COLUMBIA CENTER FOR CHILDREN'S ENVIRONMENTAL HEALTH
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Discussion of analyses of prenatal chlorpyrifos exposure and birth outcomes

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Outline

Brief background

Overview of study design

Study demographics and chlorpyrifos levels

Discussion of 2004 EHP paper

Updated analyses on chlorpyrifos and birth outcomes to address:

- Dose-response
- Imputing cord blood levels from maternal levels
- Additional potential confounders

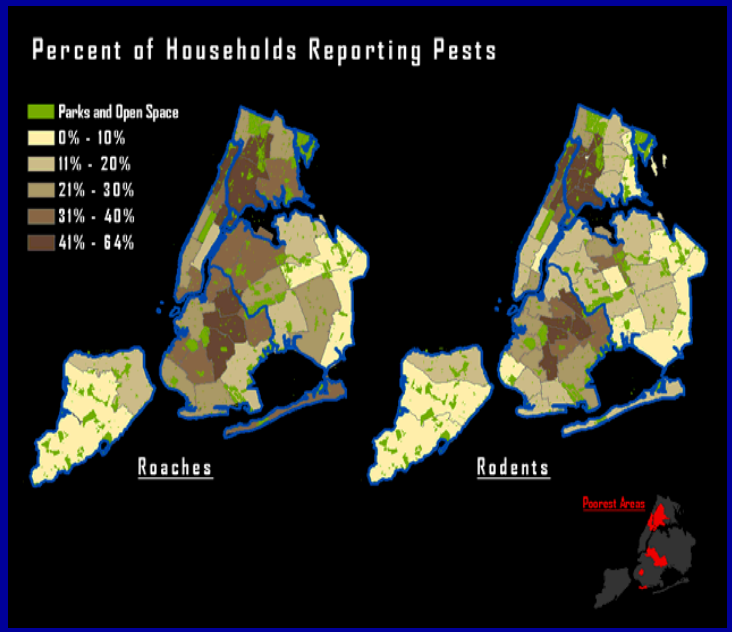
Our hypothesis that prenatal exposure to organophosphates could adversely affect fetal growth and child postnatal development is based on results from experimental data

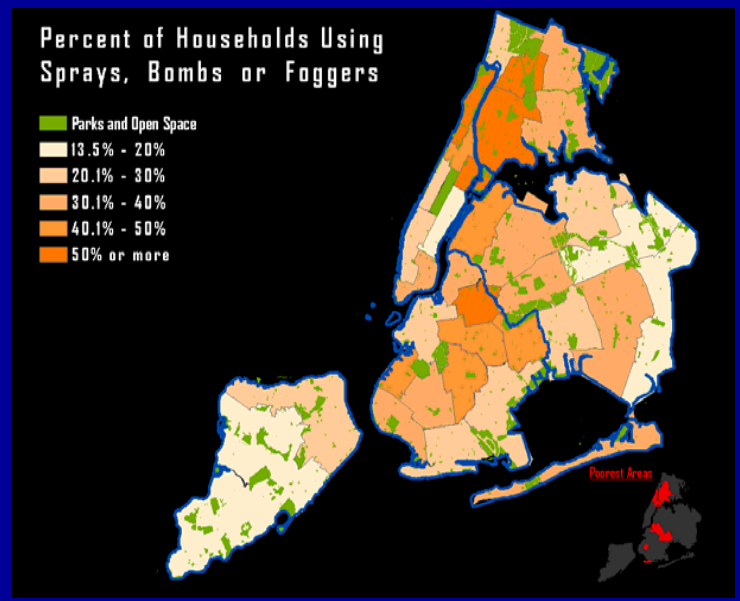
Pesticide	Exposure	Effect
Chlorpyrifos	GD15-PND21	Reduced body weight, impairment on maze, increased righting reflex time, reduced cliff avoidance, lowered activity, gait abnormalities, tremors
Diazinon	Gestation	Lower birth weight, balance, swimming, maze effects

Reviewed in Eskenazi et al., EHP, 1999

Residential use widespread in NYC

- Heaviest application in NY State in NYC
- Chlorpyrifos (CPF) applied most heavily in NYC
- Ethnic disparities in pest infestation levels and pesticide use





Cohort

Number:	725 mother/newborn pairs
Ethnicity:	African American and Dominican
Residence:	Northern Manhattan & South Bronx
Characteristics:	Non-smokers
	Non-illicit drug users
	No HIV, hypertension, diabetes

Demographic and Exposure measures: questionnaire

Were pest control measures used during pregnancy, by whom, what types, how frequently?

Environmental measures of exposure 3rd trimester of pregnancy

48-hour personal air

2-week integrated indoor air; 2 months

Biologic Samples

- umbilical cord blood
- maternal blood
- meconium
- urine

Medical record data: gestational age, gender, birth weight, length, head circumference, maternal height, pre-pregnancy weight and weight gain, medications

Insecticides measured in environmental and biologic samples

Organophosphates
Chlorpyrifos**
Diazinon
Malathion
Methyl parathion

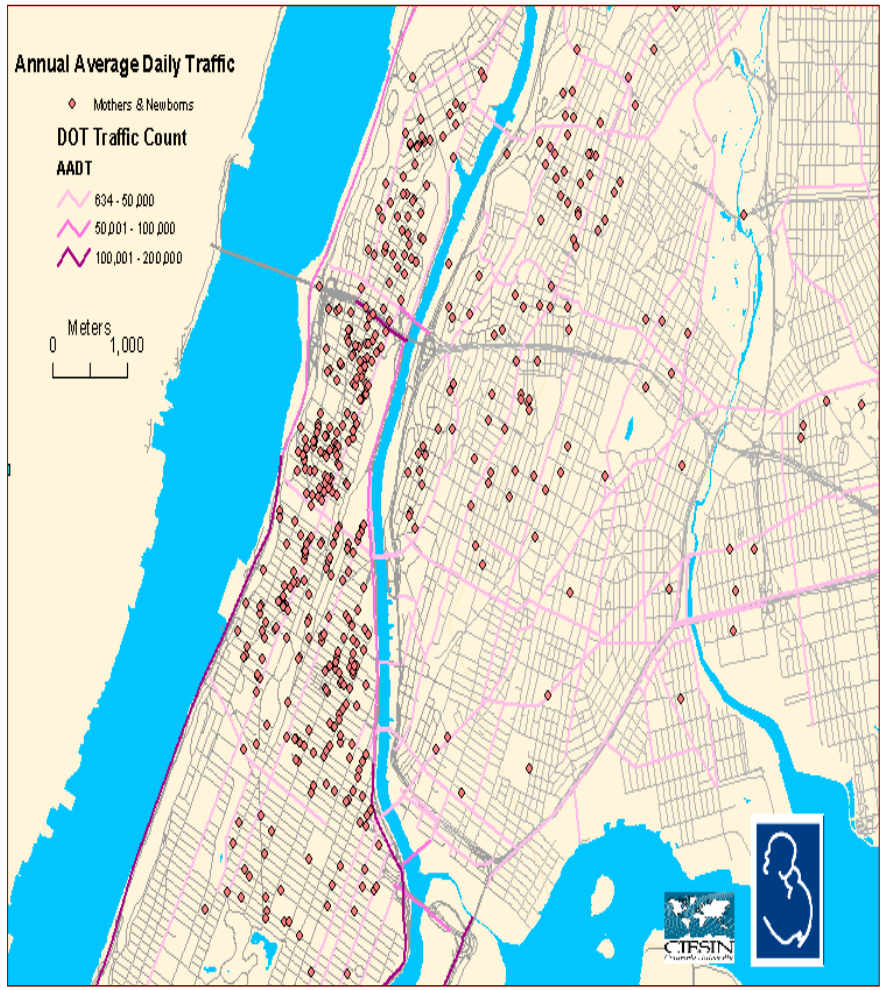
Carbamates
Bendiocarb
Carbaryl
Carbofuran
Propoxur

Pyrethroids
cis-Permethrin
trans-Permethrin

**In 6/2000 U.S. EPA began phasing out residential uses of chlorpyrifos; phase-out completed by 12/2001

Demographics of CCCEH 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%



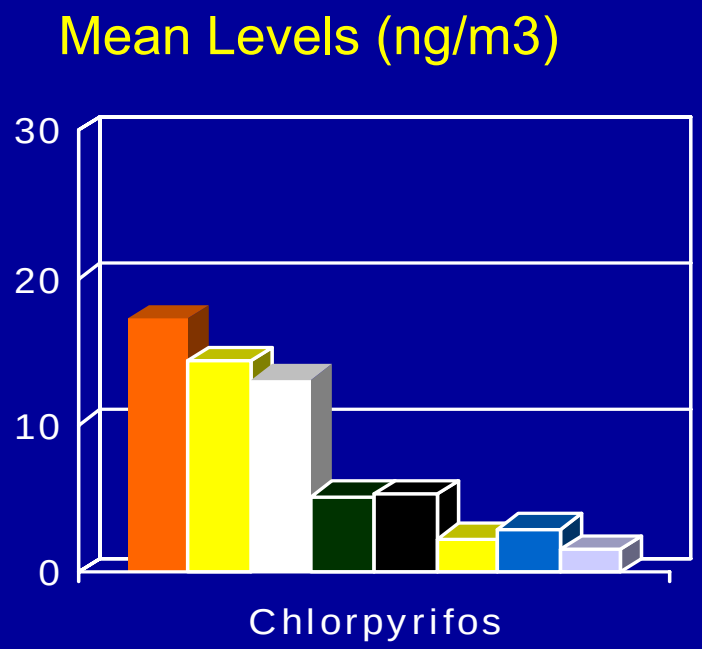
Distribution of chlorpyrifos in maternal 48 hours personal air during pregnancy and in maternal and cord blood samples at delivery (1998-2006)

	Mean±SD	10%	25%	50%	75%	90%	95%
Personal air (ng/m3, n=628)	10.3±25.0	0.9	1.8	3.6	9.3	20.9	37.3
Maternal blood (pg/g, n=425)	2.8±4.4	<LOD	<LOD	0.6	3.9	7.8	12.0
Cord blood (pg/g, n=423)	3.0±5.3	<LOD	<LOD	0.6	3.9	8.7	12.0

Maximum

Personal air: 344.8 ng/m3
Maternal blood: 35 pg/g
Cord blood: 63 pg/g

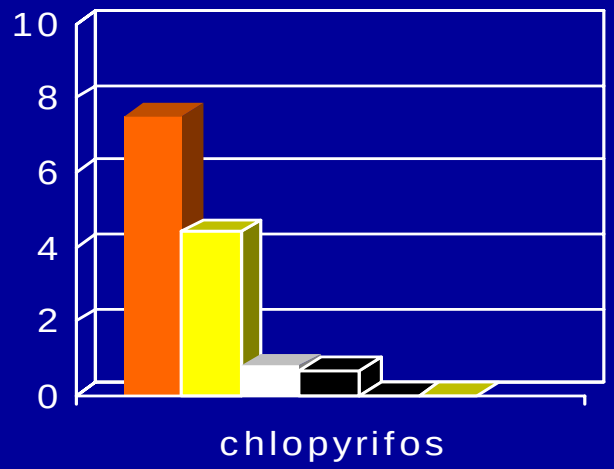
Chlorpyrifos in 48 hour personal air samples during pregnancy by year of monitoring (N=621)



Year	N > LOD (%)
1999	123/123 (100%)
2000	126/126 (100%)
2001	89/90 (99%)
2002	59/59 (100%)
2003	64/64 (100%)
2004	62/63 (98%)
2005	81/83 (98%)
2006	12/13 (92%)

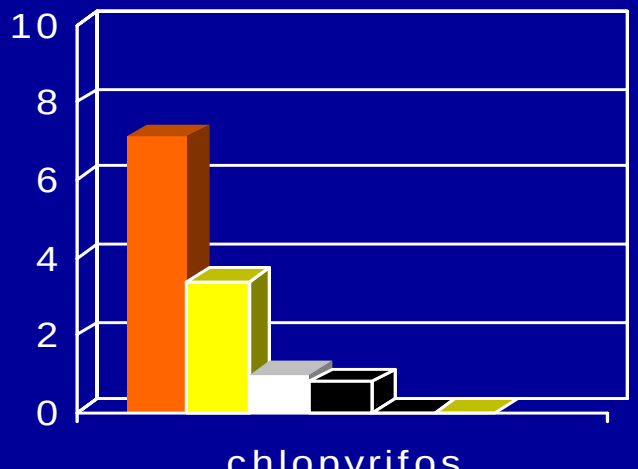
Chlorpyrifos levels in maternal and umbilical cord blood samples (pg/gram) at delivery by year of birth

Maternal blood (N=424)



Year	N > LOD (%)
1999	68/71 (96%)
2000	101/120 (84%)
2001	26/86 (30%)
2002	18/59 (31%)
2003	0/58 (0%)
2004	0/30 (0%)

Cord blood (N=395)



Year	N > LOD (%)
1999	93/110 (85%)
2000	88/110 (80%)
2001	18/71 (25%)
2002	14/36 (39%)
2003	0/43 (0%)
2004	0/25 (0%)

Correlation[1] between chlorpyrifos in maternal personal air samples during pregnancy and maternal and cord blood samples at delivery

	Maternal blood	Cord blood
Personal air	r=0.3, p<0.001, n=411	r=0.3, p<0.001, n=360
Cord blood	r=0.9, p<0.001, n=330	

[1]Spearman's rank

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Discussion of 2004 EHP paper

The EHP paper looked at the relationship between prenatal chlorpyrifos exposure and birth outcomes in the first 314 infants born in the cohort between 3/1998 and 7/2002

Regression models of covariates controlled in analyses of associations between chlorpyrifos levels and newborn birth outcomes

	Birth weight (grams) N=314		Birth length (cm) N=309	
	R^2=0.24, F=9.6, p<0.001		R^2=0.15, F=5.2, p<0.001	
	B±SE	P value	B±SE	p-value
Constant	-2227.4±733.9	P = 0.003	27.5±4.2	P < 0.001
Gestational age (weeks)	136.2±18.5	P < 0.001	0.60±0.1	P < 0.001
Maternal pre-pregnancy weight (kg)	4.8±1.5	P = 0.001	0.007±0.008	P = 0.39
Maternal net pregnancy weight gain (kg)	7.8±3.6	P = 0.03	0.002±0.02	P = 0.92
Gender of the newborn[a]	-77.5±49.5	P = 0.12	-0.68±0.28	P = 0.02
Parity[b]	41.4±49.8	P = 0.41	0.29±0.29	P = 0.31
Ethnicity[c]	-57.8±53.0	P = 0.28	0.22±0.30	P = 0.46
ETS in home[d]	-67.6±51.4	P = 0.19	-0.52±0.30	P = 0.08
Season1[e]	-120.0±70.4	P = 0.09	-0.30±0.40	P = 0.46
Season2[f]	-102.1±70.9	P = 0.15	-0.67±0.41	P = 0.10
Season3[g]	-185.4±73.6	P = 0.01	-0.63±0.42	P = 0.14
Delivery by cesarean section[h]	NA		NA	

[a] 0 = male; 1 = female; [b]0 = nulliparous; 1 = at least one prior live birth ; 0 = Dominican; 1 = African American; [d]0 = no; 1 = yes
[e]0 = summer; 1 = winter; [f] = summer; 1 = spring; [g]0 = summer; 1 = fall; [h]0=no, 1 = yes. NA = not applicable.

Change in birth weight and birth length for each log unit increase in chlorpyrifos levels in umbilical cord plasma (n=287)

	B (95% CI)	P-value
Birth weight (grams)	-42.6 (-81.1, -3.8)	p=0.03
Birth length (cm)	-0.24 (-0.47, -0.01)	p=0.04

By multiple linear regression. Independent variable: (ln)pesticide 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

Whyatt et al., EHP, 2004

Differences in birth weight (grams) and birth length (cm) by cord plasma chlorpyrifos exposure groups (n=287)

	B±SE	P value
I. Birth weight		
Group 1 versus group 2	39.2 (-107.3 – 185.7)	P = 0.60
Group 1 versus group 3	-50.9 (-188.2 – 86.3)	P = 0.47
Group 1 versus group 4	-150.1 (-287.7 – -12.5)	P = 0.03
I. Birth length		
Group 1 versus group 2	0.17 (-0.70 – 1.0)	P = 0.71
Group 1 versus group 3	-0.21 (-1.0 – 0.61)	P = 0.61
Group 1 versus group 4	-0.75 (–1.6 –0.06)	P = 0.07

Newborns were categorized into 4 groups: group 1= infants with chlorpyrifos levels< LOD; group 2= infants with the lowest 3rd of levels > LOD; group 3=infants in the middle 3rd of levels > LOD; group 4=infants with the highest 3rd levels > LOD. Dummy variables were used in the regression analyses to compare birth outcomes among newborns in exposure group 1 to birth outcomes among newborns in exposure groups 2, 3 and 4, controlling for the same potential confounders.

Change in birth weight and length for each log unit increase in chlorpyrifos levels in umbilical cord plasma among infant born before and after 1/1/01

	B (95% CI)	P-value
1. Birth weight (grams)		
Before 1/1/01 (n=222)	-67.3 (-116.6, -17.8)	p=0.008
After 1/1/01 (n=65)	30.7 (-108.6, 169.90	p=0.66

Before 1/1/01, birth weight averaged 211grams less among infants with the highest (group 4) exposures compared to those without detectable levels (group1). Only 1 infant fell into group 4 after 1/1/01.

2. Birth length (cm)		
Born before 1/1/01 (n=219)	-0.43 (-0.73, -0.14)	p=0.004
Born after 1/1/01 (n=63)	0.07 (-0.65, 0.79)	p=0.85

By multiple linear regression. Independent variable: (ln)pesticide 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.

Whyatt et al., EHP, 2004; Whyatt et al., Tox Appl Pharm, 2005

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Updated analyses (Unpublished; Prepared for EPA)

Change in birth weight for each log unit increase in chlorpyrifos levels in umbilical cord plasma among infants born before and after 1/1/01

	B (95% CI)	P-value
1. Total cohort (n=426)	-12.8 (-44.2, 18.6)	p=0.43
2. Before ban (n=233)	-71.4 (-121.1, -21.8)	p=0.005
3. After ban (n=193)	32.7 (-59.3, 124.7)	p=0.48

By multiple linear regression. Independent variable: (ln)pesticide 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

Updated analyses (Unpublished; prepared for EPA)

Among infants born before the ban, birth weight among those with the highest chlorpyrifos exposures (group 4) averaged 192.2 (95% CI -358.0, -26.4) grams less than those with exposures < LOD (group 1, p=0.02).

After the ban, only one infant fell into this highest exposure group.

Updated Analyses (Unpublished; Prepared for EPA)

Concern over imputation of cord chlorpyrifos levels from maternal blood levels

Change in birth weight for each log unit increase in chlorpyrifos levels in umbilical cord plasma only among infants born before residential ban (n=211)

B (95% CI)	P-value
-64.5 (-115.7, -13.2)	p=0.01

By multiple linear regression. Independent variable: (ln)pesticide 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

Assessing additional potential confounders

Unpublished; Prepared for EPA

Change in birth weight (grams) for each log unit increase in chlorpyrifos levels in umbilical cord plasma among infants born before residential ban (basic regression model *controlling for additional measures of SES*)

	B (95% CI)	P-value
Model 1: Marital status (n=231)[1]	-73.8 (-124.0, -23.6)	p=0.004
Model 2: Education (n=226)[2]	-70.7 (-122.4, -19.0)	p=0.008
Model 3: Income (n=222)[3]	-68.7 (120.3, -17.2)	p=0.009

[1] Never married versus ever married
[2] Less than high school versus high school or greater
[3] Annual household income less than $10,000 versus greater than $10.000

Basic model: Independent variable: (ln)chlorpyrifos 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

Assessing additional potential confounders

Unpublished; Prepared for EPA

Change in birth weight (grams) for each log unit increase in chlorpyrifos levels in umbilical cord plasma among infants born before residential ban (basic regression model *controlling for housing disrepair*, N=233)

	B (95% CI)	P-value
Model 1: No versus one or more	-70.0 (-119.7, -20.3)	p=0.006
Model 2: Number of disrepairs[1]	-71.5 (-121.3, -21.7)	p=0.005

[1] On a scale of 0 – 5 indices of housing disrepair are: holes in ceiling or walls, peeling paint, leaking pipes, water damage, or mold

Basic model: Independent variable: (ln)chlorpyrifos 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

Assessing additional potential confounders

Unpublished; Prepared for EPA

Change in birth weight (grams) for each log unit increase in chlorpyrifos levels in umbilical cord plasma among infants born before residential ban (basic regression model *controlling for measures of material hardship or maternal satisfaction)*

	B (95% CI)	P-value
Model 1: Lacked basic necessities[1]	-67.5 (-118.5, -16.6)	p=0.01
Model 2: Satisfied (yes vs no)[2]	-78.1 (-128.3, -27.8)	p=0.002

[1] Lacked shelter, food, clothing, heat, and/or medicine during pregnancy (n=227)
[2] With overall living conditions (n=231)

Basic model: Independent variable: (ln)chlorpyrifos 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

Assessing additional potential confounders

Unpublished; Prepared for EPA

Change in birth weight (grams) for each log unit increase in chlorpyrifos levels in umbilical cord plasma among infants born before residential ban (basic regression model *controlling for prenatal alcohol consumption*, N=224)

	B (95% CI)	P-value
Model 1: No vs yes	-78.3 (-128.7, -27.9)	p=0.002
Model 2: No, some, frequent[1]	-77.7 (-128.2, -27.2)	p=0.003

[1] Dummy variables: no versus some (< 1/day in any trimester); no vs frequent (≥ 1/day in any trimester).

Basic model: Independent variable: (ln)chlorpyrifos 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

Assessing additional potential confounders

Unpublished; Prepared for EPA

Change in birth weight (grams) for each log unit increase in chlorpyrifos levels in umbilical cord plasma among infants born before residential ban (basic regression model *controlling for prenatal PAH and lead*)

	B (95% CI)	P-value
Model 1: PAH (n=222)[1]	-68.7 (-120.6, -16.7)	p=0.01
Model 2: Cord lead (n=156)[2]	-82.0 (-140.9, -23.1)	p=0.007

[1] Sum of 8 PAHs measured in maternal 48 hours personal air samples during the 3rd trimester of pregnancy.
[2]Cord lead all unclotted.

Basic model: Independent variable: (ln)chlorpyrifos 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