

# ENVIRONMENTAL EXPOSURES AND NEURODEVELOPMENT

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Joseph Tart/EHP



NIH...Turning Discovery Into Health

# Today's Webinar:

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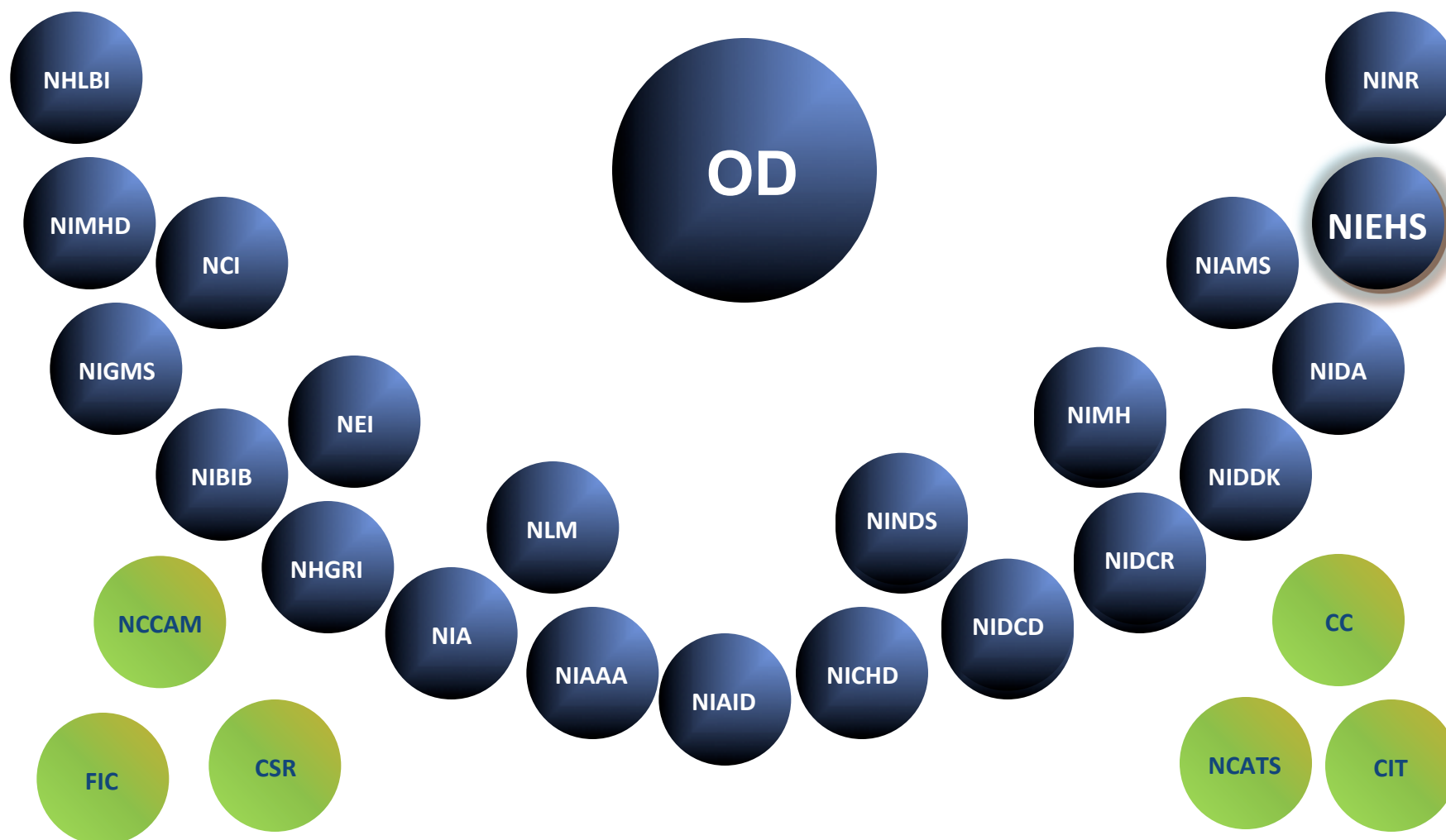
- NIEHS overview
- Shared features of central language/auditory processing disorders and other complex disorders
- What is the “environment”?
- Early development as a sensitive window
- Key studies and recent findings
- Summary

## NIEHS-

- Charged with understanding how the environment influences the development and progression of human diseases.
- Based in Research Triangle Park, North Carolina.
- Division of Extramural Research and Training funds over 500 grants.



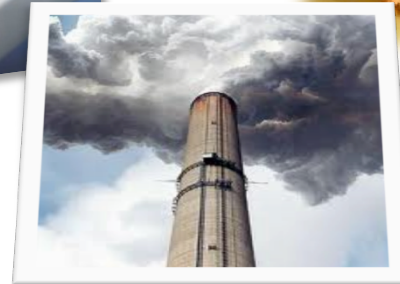
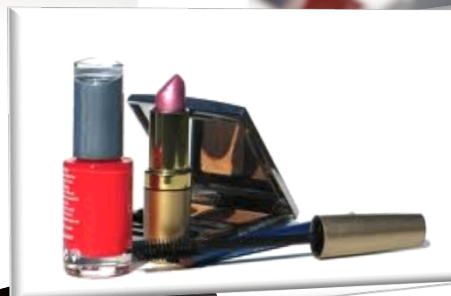
## 27 Institutes and Centers in NIH



# Assumptions

- Central Language/Auditory Processing Disorders share many features of other complex disorders
  - Wide differences in expression (e.g., mild to severe)
  - Frequent co-occurrence with other conditions
  - Difficulties in diagnosis
  - No reliable biomarker
  - Multiple causes likely
    - Some degree of heritability, with complex genetics
    - Gene environment interaction is likely
- Lessons learned in identifying causes of other complex developmental disorders can inform understanding of central auditory processing disorders

## What Do We Mean By “Environment”



# Complexities of Exposure

**Targets: Biological Pathways**

**Where: Lungs, Brain, Skin, GI, other organs**

**When: Fetal, Child, Adolescent, Young Adult, Adult, Older-adults, Elderly**

**Contact: Internal and External**

**Classes: Physical, Chemical, Biological, Psycho-social**

**Places: Home, School, Work, Neighborhood, Community, City, State, Region**

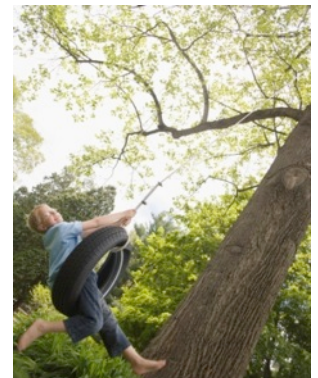
**Sources: Air, Water, Soil, Food, Consumer Products, Drugs**

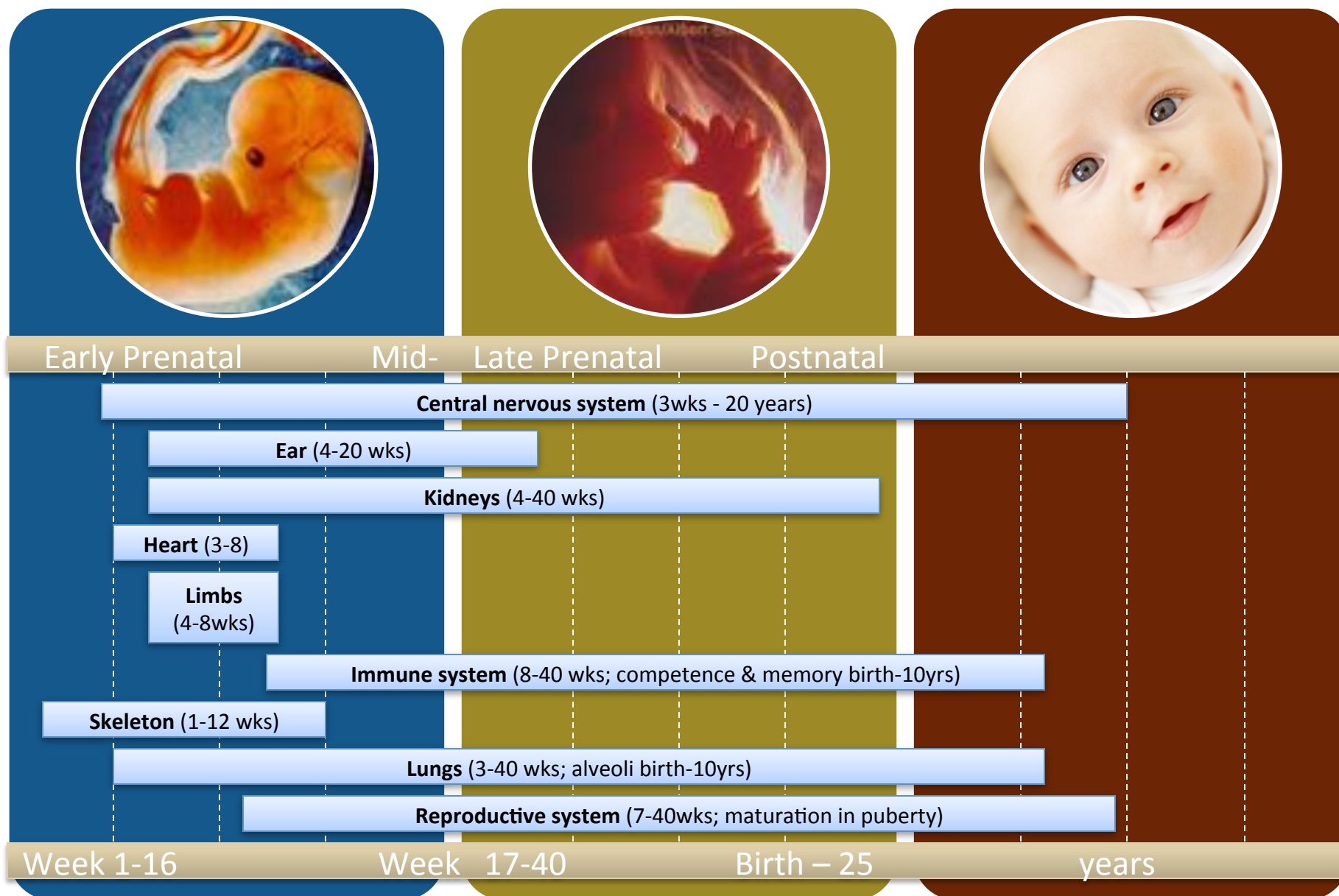


**Health / Disease**

# Child/infant/fetus as a susceptible population

- Greater/different exposures than adults
  - Unique behaviors, environments
    - Hand to mouth behavior
    - Increased or decreased time outdoors or at home
    - Proximity to soil, carpet, floors
  - Distinct physiology
    - Transplacental transport
    - Differences in metabolizing enzymes, rate of excretion, binding to target proteins
    - Greater eating, drinking, breathing per unit body weight
    - Blood brain barrier absence/immaturity

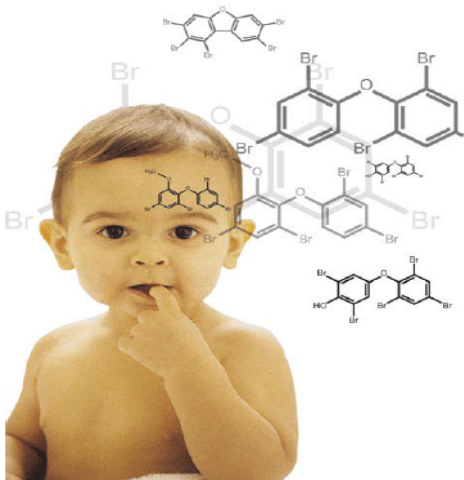




Source: Altshuler, K; Berg, M et al. *Critical Periods in Development*, OCHP Paper Series on Children's Health and the Environment, February 2003.

# Overt Effects vs. Functional Changes

- High doses
- Spontaneous abortion
- Stillbirth
- Birth Defects



- Low doses can cause functional changes
- Effects are at a cellular or molecular level
- Increased susceptibility for disease in later life after additional exposures or aging

# Neurodevelopment Investment Principles

- Research on neurodevelopment research is part of a larger NIEHS program that supports **children's environmental health** research
- A **mix of research approaches** are supported—from population-based studies to laboratory investigations of relevant cellular and molecular mechanisms
- Strong **partnerships**, with other federal entities and public stakeholders, are essential to speed discovery and ensure rapid translation to public health

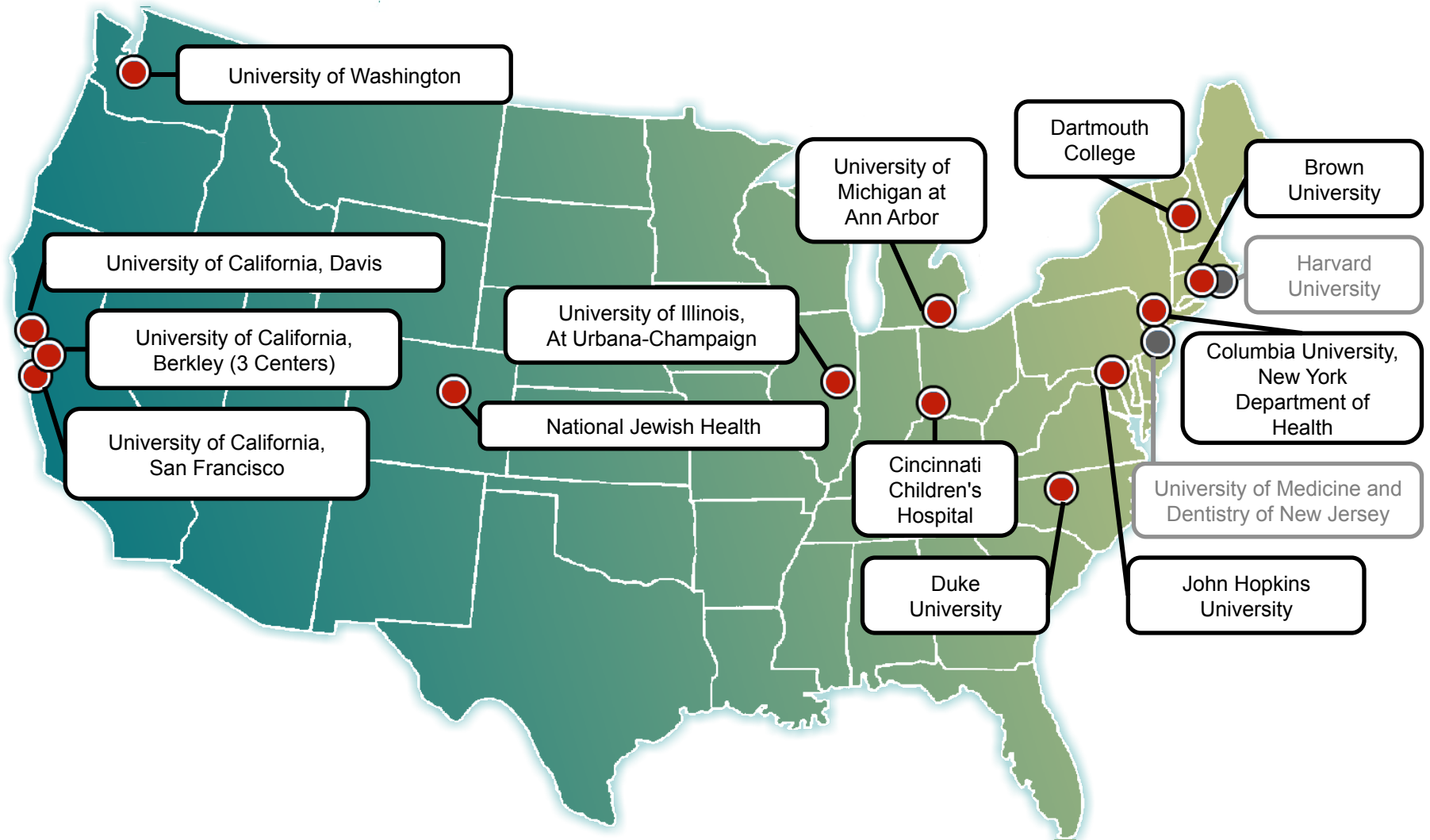
# Children's Environmental Health and Disease Prevention Centers (NIEHS/EPA Partnership)

## Program Description:

- Enhance communication, innovation and research excellence in Children's Environmental Health
- Promote multidisciplinary interactions among basic scientists, clinicians, behavioral & social scientists
- Accelerate translation of basic research findings into clinical or intervention strategies
- Provide community outreach



# NIEHS and EPA Children's Centers



## Children's Environmental Health Research: Birth Cohort Example

- Large (>700 mother/child pairs) birth cohort from NYC minority communities, N. Manhattan and S. Bronx
- Initiated in late 1990's, ongoing follow up
- Measured a variety of exposures (e.g., chlorpyrifos, PAH, phthalates, BPA)

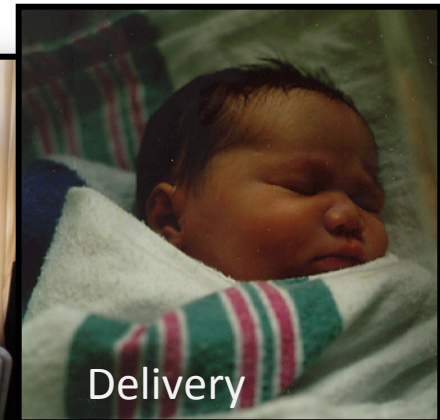
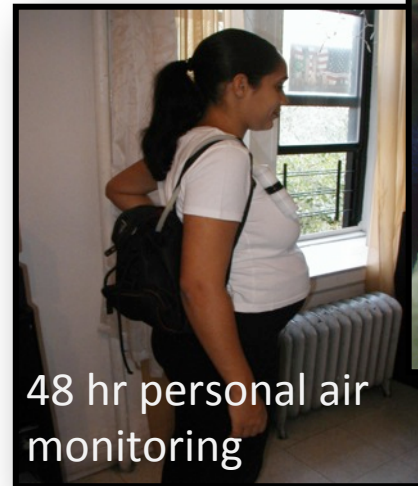


COLUMBIA CENTER FOR CHILDREN'S ENVIRONMENTAL HEALTH  
MAILMAN SCHOOL OF PUBLIC HEALTH  
Columbia University

# Columbia University Birth Cohort Study (Perera)

**Many exposures of interest,  
including:**

- Organophosphate pesticides
- Polyaromatic hydrocarbons (PAHs)
- Endocrine disruptors (bisphenol A & phthalates)



# Research Highlight

## Pesticides

# Organophosphate Pesticides (OP) and How They Affect Children

## Exposure settings and mechanisms

- Widely used in agricultural settings
- Historical use in residential settings (e.g., chlorpyrifos)
- Exposure by inhalation, ingestion, and skin penetration
- Common mechanism of cholinesterase inhibition at nerve endings
- Multiple routes and exposures can lead to additive toxicity

## Increased prenatal OP exposure leads to:

- Smaller head size, birth weight
- Altered neonatal reflexes
- Attention problems, symptoms of pervasive developmental disorder
- Reduced IQ
- Some evidence of gene environment interaction
- Structural changes in brain

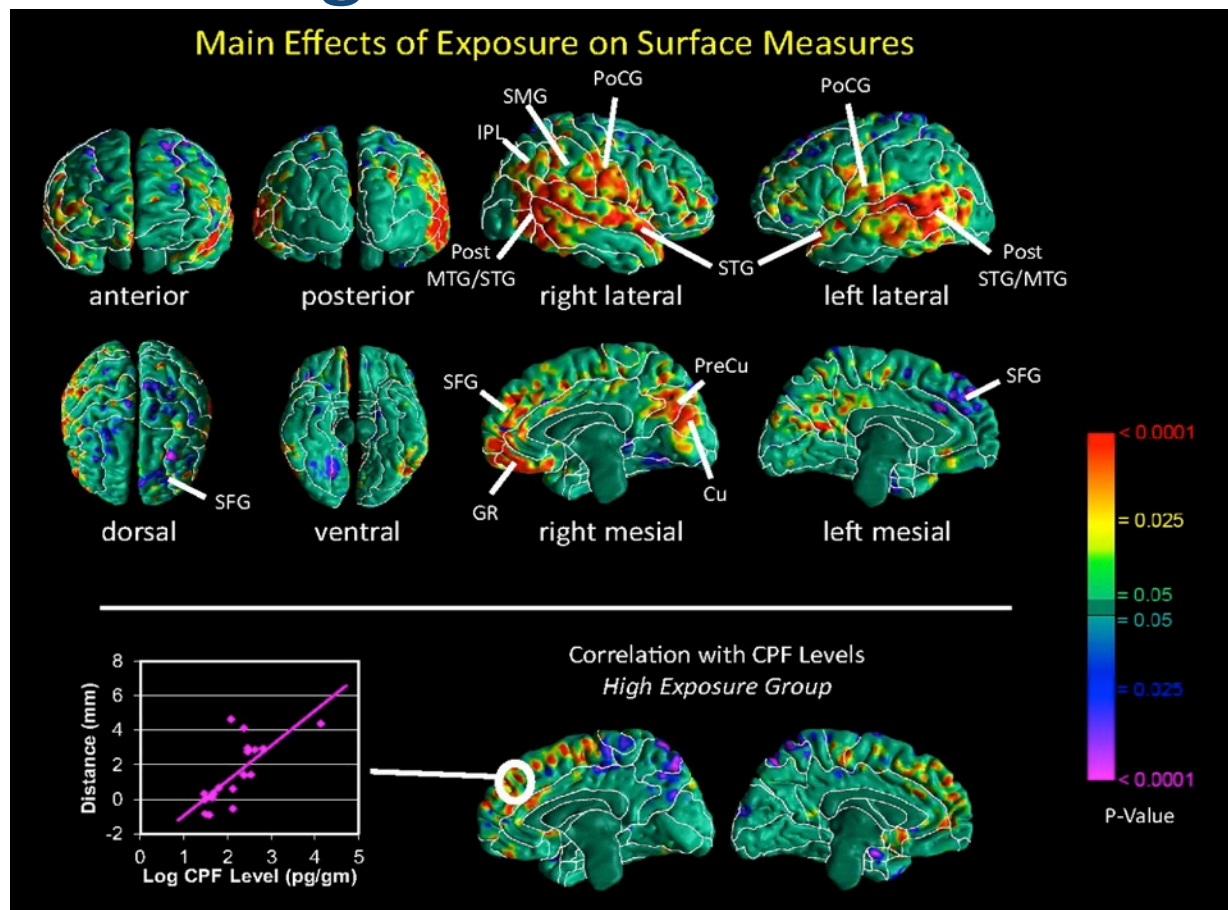
# Modest Prenatal Insecticide Exposure Has Effects on Brain Structure



- 40 children exposed prenatally to standard levels of chlorpyrifos before residential ban
- 20 children in high-exposure group, 20 in low-exposure group
- High-exposure group showed structural changes in the brain at 6-11 years old

(Rauh et al., PNAS, 2012)

# OP pesticide exposure associated with structural changes in brain



(Rauh et al., PNAS, 2012)

# Translation of OP research findings to public health

**1999:** Animal studies link OP exposure to neurodevelopmental effects

**2001:** U.S. EPA bans indoor residential use of chlorpyrifos

**2004:** CCEH researchers show decreases in children's blood levels



# Translation of OP Research Findings to Public Health

**2004:** Prenatal organophosphate exposure reduces birth weight (Whyatt, 2004)

**2005:** CCEH investigators' testimony helps pass landmark NYC laws

**2011:** Human prenatal exposure linked to cognitive deficits (Bouchard, Engel, Rauh, 2011)

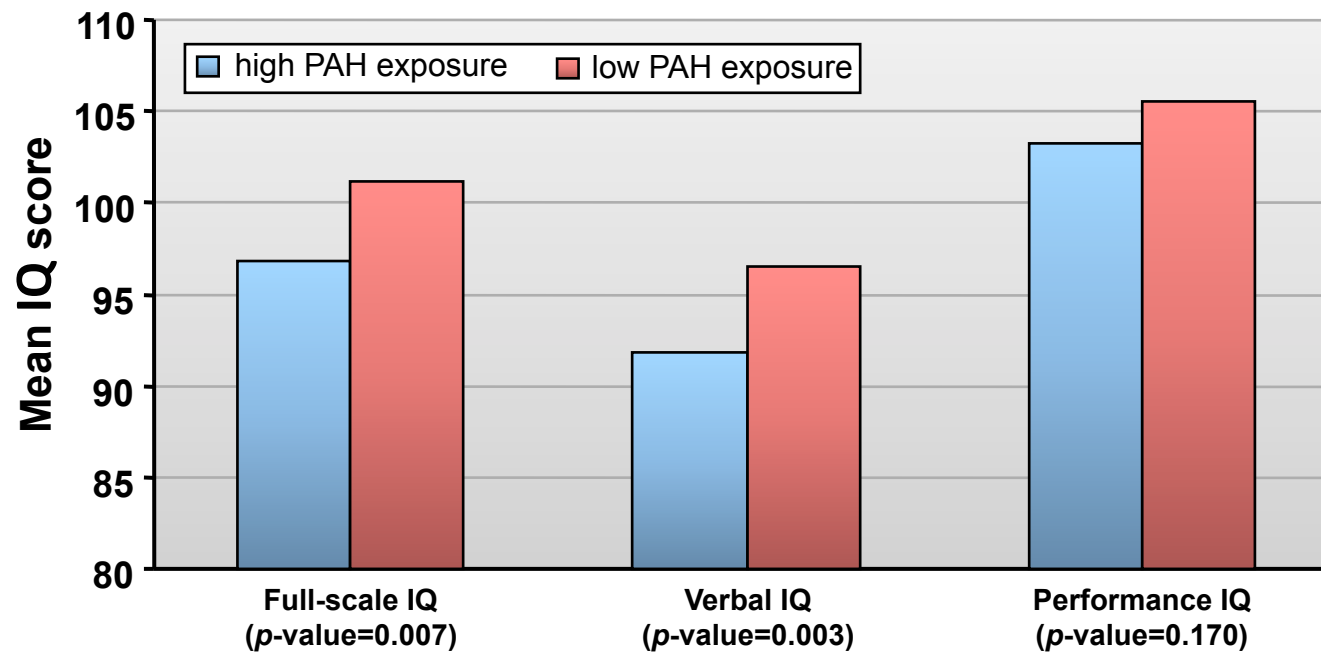


# Research Highlight

## Polyaromatic Hydrocarbons (PAHs)

# Adverse Effects of Prenatal PAHs on Children's IQ

Differences in Full-Scale, Verbal IQ and Performance IQ  
associated with high prenatal PAH exposure



(high  $n=140$ , low  $n=109$ ). Mean IQ levels are adjusted for ETS exposure during pregnancy, gender of child, ethnicity, mother's intelligence (TONI), mother's education, and the quality of the home caretaking environment (HOME).

Source: Perera FP, Rauh V. et al, 2009



# Research Highlight

## Endocrine Disrupting Chemicals (Bisphenol A)

# Prenatal Bisphenol A (BPA) Exposure and Child Behavior in an Inner City Cohort (Perera, 2012)

## **BOYS** (n=87)

- significantly higher Childhood Behavior Checklist scores (more problems):
- ↑ Emotionally Reactive (1.62 times greater)
- ↑ Aggressive Behavior syndromes (1.29 times greater)

## **GIRLS** (n=111)

- lower scores on all syndromes, statistical significance:
- ↓ Anxious/Depressed (0.75 times as high, 95% CI 0.57, 0.99) and
- ↓ Aggressive Behavior (0.82 times as high)

# Research Highlight

## Heavy Metals

### (Cadmium)

# Learning Disabilities and Cadmium Exposure

- Urinary cadmium concentration measures from NHANES data
- Neurodevelopmental outcome assessment questionnaire
- ↑ risk of LD and special education placement for children and teens with higher cadmium levels



# Research Highlight

## Autism and Nutrition

# Prenatal Vitamins, One-carbon Metabolism Gene Variants, and Risk for Autism

(Schmidt, 2011)

- Periconceptional use of prenatal vitamins may reduce the risk of having children with autism, especially for genetically susceptible mothers and children.
- Greater risk for autism was observed for children whose mothers had other one-carbon metabolism pathway gene variants and reported no prenatal vitamin intake.



# Folic Acid Intake Associated with Reduced Risk of Autism in Children (Schmidt, 2012)



Consuming the recommended amount of folic acid (600 µg) during the **first month of pregnancy** may reduce the risk of having a child with ASD, specifically when the mother and/or her child have a **specific genetic variant** (MTHFR 677 C>T) associated with less efficient folate metabolism

# Research Highlight

## Autism and Air Pollution

# Air Pollution and Autism: Increased Risk from Living Close to a Freeway (Volk, 2011)

- Traffic-related air pollution contains substances found to have adverse prenatal effects.
- Living near a freeway was associated with autism.
- Living near other major roads at birth was not associated with autism.



## In Summary

- NIEHS has a sustained and robust commitment to children's environmental health through a variety of research, training, educational and outreach translation programs.
- Exposures very early in life can have long lasting effects on development and cognition.
- NIEHS is committed to supporting new research, partnerships and tools to advance the field.
- NIEHS primary goal to protect children from environmental hazards and community engagement is essential.



# Thank you!

