

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

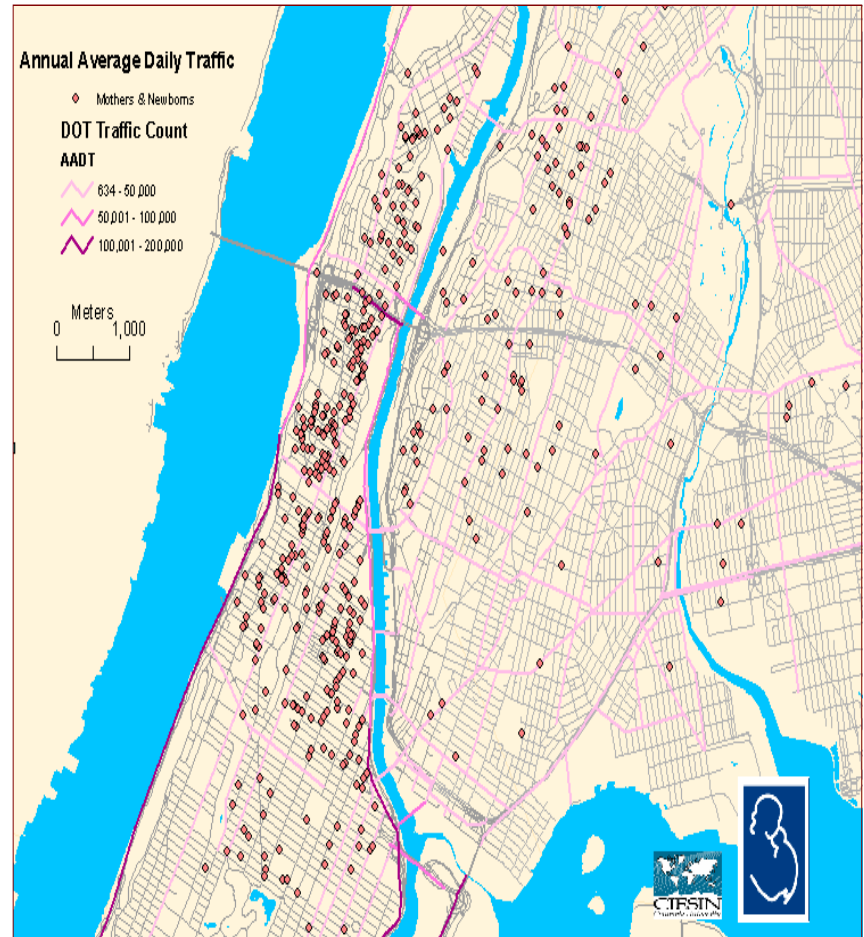
Asthma

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



Demographics: Northern Manhattan Cohort (n=720)

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





**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?

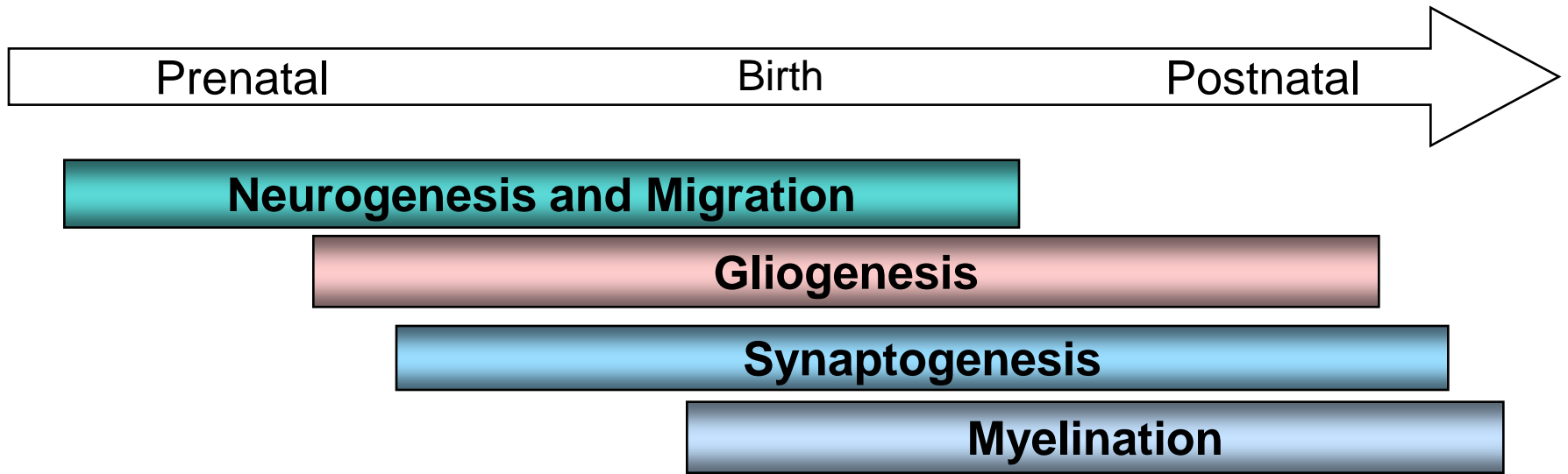
- 5000 new chemicals/year
- EPA estimates that > 25% are neurotoxic
- High vulnerability of the developing brain
- Epidemiologic and experimental data are needed to establish EPA safety standards



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

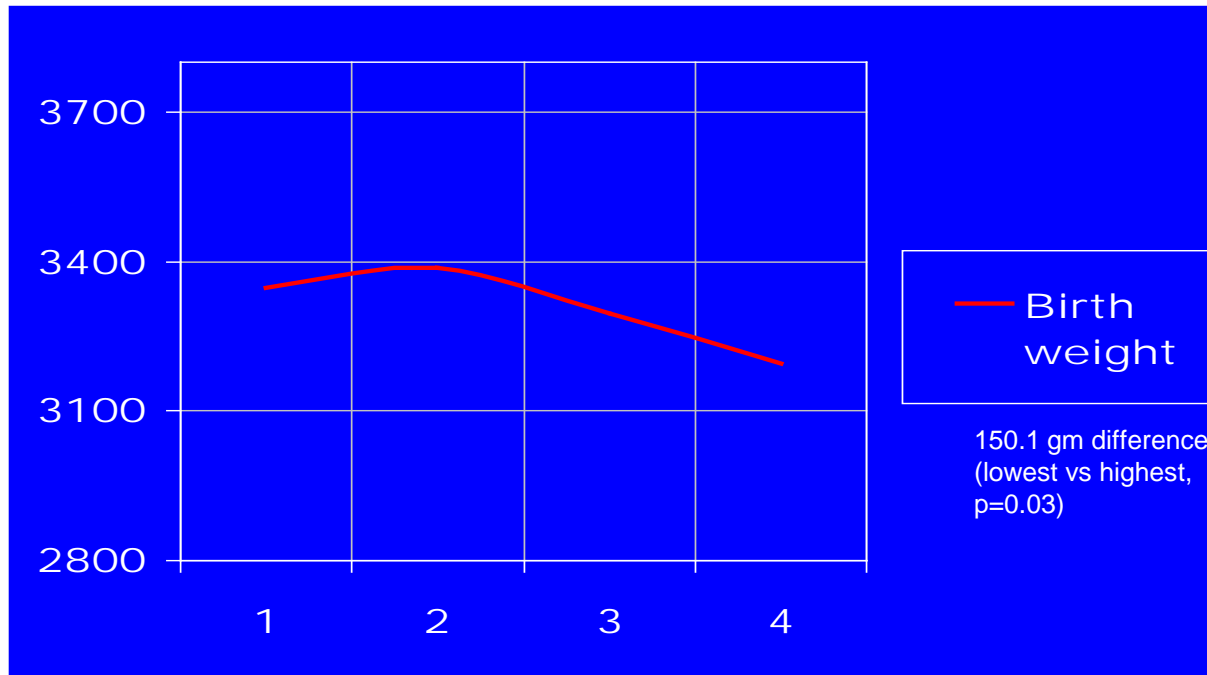


Birth weight and length by chlorpyrifos umbilical cord levels (N=314)

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)*



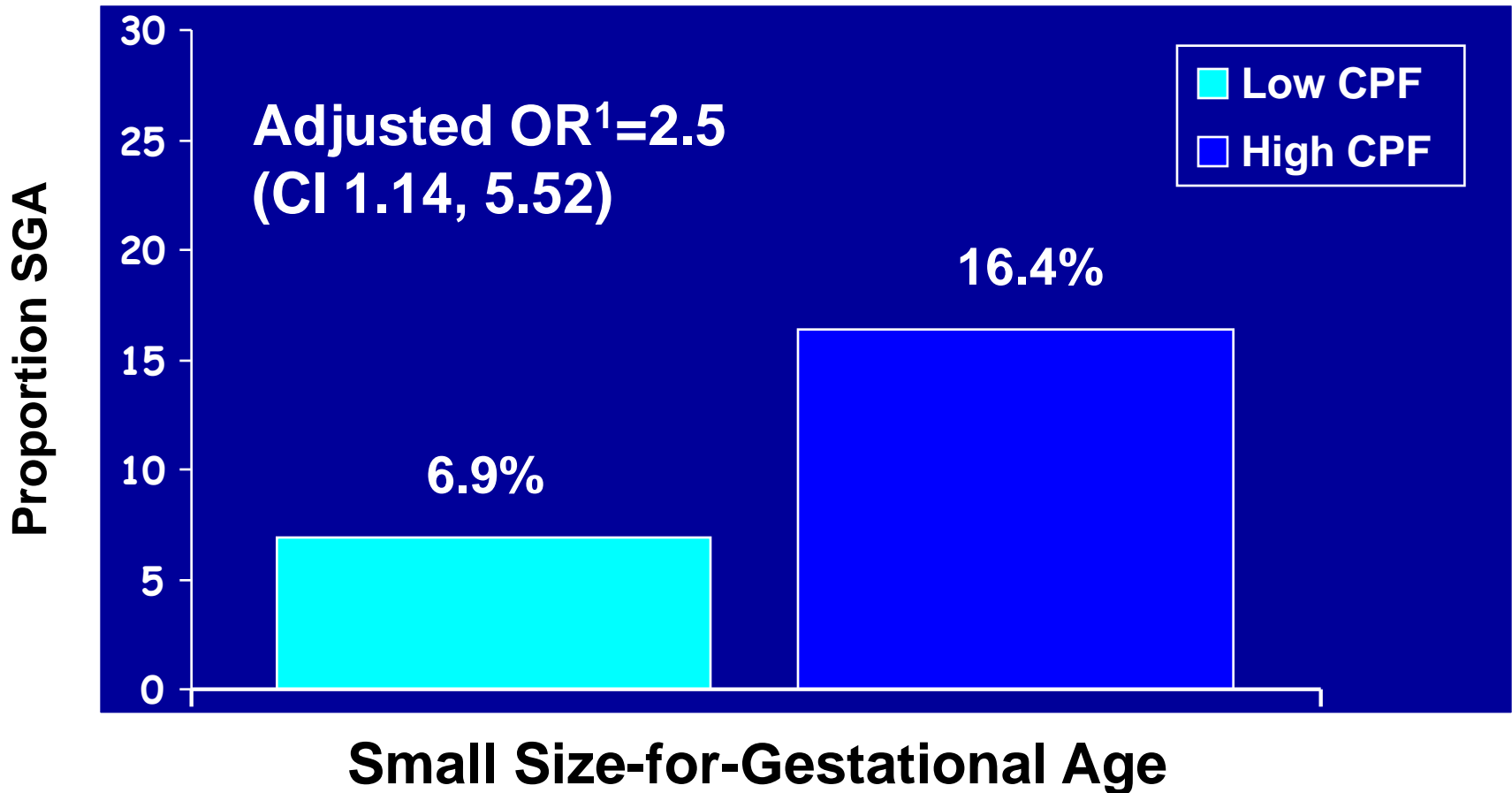
Group 1=below LOD; group 2=lowest 3rd > LOD; group 3=middle 3rd > LOD; group 4=highest 3rd > LOD. Controlling for active and passive smoking, ethnicity, parity, maternal pre-pregnancy weight and net weight gain during pregnancy, gender and gestational age of the newborn, and season of delivery

* 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)



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



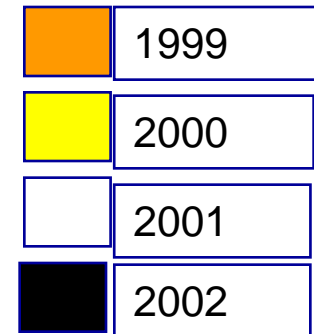
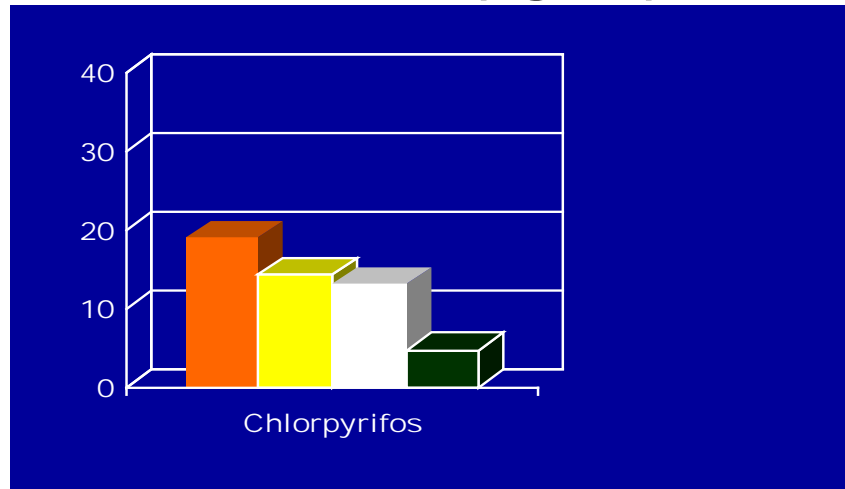
Regulatory Action

- ✓ **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**

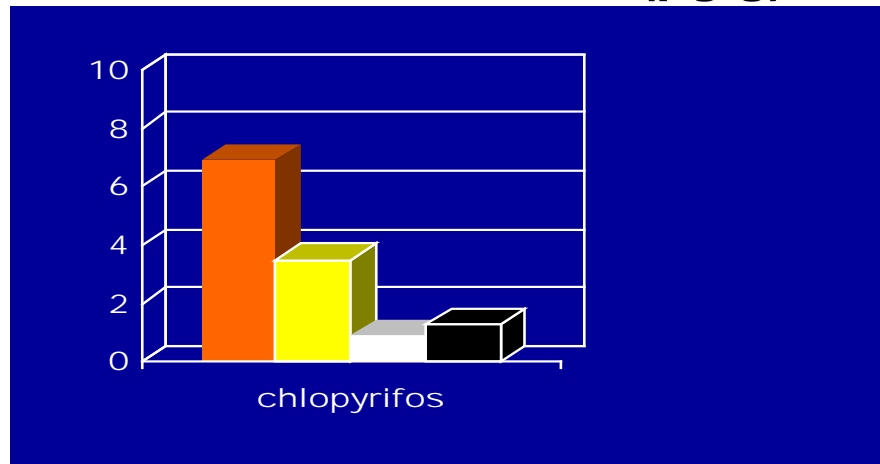


Chlorpyrifos levels in air and blood samples began to drop immediately after the EPA ban

Personal air (ng/m³)



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***

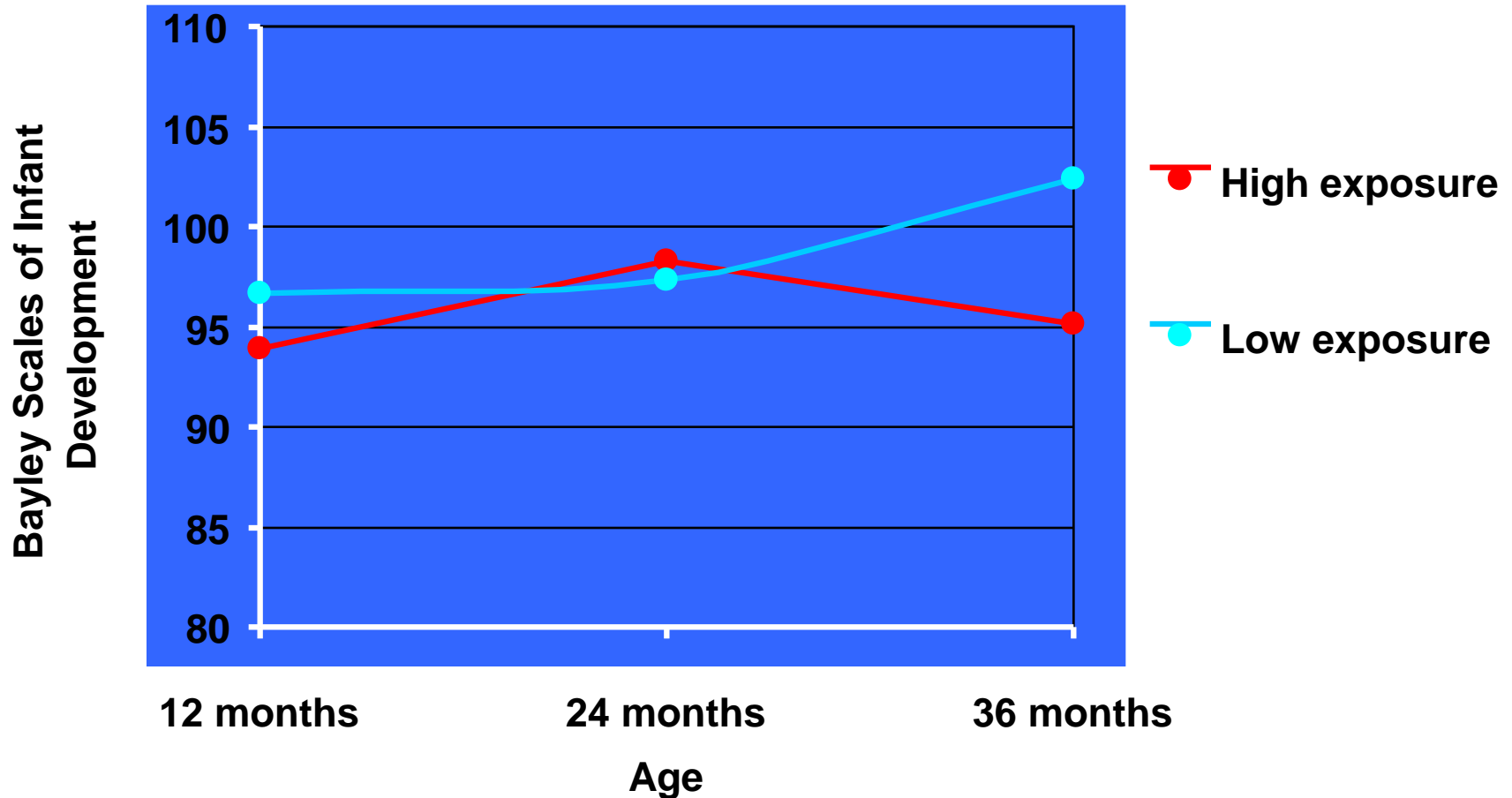


Bayley Scales of Infant Intelligence (12-36 months)





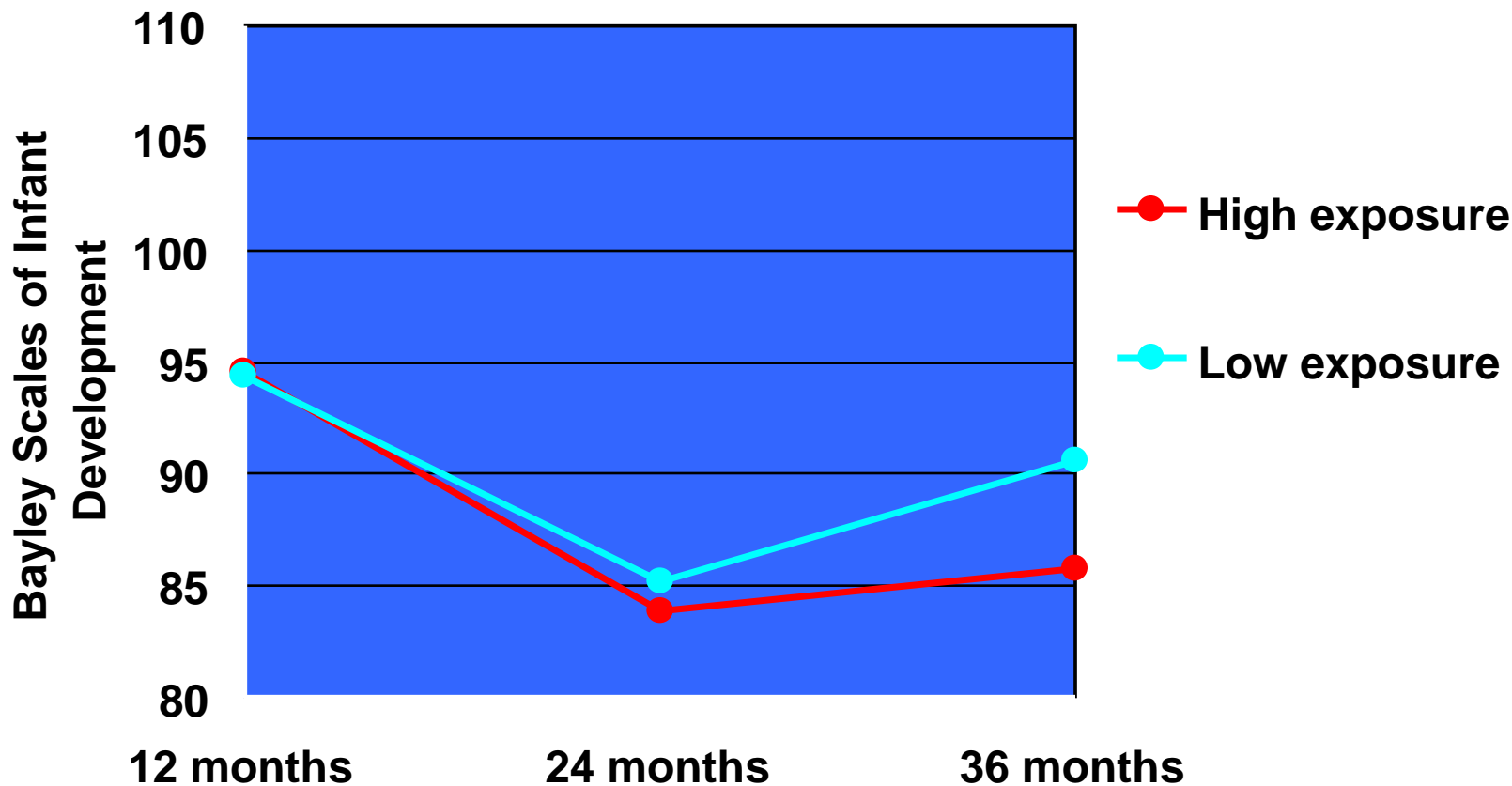
Effects of Prenatal Chlorpyrifos Exposure on Motor Development in Children 12 through 36 months of Age, using General Linear Modeling (GLM) N=228



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



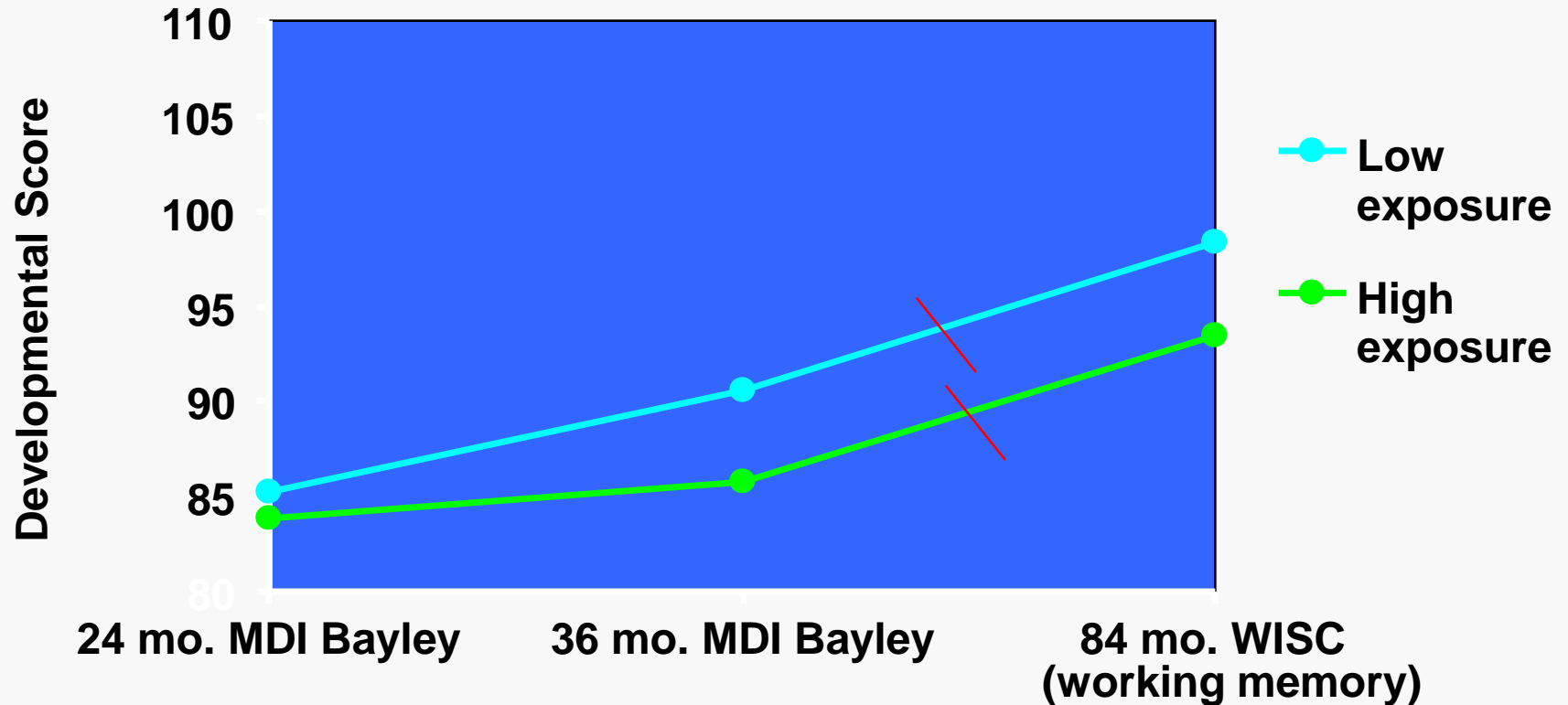
Odds of behavioral disorders on CBCL at age 36 months among infants with high versus low umbilical cord blood chlorpyrifos levels¹ (n=228)

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

¹Logistic 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

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