<b>Maternal IQ</b>	1.015	0.98, 1.05	0.985	0.96, 1.01	1.008	0.98, 1.03
<b>No HS Degree</b>	1.487	0.69, 3.22	0.951	0.52, 1.73	1.365	0.73, 2.55
<b>Home Inventory</b>	0.955	0.89, 1.02	0.963	0.92, 1.01	<b>0.912</b>	<b>0.86, 0.96</b>

# Cognitive Delay (< 85) at 12, 24 & 36 months on the Bayley, by level of chlorpyrifos exposure (N=228)



Logistic regression adjusted for race/ethnicity, sex, gestational age, ETS, maternal IQ, maternal education, HOME Inventory

\*p<.01

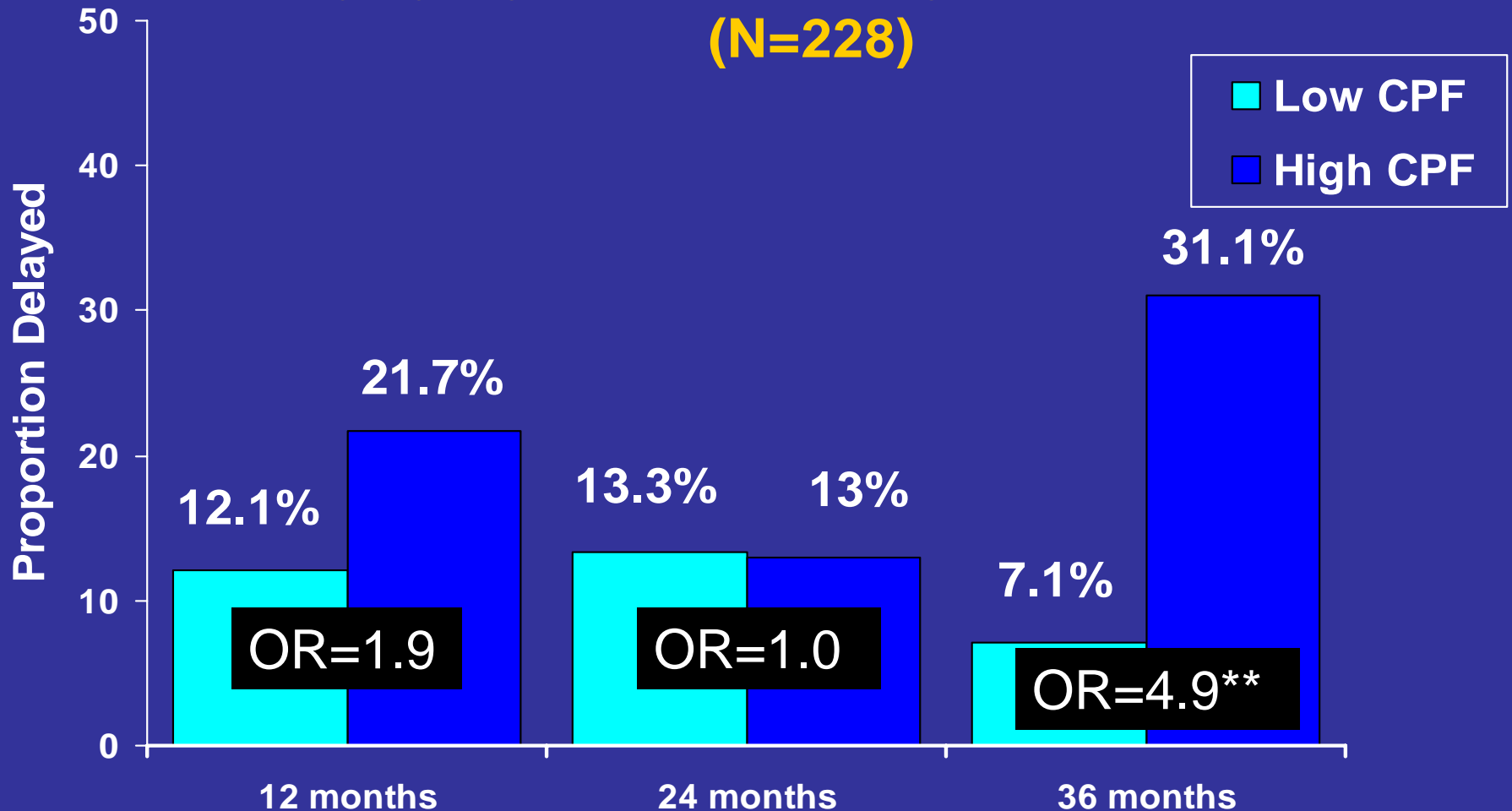


# Logistic regression models testing effects of chlorpyrifos on adjusted odds of motor delay at 12, 24, and 36 months, adjusted for race, gender, gestational age, maternal education, maternal IQ, ETS, and home environment (N=228)

	Dependent Variable: Psychomotor Delay (PDI <85)					
	Model 1: 12 months		Model 2: 24 months		Model 3: 36 months	
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<u>Prenatal Exposures:</u>						
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Home Inventory	0.985	0.92, 1.06	1.010	0.94, 1.09	0.943	0.87, 1.02



# Motor Delay (< 85) at 12, 24 & 36 months on the Bayley, by level of chlorpyrifos exposure (N=228)



Logistic regression adjusted for race/ethnicity, sex, gestational age, ETS, maternal IQ, maternal education, HOME Inventory

\*\*p<.001



# Logistic Regression Models Testing Effects of Chlorpyrifos and ETS on the Odds of Behavior Problems at 36 Months, adjusted for Race, Sex, Gestational Age, Maternal Education, IQ, ETS, and Home Environment (N=228)

Attention  
Problems

ADHD  
Problems

Pervasive  
Developmental  
Disorder Problems

Prenatal  
Exposures

OR

95% C.I.

OR

95% C.I.

OR

95% C.I.

ETS

2.59

0.41, 6.52

7.88

1.17, 53.19

0.72

0.16, 3.29

CPF

11.63

1.82, 74.22

6.30

1.03, 38.42

5.64

1.23, 25.72

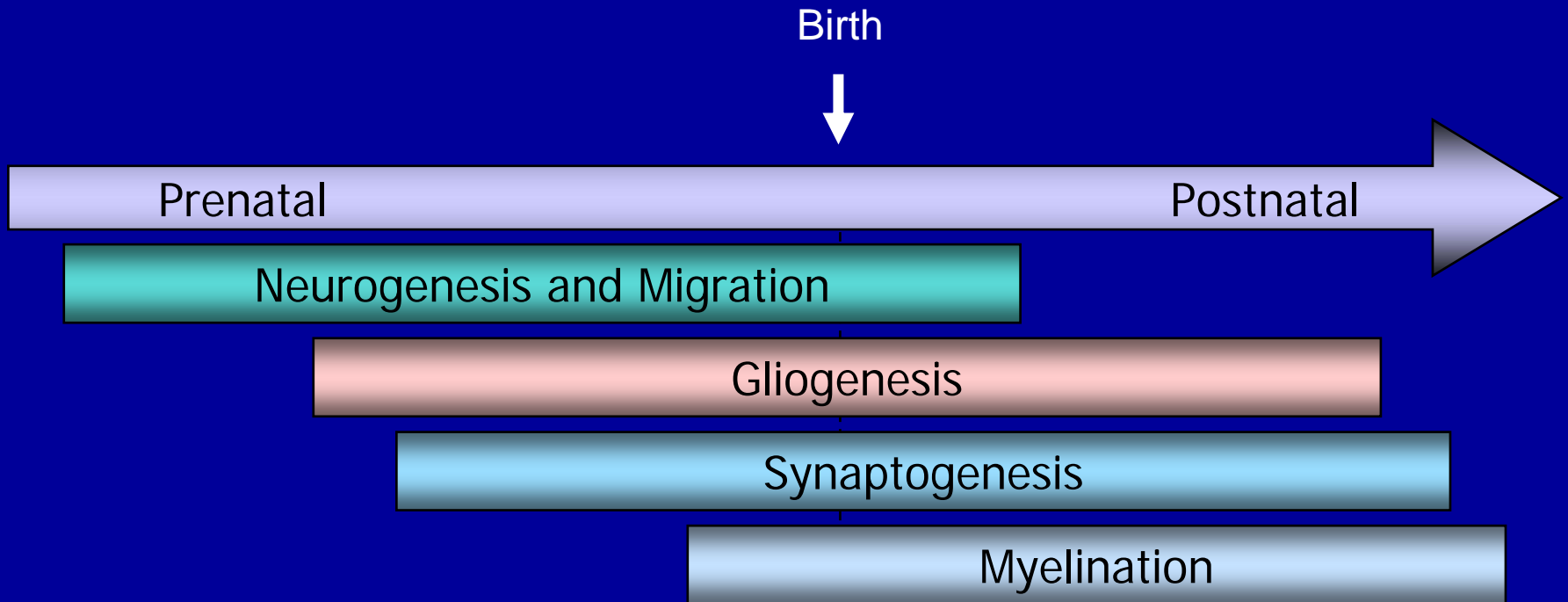
## Possible Mechanisms



- Prenatal CPF exposure has been shown in animals to inhibit acetylcholinesterase, which acts as a neurotropic factor during brain development<sup>1</sup>;
- Organophosphates may also disrupt brain development by noncholinergic mechanisms, at doses that cause only minimal acetylcholinesterase inhibition<sup>1</sup>;
- Unlike classic teratology, in which the greatest sensitivity is seen during the first trimester, the window of vulnerability for organophosphates is likely to extend from the embryonic period into postnatal life;
- Changes may emerge or re-emerge later in development, accompanied by behavioral anomalies

<sup>1</sup>Slotkin. *Cholinergic systems in brain development & disruption by neurotoxicants, nicotine, environmental tobacco smoke, organophosphates. Toxicol Appl Pharmacol. 2004; 198:132-151.*

# Multiple Mechanisms: A Shifting Target



**CPF levels in the home are fairly stable in the short-run, so that it is difficult to pinpoint time of exposure during gestation and the early postnatal period**



## Summary of Results

1. Prenatal pesticide exposure was associated with a 3.5 to 6-point adjusted mean decrement in 36-month development scores (Bayley MDI and PDI) in a low-income minority sample (**sex-dependent? cerebral cortex effects?**)
2. This mean decrement resulted in a 2-fold risk of developmental delay ( $< 80$ ) on the Bayley MDI, and a 5-fold risk of delay on the PDI
3. Prenatal pesticide exposure was associated with significantly increased risk for ADHD problems, Attention problems, and Pervasive Developmental Disorder problems (**consequence of reduced serotonergic function?**)

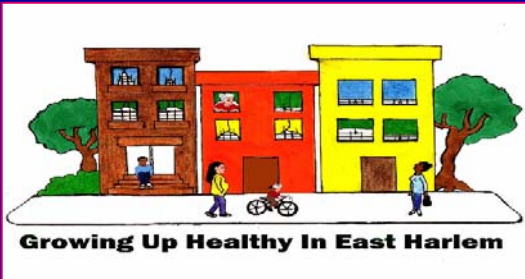


COLUMBIA CENTER FOR CHILDREN'S ENVIRONMENTAL HEALTH

MAILMAN SCHOOL OF PUBLIC HEALTH

Columbia University

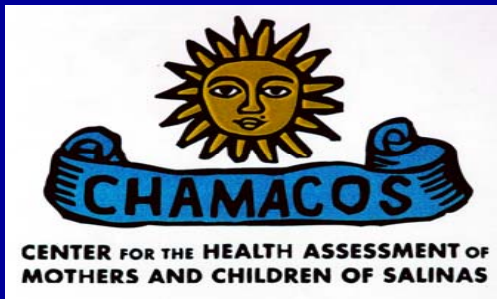
# Comparison of our results with data from other cohort studies



**Mary Wolff, Stephanie Engel, Gertrud Berkowitz**  
**Mount Sinai School of Medicine**



**Virginia Rauh, Robin Wyatt, Frederica Perera**  
**Columbia University**



**Brenda Eskenazi, Kim Harley, Asa Bradman, Amy Marks**  
**University of California, Berkeley**

# Biomarkers of Prenatal OP Pesticide Exposures

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In Urine  
Dialkyl  
Phosphates  
(DAPs)

In Blood  
Chlorpyrifos  
(CPF)

---

Berkeley

X

Mt. Sinai

X

Columbia

X

---



# Early Childhood Neurodevelopmental Outcomes

	Brazelton Neonatal	6M	Bayley 1Y	2Y	3Y	WPPSI 3.5Y	5Y
<b>Berkeley</b>	X	X	X	X		X	X*
<b>Mt. Sinai</b>	X		X	X			
<b>Columbia</b>			X	X	X		X

\* Verbal IQ assessed with PPVT

# Early Childhood Neurobehavioral Outcomes

Child Behavior  
Checklist (CBCL)

2Y

3Y

3.5Y

**Berkeley**

X

X

**Mt. Sinai**

**Columbia**

X

# Prenatal OPs and Bayley Psychomotor Development Index

	<b>Berkeley</b> (Log <sub>10</sub> DAPs) Adj b	<b>Mt. Sinai</b> (Log <sub>10</sub> DAPs) Adj b	<b>Columbia</b> (High v. Low CPF) Adj b
<b>6 Months</b>	<b>-0.7</b>	<b>--</b>	<b>--</b>
<b>1 Year</b>	<b>-0.6</b>	<b>0.1</b>	<b>-3.3</b>
<b>2 Years</b>	<b>-1.3</b>	<b>0.6</b>	<b>1.2</b>
<b>3 Years</b>	<b>--</b>	<b>--</b>	<b>-6.5**</b>

**\*\* p <0.05**

# Prenatal OPs and Bayley Mental Development Index

	Berkeley (Log <sub>10</sub> DAPs) Adj b	Mt. Sinai (Log <sub>10</sub> DAPs) Adj b	Columbia (High v. Low CPF) Adj b
6 Months	-1.2	--	--
1 Year	-1.3	-1.3	-0.3
2 Years	-3.5**	-1.9**	-1.5
3 Years	--	--	-3.3*

\* p < 0.1    \*\*p < 0.05

# Prenatal Ops and Neuro-Development at 3.5 and 5 Years

	Berkeley (Log <sub>10</sub> DAPs) Adj b (n≈300)	Columbia (High v. Low CPF) Adj b (n=231)
<b>WPPSI (3.5 yrs)</b>		
Performance IQ	-0.5	
Verbal IQ	-3.6**	
Full Scale IQ	-2.3*	
<b>WPPSI/PPVT (5 yrs)</b>		
Performance IQ	-0.7	--
Verbal IQ/PPVT	-6.1** (PPVT)	-5.6** (VIQ)
Full Scale IQ	--	-5.1**

\* p < 0.1; \*\* p < 0.05

# Prenatal OPs and Child Behavior Checklist

	Berkeley ( $\text{Log}_{10}$ DAPs)		Columbia (High v. Low CPF)
	2 Y Adj OR	3.5 Y Adj OR	3 Y Adj OR
Attention Problems	0.8	2.5	11.3*
Attention Deficit/Hyperactivity	1.3	2.6	6.5*
Pervasive Developmental Disorder	2.3**	2.3*	5.4*

\* p < 0.1, \*\* p < 0.05

## *In summary...*

- Three scientifically-rigorous, cohort studies
  - Different populations
  - Different exposure levels and sources
  - Exposure measured using biomarkers in urine (metabolites) and blood (parent compound)
- Despite these differences, some patterns emerge...

## *In summary...*

- **Prenatal OP exposure associated with:**
  - Increased odds of abnormal reflexes in neonates
  - Poorer mental development in 2 and 3 year olds
  - Poorer verbal IQ in 3½ and 5 year olds
  - Increased odds of pervasive developmental disorder in 2, 3 and 3½ year olds