

# **Impact of Prenatal Chlorpyrifos Exposure on Child Neurodevelopment**

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**Pregnancy**

**9 years**

**Exposure Assessments**

**Biomarkers of Exposure  
Effect/Susceptibility**

**Outcomes**

**PAH, PM**

**PAH-DNA adducts**

**Fetal Growth, Asthma**

**Pesticides**

**Chlorpyrifos**

**Fetal Growth,  
Neurodevelopment**

**ETS**

**Cotinine**

**Asthma,  
Neurodevelopment**

**Metals**

**Lead, Mercury**

**Neurodevelopment**

**Allergens**

**Immune changes**

**Asthma**

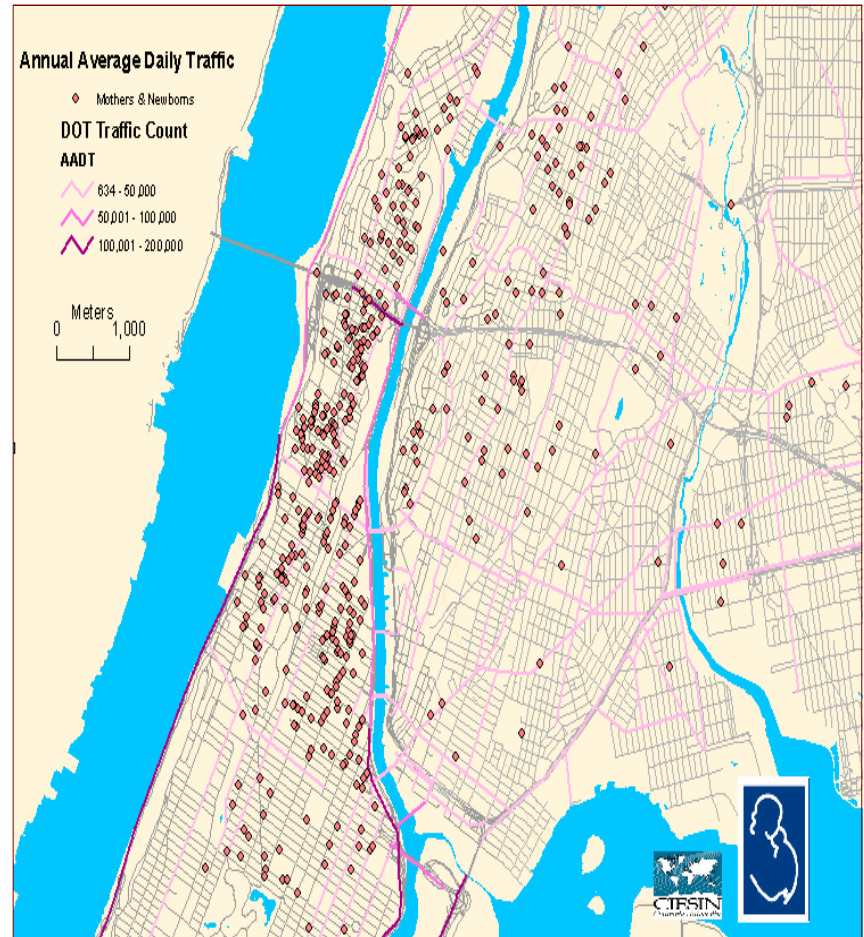
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**To date, relatively few prospective studies of pesticide effects on human neurodevelopment have been published**



# Demographics: Northern Manhattan Cohort (n=720)

<b>Maternal Age</b>	<b>25 (15-38)</b>
<b>Ethnicity</b>	
Latina	<b>64.8%</b>
African American	<b>35.2%</b>
<b>Medicaid</b>	<b>90.8%</b>
<b>Marital Status</b>	
Never married	<b>65.6%</b>
<b>Education</b>	
< High School	<b>35.7%</b>
<b>Annual Household Income</b>	
<\$10,000	<b>45.5%</b>
<b>Lacked basic necessities</b> shelter, food, clothing, heat, medicine	<b>43.5%</b>





**What is chlorpyrifos and what  
is the extent of exposure  
among pregnant women in  
Northern Manhattan?**



# Chlorpyrifos is a Broadband Organophosphate Insecticide

- Used to control cutworms, cockroaches, grubs, beetles, flies, termites, fire ants, and lice
- Used on grain, cotton, corn, fruits, nuts and other vegetable crops, lawns and ornamental plants
- Registered for direct use on sheep and turkeys, for horse site treatment, dog kennels, farm buildings, and commercial establishments
- Also used as a nerve gas in warfare to induce toxicity (tremors, convulsions, death)



# Exposure in NYC and the Cohort

**Insecticides were frequently detected in air and blood samples**

**Chlorpyrifos: 99% of air & 70-71% of blood samples**

**Diazinon: 100% of air & 48-49% of blood samples**

- **In 1997, the amount of insecticide applied by licensed applicators in NYC exceeded the amount applied in any other NY county, including farming regions**
- **86% of cohort women reported using pest control methods during pregnancy**
- **Maternal and newborn blood levels were highly correlated showing that these insecticides readily crossed the placenta**



# Why study chemical exposures and their effects on children?

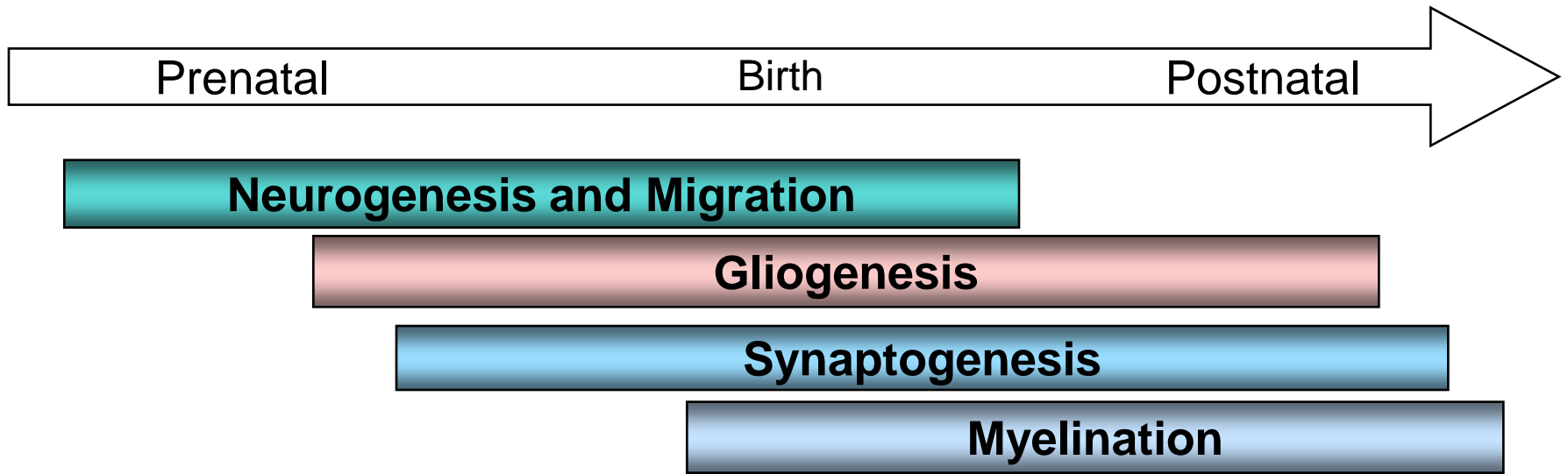
- 5000 new chemicals/year
- EPA estimates that > 25% are neurotoxic
- High vulnerability of the developing brain
- Epidemiologic and experimental data are needed to establish EPA safety standards



**What are the mechanisms by which CPF could harm developing organisms?**



# Multiple Mechanisms: A Shifting Target



Systemic toxicity is related to cholinesterase inhibition, but developmental neurotoxicity may be unrelated to this mechanism

EPA uses cholinesterase inhibition as the biomarker to establish safety standards



# **Associations between prenatal chlorpyrifos exposure and fetal growth in the NYC cohort**

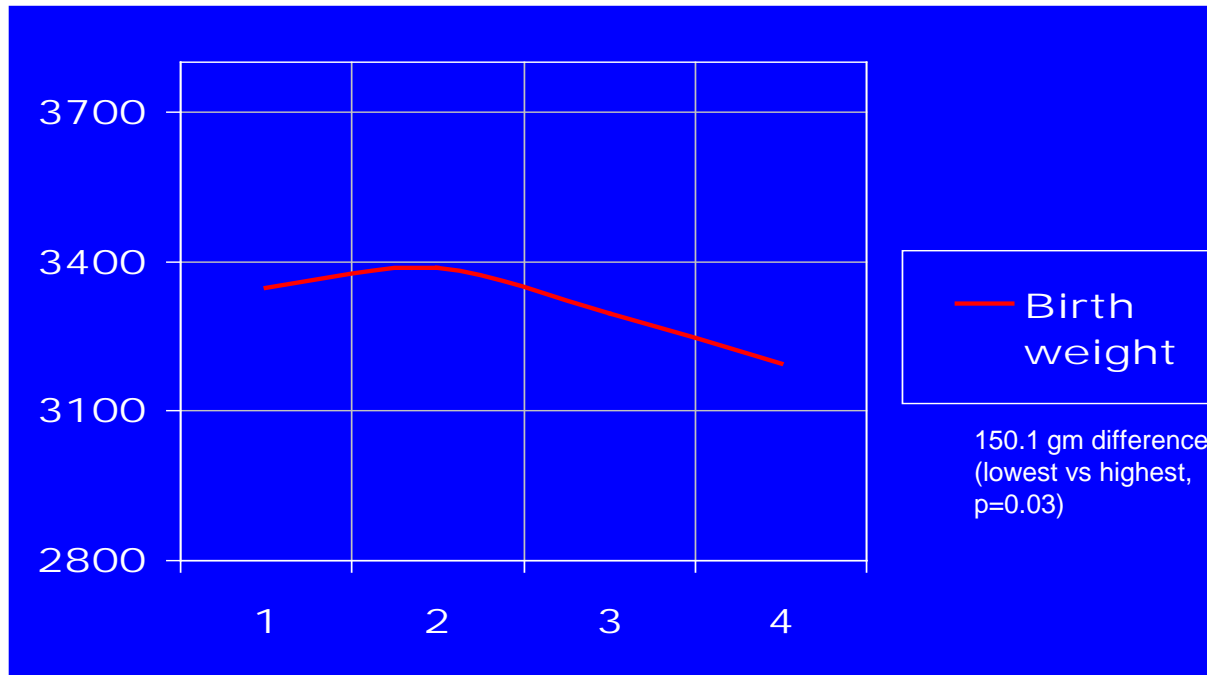


# Birth weight and length by chlorpyrifos umbilical cord levels (N=314)

N  
N=314

Birth weight (gm)  
B= -42.6 (-81.8 to -3.8)\*

Birth length (cm)  
B= -0.24 (-0.47 to -0.01)\*



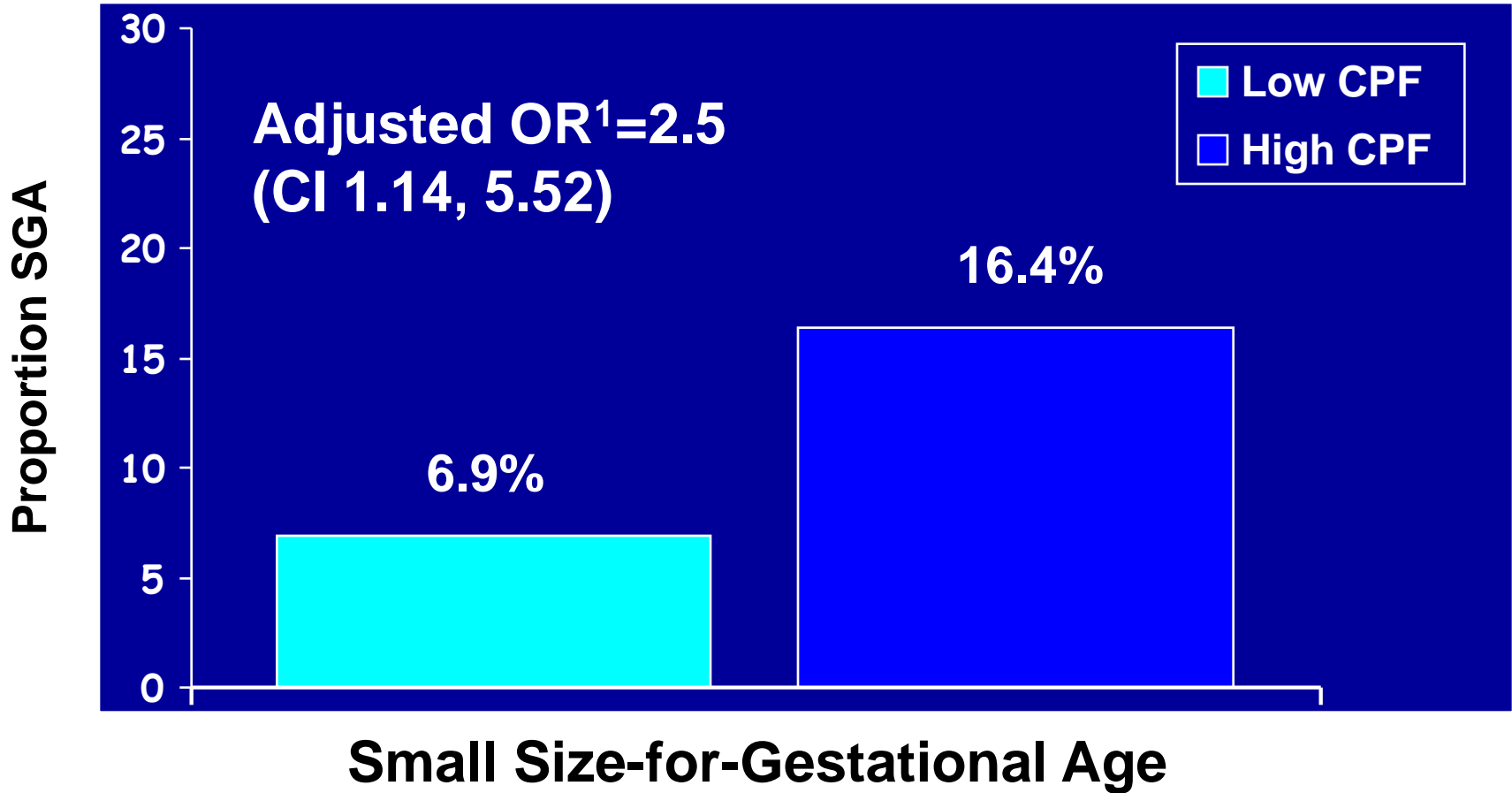
Group 1=below LOD; group 2=lowest 3rd > LOD; group 3=middle 3rd > LOD; group 4=highest 3rd > LOD. Controlling for active and passive smoking, ethnicity, parity, maternal pre-pregnancy weight and net weight gain during pregnancy, gender and gestational age of the newborn, and season of delivery

\* p < 0.05

Whyatt et al, EHP, 112: 1125, 2004



# Logistic regression showing the effect of high chlorpyrifos (CPF) exposure on the odds of SGA in a cohort of inner city children (n=385)



<sup>1</sup>Logistic regression adjusted for maternal short stature, maternal low BMI, net weight gain in pregnancy, race/ethnicity, and exposure to secondhand smoke



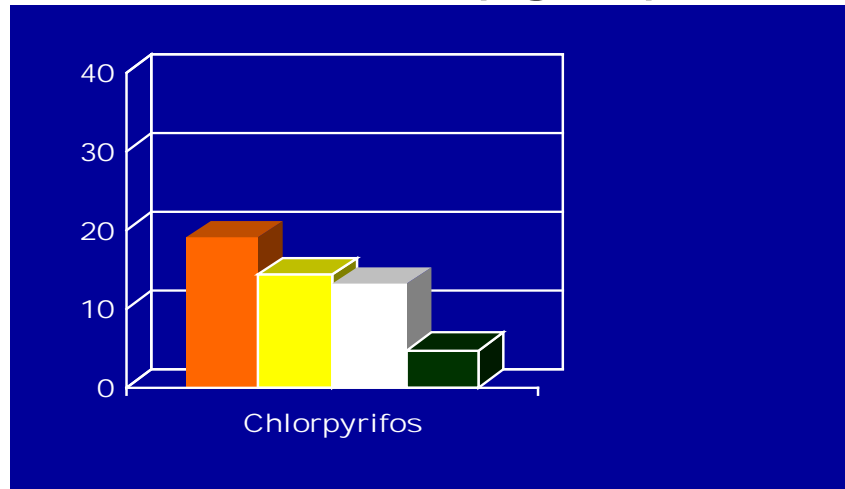
# Regulatory Action

- ✓ **In 2001, EPA banned (phased out) the sale of chlorpyrifos for all residential and indoor use**
- ✓ **Agricultural use still permitted**
- ✓ **Replacement pesticides are now being used (e.g., pyrethroids, carbamates)**
- ✓ **Long-term effects of CPF on children and adolescents are not known**

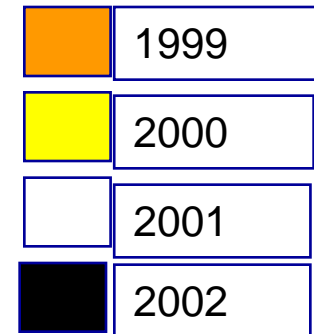
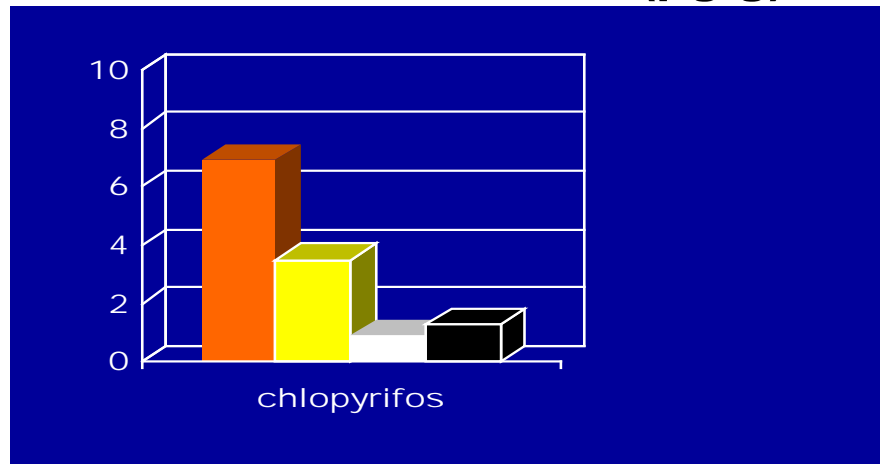


# Chlorpyrifos levels in air and blood samples began to drop immediately after the EPA ban

### Personal air (ng/m<sup>3</sup>)



### Umbilical cord blood (pg/g)



\*  $p < 0.05$  linearity trend test

Whyatt et al., EHP, 111: 749-756, 2003



# **Associations between prenatal chlorpyrifos exposure and neurodevelopment**

OR

***How exposure to a  
common pesticide can  
damage the developing  
brain***

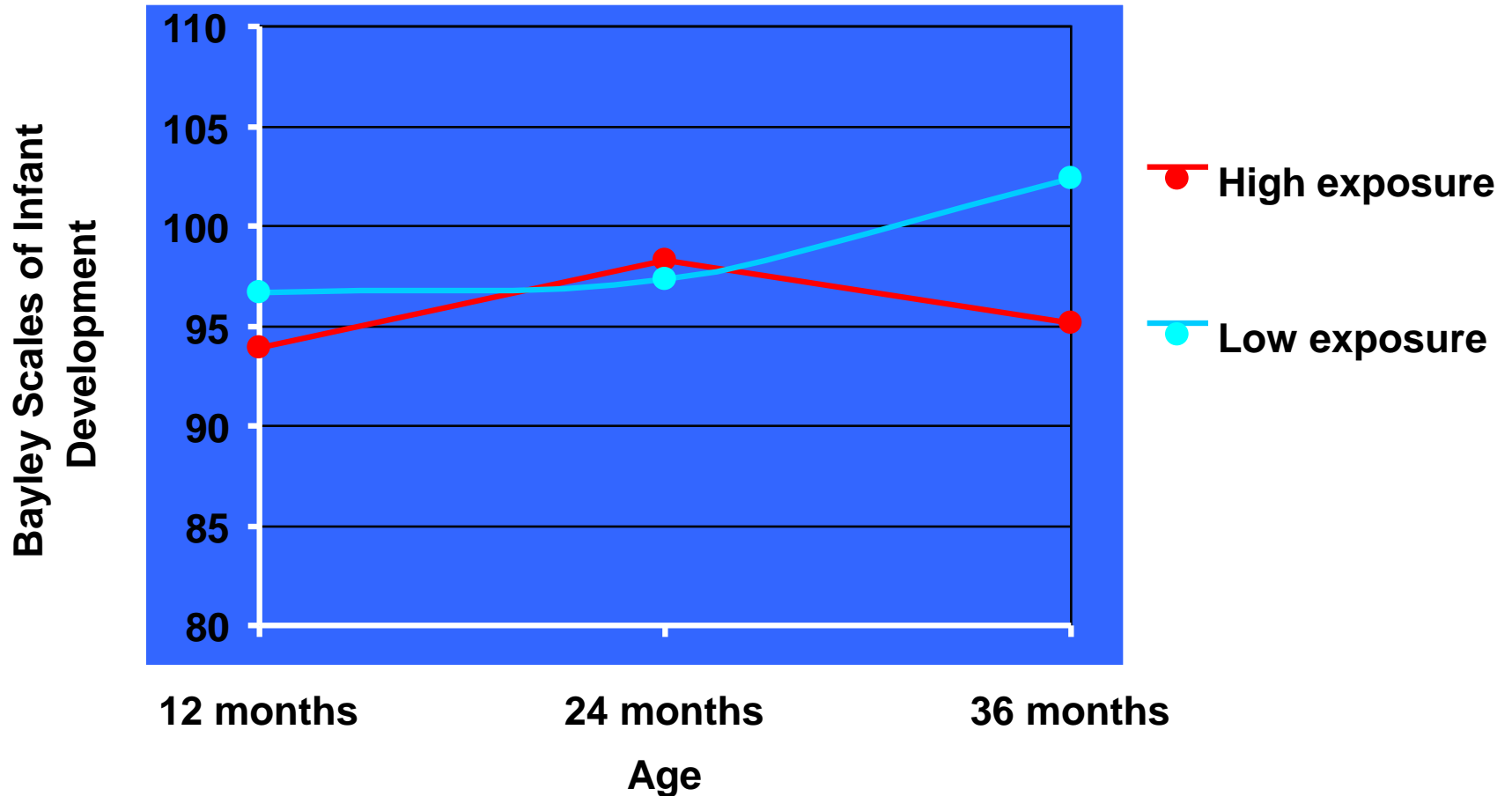


# Bayley Scales of Infant Intelligence (12-36 months)





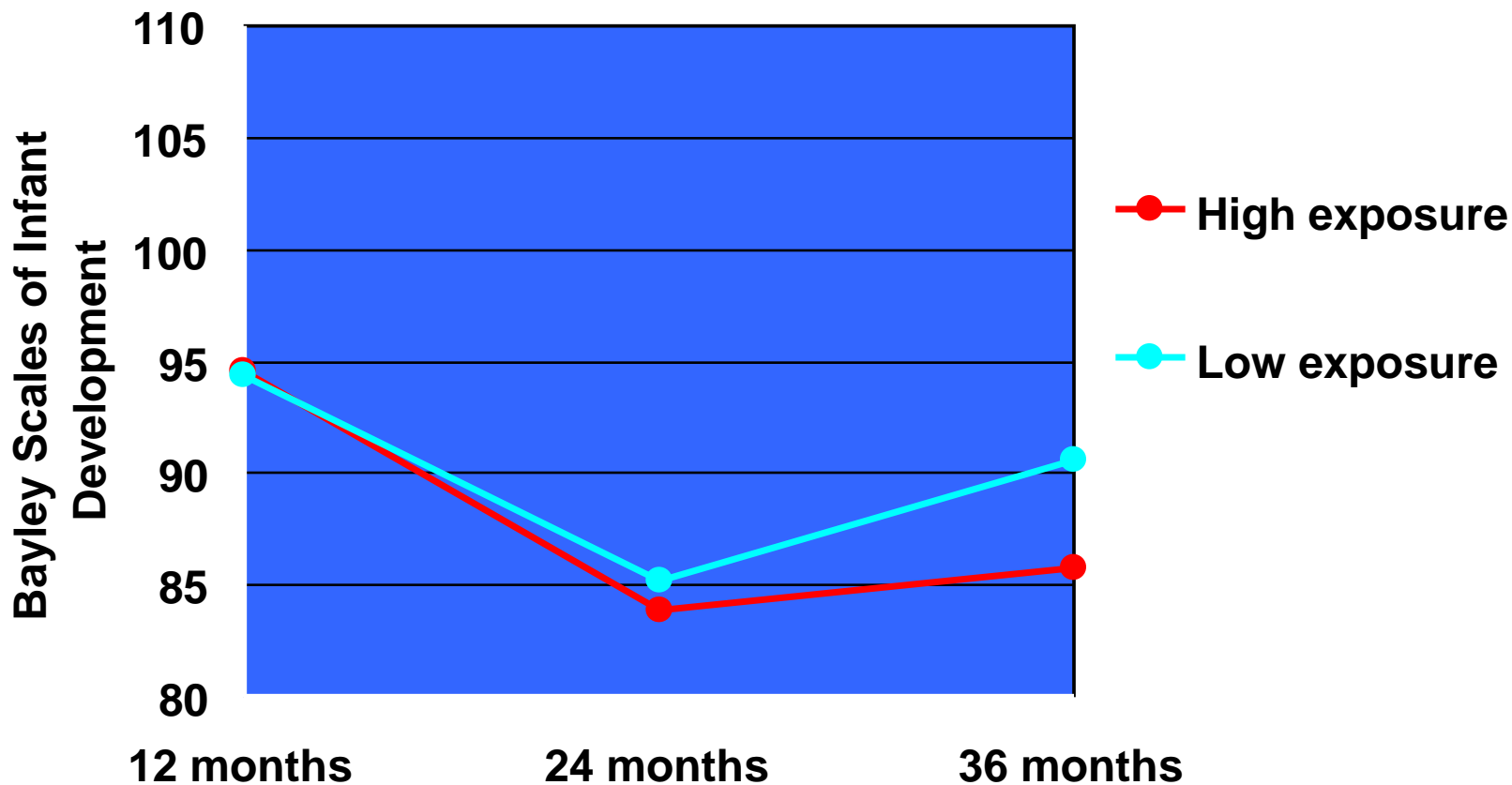
# Effects of Prenatal Chlorpyrifos Exposure on Motor Development in Children 12 through 36 months of Age, using General Linear Modeling (GLM) N=228



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



# 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 chlorpyrifos (upper quartile) versus all other levels



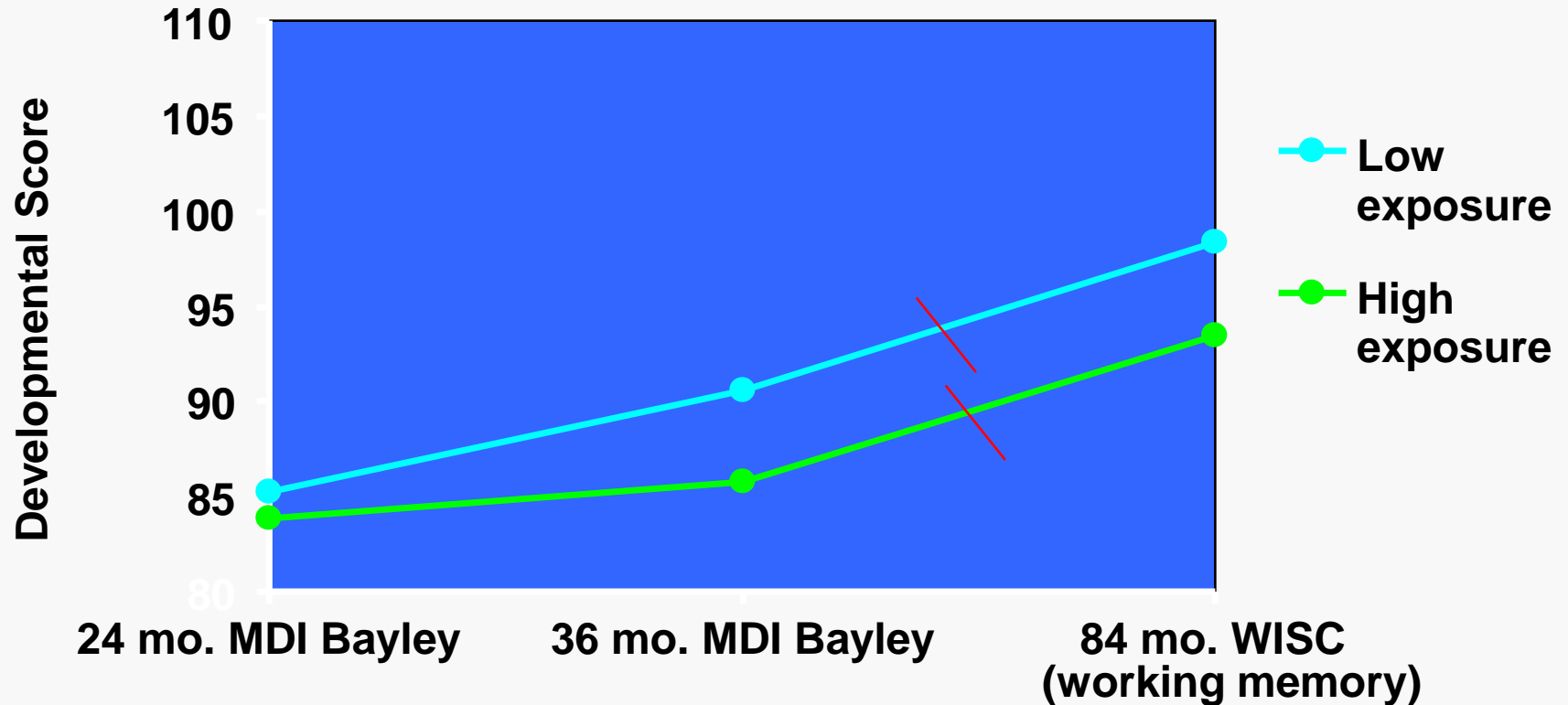
# Odds of behavioral disorders on CBCL at age 36 months among infants with high versus low umbilical cord blood chlorpyrifos levels<sup>1</sup> (n=228)

	<u>Odds Ratio</u>	<u>95% CI</u>
<b>Attention Syndrome</b>	<b>11.26</b>	<b>1.79, 70.99</b>
<b>ADHD Problems</b>	<b>6.50</b>	<b>1.09, 38.69</b>
<b>Pervasive Developmental Disorder Problems</b>	<b>5.39</b>	<b>1.21, 24.11</b>

<sup>1</sup>Logistic regression controlling for race, gender, gestational age, maternal education, maternal IQ, ETS, and home environment (Home Scale)



# Estimated Effects of Prenatal Chlorpyrifos (CPF) Exposure\* on Cognitive Developmental in Children 24 through 84 months of Age, using General Linear Modeling (GLM)



Models are adjusted for race/ethnicity sex, age at testing, gestational age, maternal education (<HS), maternal IQ, Home Scale, poverty,ETS

\*High CPF (upper quartile: >6.17 pg/g) versus all other levels



# Summary: Prenatal Exposure to Pesticides Increases Risk of Adverse Health Outcomes

- Reduction in birth weight by an average of 6.6 ounces (equivalent of weight reduction seen in babies born to women who smoked)
- Delay in psychomotor and cognitive development at age 3
- Symptoms of ADHD and personality disorder at age 2-3
- Inversely associated with verbal comprehension and working memory performance at age 7





# Pilot Study

## MRI Analysis underway

**Design:** 10 high CPF-exposed children were compared to 15 unexposed children, with very low or no prenatal exposure to CPF, ETS, and PAH

### **Areas of Inquiry:**

- **Working Memory** (strongly related to complex tasks such as reading comprehension, problem solving, and IQ)
- **Executive Function** (ability to maintain task-relevant representations in the face of distracting information)
- **Reading Ability/Disability**



# Conclusions

**Umbilical cord chlorpyrifos levels were:**

- **Inversely associated with birth weight, length and SGA;**
- **Inversely associated with mental and motor development at 3 years, and positively associated with behavior problems at 3 years;**
- **Inversely associated with verbal comprehension and working memory performance at 7 years**



# From Research to Policy

- ✓ **2007-08: Dow Chemical scientists write commentaries rebutting the fetal growth and developmental findings**
- ✓ **2008: NRDC petitioned EPA to ban CPF for all uses and prepares a law suit**
- ✓ **2008: Dow Chemical petitioned EPA to register CPF for additional agricultural uses**
- ✓ **8/2008: EPA prepared report for the Scientific Advisory Panel based on this work and the work of others**
- ✓ **9/16/08: Public hearing took place**



# Acknowledgements

## Investigators

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