COLUMBIA CENTER FOR CHILDREN'S ENVIRONMENTAL HEALTH
MAILMAN SCHOOL OF PUBLIC HEALTH
Columbia University

Developmental Effects of Prenatal Exposure to Organophosphate Pesticides

Research findings from the Columbia Center for Children's Environmental Health

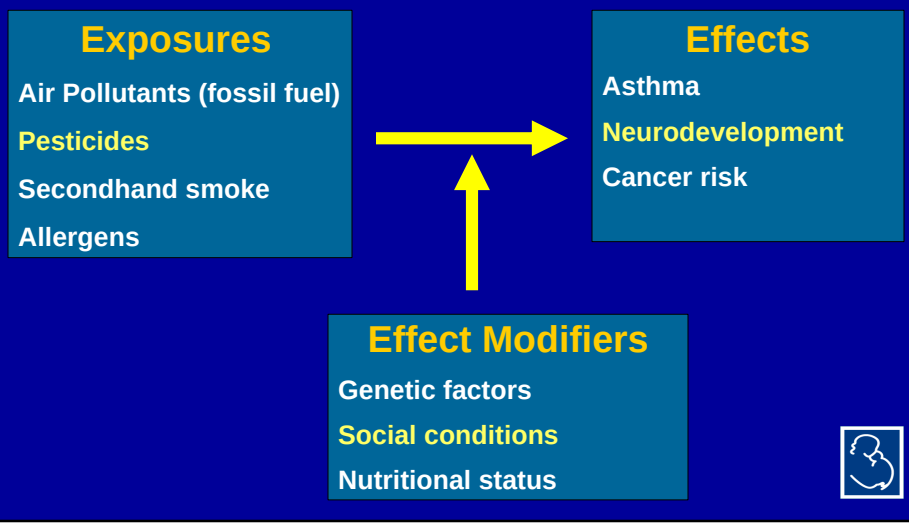
Rauh[1], Garfinkel[1], Perera[1], Andrews[1], Hoepner[1], Barr[2], Whitehead[2], Tang[1] , and Whyatt[1]

[1]Columbia Center for Children's Environmental Health

[2]The Centers for Disease Control and Prevention

No conflicts of interest

The purpose of the cohort study was to assess the impact of prenatal exposure to ambient and indoor air pollution on child health & development



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

Pregnancy . . . . 8 years

Exposure Assessment	Biomarkers of Exposure Effect/Susceptibility	Outcome
PAH, PM	PAH-DNA adducts	Fetal growth
Pesticides	Chlorpyrifos	Neurobehavior and Development
ETS	Cotinine	
Metals	Lead, Mercury	
Allergens	Immune changes	Asthma

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

Columbia Center for Children's Environmental Health

Environmental Measures (Air)

48-hour personal air monitoring (begun in1999)

2-week integrated indoor air samples (begun in 2001)

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

Insecticides frequently detected in urban air and blood samples:

Residential use of pesticides is heavy in many urban areas. In 1997, the amount of the insecticide applied by licensed applicators in New York City exceeded the amount applied in any other county in the state, including agricultural communities.

Chlorpyrifos:	**99% of air and 70-71% of blood samples**
Diazinon:	100% of air and 48-49% of blood samples
Propoxur:	100% of air and 40-41% of blood samples

In this cohort, maternal and newborn blood levels were similar and highly correlated showing that these insecticides readily crossed the placenta.

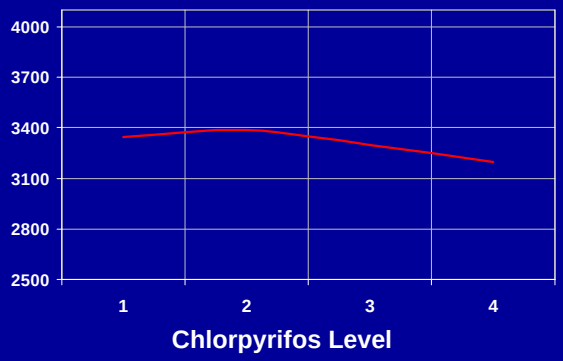
Effects of CPF on fetal growth

Among infants exposed to the highest levels of CPF:

- Significant deficits in birth weight and birth length were associated with cord plasma CPF level
- First evidence that exposures were sufficiently high to produce fetal growth deficits

Whyatt et al., Environ. Health Perspect. 2004; 112: 1125-1132

Birth weight by chlorpyrifos level in cord plasma



150.1 gm difference (lowest vs highest)

p=0.03

CPF levels: Group 1=below LOD; group 2=lowest 3rd ; group 3=middle 3rd ; group 4=highest 3rd > (> 6.17 pg/g plasma)

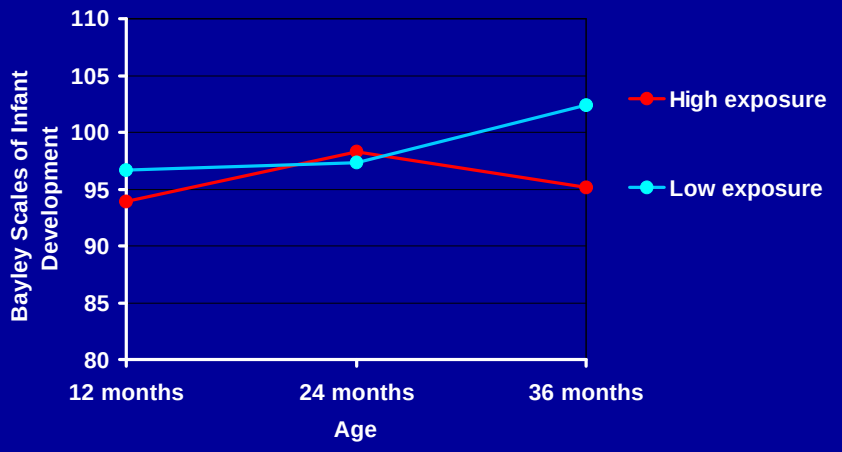
18.3 % of the sample was in the high CPF exposure group (level 4)

Whyatt et al., EHP, 2004

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)
Mental Development	94.03 (9.8)	85.10 (12.4)	89.58 (11.4)
Motor Development	96.22 (12.2)	97.04 (11.5)	100.46 (13.0)
	%	%	%
Mental Delay (<85)	14.30	29.20	22.60
Motor Delay (<85)	12.20	15.30	9.20

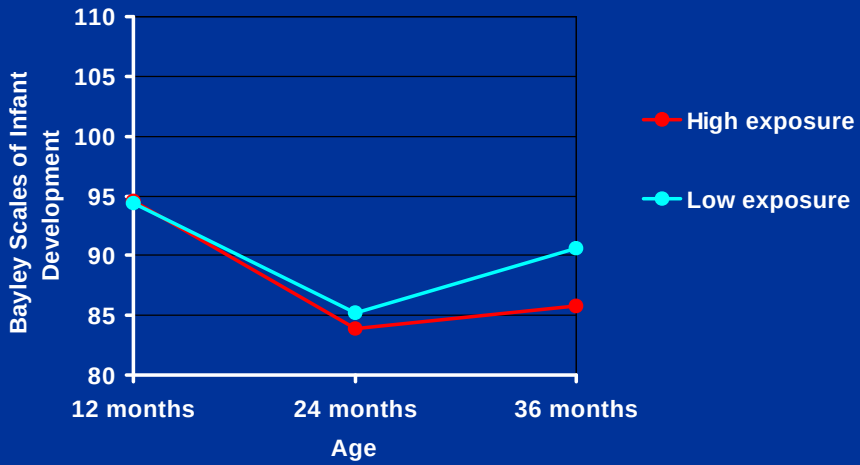
Estimated Effects of Prenatal Chlorpyrifos Exposure on Motor Development in Children 12 through 36 months of Age, using General Linear Modeling (GLM)



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

High chlorpyrifos (upper quartile) versus all other levels

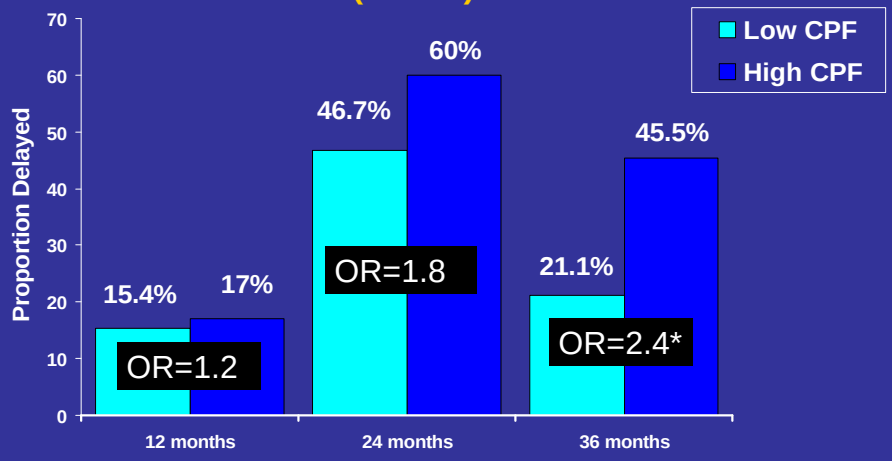
Estimated Effects of Prenatal Chlorpyrifos Exposure on Cognitive Development in Children 12 through 36 months of Age, using General Linear Modeling (GLM)



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

High chlorpyrifos (upper quartile) versus all other levels

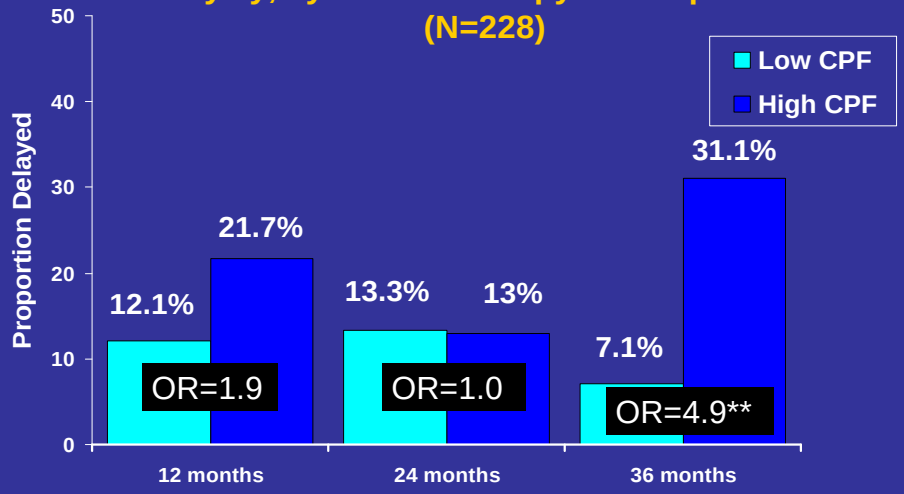
Cognitive Delay (< 85) at 12, 24 & 36 months on the Bayley, by level of chlorpyrifos exposure (N=228)



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

*p<.01

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



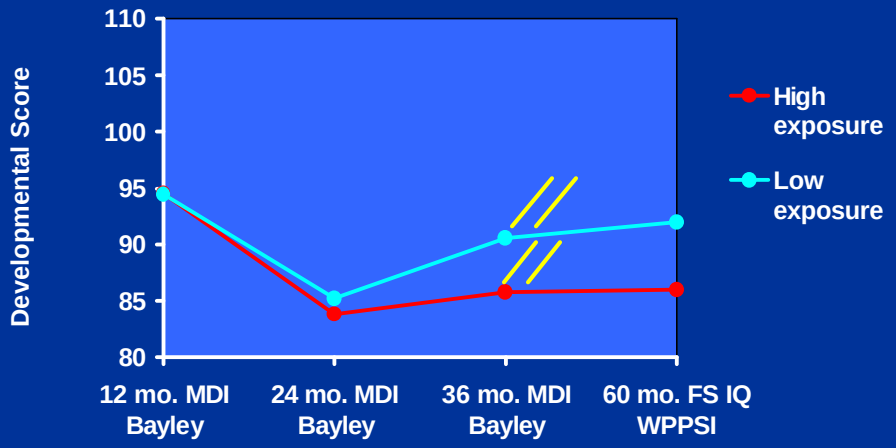
Logistic regression adjusted for race/ethnicity, sex, gestational age, ETS, maternal IQ, maternal education, HOME Inventory

**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 and 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

Effects of Prenatal CFP Exposure* on Developmental Quotient in Children 12 through 60 months of Age, using General Linear Modeling (GLM)



Models are adjusted for race/ethnicity, sex, gestational age, maternal ed (<HS), maternal IQ, Home Scale, poverty, ETS, and head circumference

*High CPF (upper quartile) versus all other levels

Rauh, Whyatt et al. , 2007

Possible Mechanisms

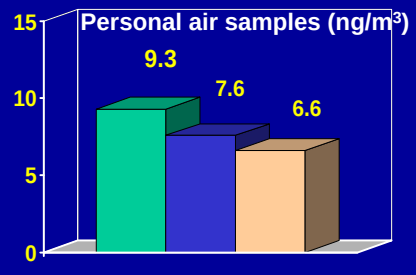
- Prenatal CPF exposure has been shown experimentally to inhibit acetylcholinesterase, which acts as a neurotropic factor during brain development[1];
- Organophosphates may also disrupt brain development by noncholinergic mechanisms, at doses that cause only minimal acetylcholinesterase inhibition[1];
- 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

[1]Slotkin. Cholinergic systems in brain development and disruption by neurotoxicants: nicotine, environmental tobacco smoke, organophosphates. Toxicol Appl Pharmacol. 2004; 198:132-151.

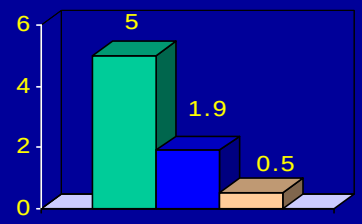
Regulatory Action

- ✓ **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)**

Geometric mean chlorpyrifos levels by year of assessment



Cord blood levels (pg/g) *



Year of Birth

1999 pre-ban

2000 mid-ban

2001 post-ban

* p<0.05 linearity trend test

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

Summary of Results

- **Prenatal pesticide exposure was associated with a 3.5 to 6-point adjusted mean decrement in 36-month development scores (Bayley MDI and PDI), resulting in a 2-fold risk of developmental delay (< 80) on the Bayley MDI, and a 5-fold risk of delay on the PDI**
- **Prenatal pesticide exposure was associated with an approximately 5-point adjusted mean decrement in WPPSI full-scale IQ scores at 60 months of age**
- **Prenatal pesticide exposure was associated with significantly increased risk for ADHD problems, Attention problems, and Pervasive Developmental Disorder problems at 36 months of age**

Summary of Results (continued)

- **Long-term effects of prenatal exposure in children and adolescents are not known**
- **New data suggests that although blood levels have dropped, CPF levels are unchanged in the home**
- **Despite the EPA ban, agricultural use continues and replacement insecticides are being introduced**

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