Pediatric Environmental Health: Why should we care?

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Disclosures

• I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this presentation.

• I receive funding from Meridian Biosciences for a clinical trial unrelated to today’s presentation.

• I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Learning Objectives

• Introduce concepts of Pediatric Environmental Health
• Explore research regarding two neurodevelopmental toxicants
  – Lead
  – Traffic-Related Air Pollution
• Discuss Pediatric Environmental Health Specialty Units
Francisco Goya
Saturn devouring his son, 1819-1923
Concepts
Environmental burden of disease globally

Environmental burden of disease as % of total disease burden

- 10 - 12.5 %
- 12.5 - 15 %
- 15 - 20 %
- 20 - 25 %
- 25 - 30 %
- 30 - 35 %
- No data

Based upon data in Smith, KR, Corvalan, C, Kjellstrom, T (Epidemiology, 1999)
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What is Pediatric Environmental Health (PEH)?

- Pediatric environmental health focuses on the prevention and control of environmental exposures and associated adverse health effects on infants, children, adolescents, and young adults.
- Recognized by American Academy of Pediatrics in 1950’s (radioactive fallout)

http://www.aap.org/healthtopics/environmentalhealth.cfm (Accessed 07/07/09)
What is Pediatric Environmental Health?
Understanding the interaction between:

- Biological
- Physical
- Context

Akin to Occupational Health in adults
Traditional Epidemiological Triad

- Host
- Vector
- Agent
- Environment
A child’s occupation?

• Grow
• Develop
• Explore
• Problem solve
• Learn new things
• Become an adult
  – Happy
  – Healthy
Children are Different

- Windows of vulnerability
- Breathing zones
- Oxygen, Food & Water consumption
- Hand-Mouth behaviors
- Time
Windows of Vulnerability

- Children naturally grow and develop
- Effect of exposure based on stage of development
- Multiple exposures at once
- Genetic predisposition to adverse effects
Brain Development

<table>
<thead>
<tr>
<th>Prenatal Period (Months)</th>
<th>Postnatal Period (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9</td>
<td>Birth 1 2 3 4 5 6 7 8</td>
</tr>
</tbody>
</table>

- **Cell Proliferation**
  - radial glia, neurons
  - glia

- **Migration of Neurons**
  - brain, spinal cord
  - ext. granular layer cerebellum

- **Subplate Neurons**

- **Synapse Formation**
  - mz  sp  hp  rf  visual cortex  association  cortex

- **Myelination**

Key: mz – marginal zone; sp – subplate; hp – hippocampus; rf – reticular formation

Source: GBPSR
Lung Development

- Pseudoglandular period (5-17 weeks)
- Canalicular period (16-25 weeks)
- Terminal sac period (24 weeks to birth)
- Alveolar period (late fetal to age 8 years)

http://www.cincinnatichildrens.org/research/div/pulmonChildren/morphogenesis.html
Lung Function

Minute ventilation = respiratory rate X tidal volume

Adapted from Snodgrass in Guzelin, Henry Olin, eds, 1992
Breathing zones

• Closer to the ground
  – Closer to dust
  – Heavy than air chemicals accumulate
• Infants tend to be indoors
  – Bedrooms
  – Automobiles
• School-aged children
  – School buses
Food and Water

Grams of Food or Water per kg Body Weight per Day

- Infant
- Child 1-6
- Adult

Adapted from Plunkett in Guzelin, Henry Olin, eds, 1992
Differences in diet

• **Infants**
  – Limited diet: Breast milk or formula
  – Complementary foods

• **Toddlers**
  – Limited diet
  – Tend to eat off of the floor
  – Non-food items

• **Older Children & Adults**
  – Varied diet
Hand to mouth behaviors

- Young children: stage of oral exploration
  - Lead dust
  - Arsenic on play equipment
  - Pesticides
- Older children: independent
- Adolescence
  - More independent
  - Lack of abstract reasoning
Differences in GI absorption

- Gastrointestinal absorption of lead decreases with age
- Diet plays a part in changes in absorption
- Higher Pb absorption in Fe-deficient state
- Higher Pb absorption between meals

Adapted from Plunkett in Guzelin, Henry Olin, eds, 1992 White, et al., Env Health Perspectives, 106:6, 1998
Time

• Latency time
  – Time between exposure and development of disease
  – Decades may pass between radiation exposure and development of cancer

• Females in Hiroshima/Nagasaki Cohort
  – Increased breast cancer
  – Based on exposure at younger age

Two important toxicants

- Widespread
- Negative impact on children’s health
- Lead
- Traffic-related air pollution
Lead - Review

- Malleable, corrosion-resistant metal
- Used by humans since 6500 BCE (Turkey)
- Toxicity described by Greek Physician Nicander in 2nd Century BCE
- “The first pollutant”

NIOSH/CDC, 2019
Historical Perspective on Lead Exposure

**FIGURE 1-1** Body burdens of lead in ancient people uncontaminated by industrial lead (left); typical Americans (middle); people with overt clinical lead poisoning (right). Each dot represents 40µg of lead. Source: Patterson et al., 1991; adapted from NRC, 1980.
# Modern History of Lead Paint

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1887</td>
<td>U.S. medical authorities diagnose childhood lead poisoning</td>
</tr>
<tr>
<td>1904</td>
<td>Dr. John Lockhart Gibson describes childhood lead poisoning from paint</td>
</tr>
<tr>
<td>1909</td>
<td>France, Belgium, and Austria ban white-lead interior paint</td>
</tr>
<tr>
<td>1914</td>
<td>Pediatric lead-paint poisoning death from eating crib paint described</td>
</tr>
<tr>
<td>1921</td>
<td>National Lead Company admits lead is a poison</td>
</tr>
<tr>
<td>1922</td>
<td>League of Nations bans white-lead interior paint; U.S. declines to adopt</td>
</tr>
<tr>
<td>1943</td>
<td>Report concludes eating lead paint chips causes physical and neurological disorders, behavior, learning and intelligence problems in children</td>
</tr>
<tr>
<td>1971</td>
<td>Lead-Based Paint Poisoning Prevention Act passed</td>
</tr>
<tr>
<td>1978</td>
<td>Lead-based house paint banned in U.S.</td>
</tr>
</tbody>
</table>

Adapted from Gilbert & Weiss, Neurotoxicology, 2006
THE DUTCH BOY'S LEAD PARTY

A Paint Book for Girls and Boys

With which is bound
COLOR HARMONY IN THE HOME
A Booklet for the Grown-ups
Electric light bulbs, cut glass, the lenses of cameras, telescopes, microscopes and eyeglasses—in fact all fine glass is made by fusing sand and red-lead together. Red-lead is a fine, orange-red powder. It is a lead oxide, that is, a chemical compound of lead and oxygen. Lead in glass gives brightness and greater power.

The first one at the party
Was gay Electric Light.
He said, “I’m very brilliant,
I always shine at night!”

“No little of my brilliance
Is due to my glass head,
Which gives a light much brighter
Because it’s made with lead.”
Implications of lead exposure in children
Blood Lead Level and IQ

Log-linear model (95% CIs shaded) for concurrent blood lead concentration, adjusted for HOME score, maternal education, maternal IQ, and birth weight. The mean IQ (95% CI) for the intervals < 5 μg/dL, 5–10 μg/dL, 10–15 μg/dL, 15–20 μg/dL, and > 20 μg/dL are shown.

Greatest apparent decrease at lowest lead levels

Log-linear model (95% CIs shaded) for concurrent blood lead concentration, adjusted for HOME score, maternal education, maternal IQ, and birth weight. The mean IQ (95% CI) for the intervals < 5 μg/dL, 5–10 μg/dL, 10–15 μg/dL, 15–20 μg/dL, and > 20 μg/dL are shown.

Predicted probabilities of scoring “less than proficient” on 3 tests of the Michigan Educational Assessment Program as a function of blood lead level:
Detroit Public Schools, MI, 2008–2010

Zhang, AJPH, 2013
Behavioral Problems

• Attention Deficit-Hyperactivity Disorder
  – Estimated 25% of ADHD may be attributable to lead exposure (BLL >1.3 mcg/dL)

• Antisocial behavior

• Increased adult criminal behavior & incarceration

Economics of Lead exposure

- $50.9 Billion/year
  - Medical costs
  - Special education
  - Incarceration
  - Lost IQ/productivity
- Cost to Mahoning County, OH $500K
- ROI for lead poisoning prevention
  - $1 → $17-$221
  - Vaccines $1 → $5.30 (direct) $16.50 (indirect)

Risk factors for incarceration

Relative contribution of nonbiological risk factors

Farrington, JAMA Pediatrics, 2018
Numerous uses for lead

- Storage Batteries
- Metallurgy
- Electronics
- Cosmetics
- Home remedies
- Pottery glaze
- Gasoline additive
- Plumbing
- Paint
- Rubber Materials
- Electrical solder
- Munitions
- Art Supplies
- Crayons
- Stabilizer for plastics
Cortical Gray Matter Loss in Relationship to Postnatal Lead Exposure to Six Years

Map of strength of association between blood lead concentration and population-wide loss of gray matter volume. Single-voxel minimum significance threshold is $p < 0.001$ (uncorrected), found within a cluster of at least 700 voxels (Cecil, et al)

Composite rendering

More significant

Less significant
Clinical Vignette
Two children with elevated blood lead levels

• Dad worked at e-waste recycler
  – Operated CRT grinder
  – “I throw the CRTs and all this dust comes out”
  – Wears clothes home from work
• “He comes home covered with dust”
  – Children would run to meet him at the door
  – Played with children at the door
• Average 25” TV tube has 1-2kg of lead
Course of Events

Clinical Evaluation

Cincinnati Health Dept

NIOSH/OSHA
Angel-Devil Machine
Work site investigation

- Dust wipe samples from cathode ray tube area showed high levels of lead
- CRTs are made from leaded glass
- Some employees continued to have detectable lead on their hands despite hand washing
- 12/13 uniforms tested positive for lead
Investigation of Childhood Lead Poisoning from Parental Take-Home Exposure from an Electronic Scrap Recycling Facility — Ohio, 2012

Nick Newman, DO1; Camille Jones, MD2; Elena Page, MD3; Diana Ceballos, PhD3; Aalok Oza, MS3 (Author affiliations at end of text)

Lead affects the developing nervous system of children, and no safe blood lead level (BLL) in children has been identified (1). Elevated BLLs in childhood are associated with hyperactivity, attention problems, conduct problems, and impairment in cognition (2). Young children are at higher risk. The child's BLL was confirmed at 19.3 μg/dL, and the father was advised to notify the Occupational Safety and Health Administration of his BLL; it is not known if he did. The father left his job soon after the elevated BLLs were recognized, and the children's BLLs decreased to 8.7 μg/dL and 7.9 μg/dL, respectively, over the next 3 months.
Using data to target outreach

Percentage of Children with BLL =>5 by Zip Code

Hamilton County Zip Codes

Percentage of Children with BLL =>5 ug/dL
Title: The Midnight Mass
Artist: Edward Timothy Hurley (American, b.1869, d.1950), painter
Date: 1911
Place: Cincinnati/Ohio/United States
Courtesy: Cincinnati Art Museum
Traffic Related Air Pollution

• Complex mixture
  – Particulate matter (PM2.5, PM10, Ultrafines)
  – Vapors (PAH, VOC)
  – Gases (NOx, CO, CO\textsubscript{2}, SOx)

• Dynamic chemistry
  – Sunlight
  – Heat
  – Humidity
Ultrafine particles: diesel exhaust particles

- Traffic-Related Air Pollution (TRAP)
  - “Elemental Carbon Attributed to Traffic”
  - Ultrafine particles <100nm diam
  - Translocate to brain, liver, spleen, and kidneys

- Pathophysiology
  - Oxidative stress at cellular level

Clean Air Task Force, 2005
Oberdorster, Nanotox 2007; Unfried Nanotox2007
Traffic-Related Air Pollution Exposure in the First Year of Life and Behavioral Scores at 7 Years of Age

Nicholas C. Newman,1 Patrick Ryan,2,3 Grace LeMasters,3 Linda Levin,3 David Bernstein,4 Gurjit K. Khurana Hershey,5 James E. Lockey,3 Manuel Villareal,4 Tiina Reponen,3 Sergey Grinshpun,3 Heidi Sucharew,2 and Kim N. Dietrich3

1Division of General and Community Pediatrics, and 2Division of Biostatistics and Epidemiology, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, USA; 3Department of Environmental Health, and 4Department of Medicine, Division of Immunology, Allergy and Rheumatology, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA; 5Division of Asthma Research, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, USA
Why ADHD?

• Common illness, expected to be found in our population
• Symptoms related to “dysfunction” in prefrontal/frontal cortex
• Ultrafine particles have been found in prefrontal cortex in human cadaver studies

Calderón-Garcidueñas, et al., 2008; Biederman & Faraone, 2005
Cincinnati Childhood Allergy and Air Pollution Study

- Prospective birth cohort identified 2001-2003
- Geocoded birth addresses, those <400m or >1500m from major highway were eligible
- All children had parent with positive SPT
- 762 children at enrollment
- 597 at age 7 years with BASC-2
Behavioral Measurement

• Behavioral Assessment System for Children-Parent Rating Scale, 2nd Edition (BASC-2)
• Validated measure used in clinical psychology
• T score calculated for composites & subscales
  – Mean 50, Standard Deviation 10
  – 60+ at risk
• Internal validity measures removed questionable data (n=21)

Reynolds & Kamphaus, 2004
## Descriptive Statistics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>%</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Mother’s education (HS/GED or less)</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Family income &lt;$30k/year</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>TRAP (ECAT) Exposure, Year 1</td>
<td></td>
<td>0.4 (0.1) μg/m³</td>
</tr>
<tr>
<td>Cigarette Exposure, Year 1</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Home built prior to 1950</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>BASC-2 Hyperactivity Score &gt;59 (at risk range)</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

n=576
Hyperactivity adjusted odds ratios

Logistic Regression

TRAP dichotomized at highest tertile 0.4μg/m³

Unadjusted

Adjusted for gender, year 1 cigarette exposure, maternal education

0.10 1.00 10.00

1.04 1.69 2.73

1.22 1.87 2.88

1.04 1.69 2.73

0.10 1.00 10.00
Stratified Model: Hyperactivity, adjusted odds ratios

Maternal education greater than high school
- 1.31
- 2.31
- 4.06

Maternal education high school or less
- 0.36
- 0.90
- 2.24

Non-stratified
- 1.04
- 1.69
- 2.73
Maternal Education

• Why does maternal education matter?
  – Is this a surrogate marker of maternal ADHD?
    • Lower educated mothers more likely to have ADHD?
  – Are more highly educated parents more likely to report symptoms in their children?

• Maternal education strongly correlated with income, breast feeding duration
Discussion: Biological Plausibility

- TRAP exposure associated with:
  - Neuroinflammation
  - Mucososal inflammation of respiratory tract
- Neurological and immunological systems immature during first year and may be particularly vulnerable to TRAP exposure
- Dopaminergic pathways may be more sensitive to oxidative stress of TRAP exposure

Block, 2004; Ryan, 2007; Sunyer 2010; Calderon-Garciduenas, 2008
Future directions

• CCAAPS Brain – ongoing
  – Neuroimaging
  – Extensive neurobehavioral assessment
  – Additional biomarkers
  – Information regarding parents
• Exposure to TRAP after the first year of life
• Gene x Environment interaction
Fig 1. Statistically significant clusters using threshold free cluster enhancement.

https://doi.org/10.1371/journal.pone.0228092
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0228092
Pediatric Environmental Health Specialty Units (PEHSU)

- April 1997, Executive Order “Protection of Children from Environmental Health Risks and Safety Risks”
- First programs in Boston & Seattle (1999)
- Experts on environmental conditions effecting children
- Funding for the PEHSU program is provided by ATSDR, with support from EPA
Translating into practice

- Environmental health is not part of standard medical school curriculum
- Environmental health is not required as part of pediatric training
- PEHSU Network provides consultation, education and outreach
Cincinnati Children’s Environmental Health & Lead Clinic

- Lead poisoning
  - Outpatient
  - Inpatient
- Other metals
- Mold
- Indoor Air Quality
- Pesticides

Approximately 200 new cases/year overall
Summary

• Lead exposure in childhood is a risk factor for poor adult functioning
• Traffic-related air pollution is becoming recognized as a neurodevelopmental toxicant
• Translating research into action is a slow, painstaking process
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• Camille Jones, MD

• Elena Page, MD
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  – Jeff Burkle
  – Bridget Whitehead
  – Clinical staffs

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  – P30-ES006096
  – R01-ES11170

• CCAAPS families
Post-test quiz

• True or False
  – Childhood lead exposure is a risk factor for adult incarceration
    • True
  – Traffic-related air pollution exposure is a risk factor for childhood behavioral problems
    • True
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