Prevention of Health Effects in Children from Energy-Related Air Pollution

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Columbia Center for Children's Environmental Health
Prevention of Health Effects in Children from Energy-Related Air Pollution

The Columbia Center for Children’s Environmental Health (CCCEH)

Desert Research Institute (DRI)

Shanghai Fudan University School of Public Health

Natural Resources Defense Council, Inc. (NRDC)

ChongQing University of Medical Sciences (CQUUMS)

Tongliang County Hospital, Chinese Medicine Hospital and Maternal Children Hospital

Columbia University’s Center for International Earth Science Information Network (CIESIN)

Chongqing Institute of Environmental Sciences (CQIES)
Introduction

• Air pollution from burning of coal can cause serious illness ranging from respiratory problems to cancer and developmental disorders in children.

• There is evidence that the fetus and young child are inherently more sensitive than adults to the toxic effects of air pollution.

• In addition to the intangible costs of human suffering, air pollution imposes major financial costs on society in terms of health care alone.

• There is an urgent need for prevention.
Columbia Center for Children’s Environmental Health

- Poland
  - Growth & Development
    - Asthma
      - Cohort
  - Cancer Risk
- New York City
  - Growth & Development
    - Asthma
      - Cohorts
  - Cancer Risk
- China
  - Growth & Development
  - Asthma
  - Cancer Risk
  - Serial Birth Cohorts
  - Environmental Intervention
  - Policy
- WTC Cohort
Hypotheses

Prenatal Environmental Exposures Is Associated With Adverse Effects of Child Health

Exposures: Combustion related air pollutants, polycyclic aromatic hydrocarbons (PAHs), particulate matter (PM$_{2.5}$), heavy metals

Biomarkers: PAH-DNA adducts, PAH metabolites, and DNA methylation, heavy metals, gene polymorphisms

Child development, Asthma and Cancer Risk
Study Sites of CCCEH China Projects

- Taiyuan-ChangZhi Children's Cohort
- Linfen Children's Study
- Tongliang Children's Cohorts
- CCCEH Molecular Epidemiology Lab at Shanghai
Taiyuan-Changzhi Children Study

In collaboration with Dr. Niu, School of Public Health, Shanxi Medical University

Taiyuan (太原)  
Changzhi (长治)

200 pairs  
Mother/Newborn

200 pairs  
Mother/Newborn

1. Air monitoring data, questionnaire and GIS/GPS
2. Biomarker data; PAH-DNA adducts, PAH metabolites, and DNA methylation, heavy metals, gene polymorphisms
3. Fetal/Child growth and neurodevelopment (NBNA)
4. PAH neurotoxicity animal studies *
Taiyuan-Changzhi Children Cohorts

- Taiyuan (太原)
- Changzhi (长治)

2009:
- 200 pairs Mother/Newborn

2010:
- 200 pairs Mother/Newborn

2011:
- 200 pairs Mother/Newborn

Follow-up (yr):
- 0
- 1
- 2
- 3
- 4
- 5

Assessments:
- NBNA
- Gesell
- Visc
Study Sites of CCCEH China Projects

- Taiyuan-ChangZhi Children's Cohort
- Linfen Children's Study
- Tongliang Children's Cohorts
- CCCEH Molecular Epidemiology Lab at Shanghai
Linfen (临汾) Children Study

In 1996, Linfen, China was ranked the most polluted city on earth by Blacksmith Institute in New York.
Linfen has shutdown 160 of 196 iron foundries, and 57 of 153 coking plants in 2007.

“Therefore, the improvement in Linfen is remarkable. The changes are being driven by business (nobody wants to invest in such a polluted place), bureaucratic self-interest (local officials find it difficult to be promoted) and shifting political priorities,” The Guardian, UK reports.
Linfen (临汾) Children Study

In collaboration with Dr. Niu, School of Public Health, Shanxi Medical University

Strict Environmental Regulations

Exposure

2004 2005 2006 2007 2008 2009 2010 2011

Cord Blood

Validation

Retrospective exposure estimate

Guthrie Cards

Health Effects
Linfen (临汾) Children Study

1. **LINE-1 and Alu methylation**

2. **Fusion genes**

Mother’s Name | Mother’s Age | Gestational Age | Birth Order | Apgar Score | Genital Abnormalities | Anti-Hyper-thyroidism Medication | Maternal Hyper-thyroidism | Murmur | Antenatal Lacto-mumming

Gender | Birth Weight | Date of Birth | Date of Collection | Address | Test Result | Genital Abnormalities

1. **LINE-1 and Alu methylation**

2. **Fusion genes**

1. **LINE-1 and Alu methylation**

2. **Fusion genes**
Figure 1. Specific Aims

Specific Aims 1 and 2: Biomarkers of Prenatal Exposure

- **Heating Season**
  - Recruit 30 women from prenatal clinic

  - **Personal Air Monitoring:** PAHs

  - **Cord Blood:** PAH-DNA Adducts

  - **Cord Blood:** \( \text{LINE-1 and Alu} \) methylation

  - **NBS (Guthrie cards):** \( \text{LINE-1 and Alu} \) methylation

Specific Aims 3 and 4: Association Between Biomarkers and Birth Outcomes

- **2004**
  - preterm cases
  - birth defect cases
  - controls

- **2005**
  - preterm cases
  - birth defect cases
  - controls

- **2006**
  - preterm cases
  - birth defect cases
  - controls

- **2007**
  - preterm cases
  - birth defect cases
  - controls

- **2008**
  - preterm cases
  - birth defect cases
  - controls

- **2009**
  - preterm cases
  - birth defect cases
  - controls

- **2010**
  - preterm cases
  - birth defect cases
  - controls

*Neonatal Blood Spots (NBS) on Guthrie Cards*
Biomarkers of Prenatal Exposure


Recruit women from prenatal clinic

- **Personal Air Monitoring:** PAHs
- **Cord Blood:** PAH-DNA Adducts
- **Cord Blood:** \textit{LINE-1} and \textit{Alu} methylation
- **Guthrie cards:** \textit{LINE-1} and \textit{Alu} methylation
Exposure assessment

- Newborn (H/L)
- 6 yr (H/L)
- Animal Model (SD rat)

- [BaP] in air
- [BaP] in cord blood
- [I-OH] Newborn/Maternal urine
- [1OH] 6 yr urine
- [BaP] 50, 100, 200 mg/kg injection

Neurodevelopment

- NBNA
- M-WISC/WHO
- Neurobehavioral Tests, incl: flip, hearing reflex and Morris water maze...
- CBP, P300, H3, H4 in lymphocytes
- CBP, P300, H3, H4 in lymphocytes
- BDNF in plasma
- BDNF in plasma
- Hippocampal LPT
- Tunel assay/ apoptosis of Hippocampal cell
- Expression of CBP, P300, HDAC4, HDAC5, NMDA and BDNF
CREB Binding Protein (CBP) is a transcription factor capable of binding DNA and regulating gene expression. CREB proteins in neurons are thought to be involved in the formation of long-term memories.

Histone acetylation is catalyzed by histone acetyltransferases (HATs) and histone deacetylation is catalyzed by histone deacetylases (denoted by HDs or HDACs). CBP/p300 is probably the most important, since it can interact with numerous transcription regulators.

Brain-derived neurotrophic factor (BDNF) acts on certain neurons of the central nervous system and the peripheral nervous system, helping to support the survival of existing neurons and encourage the growth and differentiation of new neurons and synapses. In the brain, it is active in the hippocampus, cortex, and basal forebrain—areas vital to learning, memory, and higher thinking. BDNF itself is important for long-term memory. BDNF was the second neurotrophic factor to be characterized after nerve growth factor (NGF).

The Hippocampal long-term potentiation (LPT) of synapses in cell culture seems to provide an elegant substrate for learning and memory, the contribution of LTP to behavioral learning — that is, learning at the level of the whole organism — cannot simply be extrapolated from in vitro studies. For this reason, considerable effort has been dedicated to establishing whether LTP is a requirement for learning and memory in living animals.
200 Pregnant women reside in or near Tai Steel Co. [Bap] = 15ng/m³

200 Pregnant women reside in Changzhi City [Bap] = 15ng/m³

**Collection**
- Cord blood 10 ml (40)
- Maternal Urine 20 ml (50)
- Questionnaire (w/ours)
- Birth outcomes; Physical and Neuro. assessments

**GIS?**

**Biomarkers**
- PAH-DNA adducts, Methylation and metals.
Better Policy
Cleaner Environment
Healthier Children
Polycyclic aromatic hydrocarbons (PAH), especially benzo(a)pyrene (BP) as a representative member of this class of hydrocarbons, are an important class of carcinogens that are widespread in the ambient environment due to incomplete fossil fuel combustion for energy production, transportation and industry. PAH are also found in tobacco smoke and foods such as charred and broiled meat.
Glutathione (GSTs) → BP-7,8-epoxide → BP-7,8-dihydrodiol → Sulfate esters

CYP1A1

Reductase

BP-7,8-diol 9,10-epoxide

EH

Guanine

GSTs

Tetrol, Triol

Repair

BPDE-DNA Adduct

Mutation

CANCER
Benzo[a]pyrene (PAH)-DNA Adduct

- Phosphate Group
- Benzo[a]pyrene
- DNA Backbone
- Nitrogen Base Pair
- Yellow - Phosph.
- Red - Oxygen
- Blue - Nitrogen
- White - Carbon
PAH DNA Adducts - An Integrated Biological Dosimeter of PAH Exposure

*Multiple exposure routes
*Abortion, metabolic rate
*Susceptibility factors

Molecular Epidemiology

Exposure

Biological Exposure Assessment

Internal Dose → Biologically effective dose → Preclinical effect

Markers of Susceptibility

Clinical Disease
Tongliang County, Chongqing, China

10 km²

Population: 800,000

Birth Rate: 1/1000

No other major pollution sources

Study Site Selection

Image provided by Columbia University's Center for International Earth Science Information Network (CIESIN)

Beijing

Shanghai

Tongliang
TongLiang Power Plant

Generator (46,000 kW)
Fuel: Coal (24,000T/yr)
Coal: S=2-5%, Ash=30%
Operation: Dec.-June
Emission:
SO$_2$: 2500-4000 mg/m$^3$
(1800mg/m$^3$)
Particles: 2000mg/m$^3$
(250mg/m$^3$)

Image provided by Columbia University’s Center for International Earth Science Information Network (CIESIN)
Mother/Newborn Study Design

- **Cohort I**
  - 3/02-6/02
  - 150 pairs

- **Cohort II**
  - 3/05-6/05
  - 150 pairs

- **Cohort III**
  - 3/07-6/07
  - 150 pairs

5/2004

Comparing before and after:
1. Air monitoring data
2. Biomarker data
3. Fetal/Child growth and development
4. Respiratory illness
Ambient Air Monitoring

University of Nevada, Desert Research Institute (DRI)
Chongqing Institute of Environmental Sciences (CQIES)
Harvard University, Department of Environmental Health

Image provided by Columbia University's Center for International Earth Science Information Network (CIESIN)
Results of Air Monitoring for the Period from March 2002-Feb 2003

The average PM$_{2.5}$ values (115.4 µg/m$^3$) are 7-8 times higher than the annual PM$_{2.5}$ U.S. National Ambient Air Quality Standard (NAAQS) of 15 µg/m$^3$.

Average benzo(a)pyrene (BaP)(a PAH) levels (13.23 ng/m$^3$) are about two orders of magnitude higher than BaP levels (0.03-0.1 ng/m$^3$) in Southern California or NYC (0.5 ng/m$^3$).

Elevated benzonaphthothiophene (sulfur PAH) indicates contribution from coal combustion.

Chow et al., 2006 J Environ Sci Health A Tox Hazard Subst Environ Eng.
Table 2. Association between cord blood PAH-DNA adducts (dichotomized high/low) and birth outcomes/physical growth.a

<table>
<thead>
<tr>
<th></th>
<th>Birth</th>
<th>18 months</th>
<th>24 months</th>
<th>30 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ ($n$)</td>
<td>$p$-Value</td>
<td>$\beta$ ($n$)</td>
<td>$p$-Value</td>
</tr>
<tr>
<td>Weight</td>
<td>-0.007 (112)</td>
<td>0.738</td>
<td>-0.048 (110)</td>
<td>0.03</td>
</tr>
<tr>
<td>Length or height</td>
<td>-0.001 (112)</td>
<td>0.89</td>
<td>-0.005 (110)</td>
<td>0.483</td>
</tr>
<tr>
<td>Head circumference</td>
<td>-0.011 (112)</td>
<td>0.057</td>
<td>-0.012 (109)</td>
<td>0.085</td>
</tr>
</tbody>
</table>

*aModels included ETS, sex, maternal height, and maternal weight as covariates. Gestational age was additionally considered as a covariate for birth outcome analysis, and maternal head circumference and cesarean status were additionally considered as covariates for all analyses involving head circumference.

Tang et al., *Environmental Health Perspectives* Volume 114, Number 8, August 2006 1297-300
Analysis was based on 88 detectable cord adducts adjusting for gender, gestational age, blood lead level and maternal education level.
Mother/Newborn Study Design

Cohort I
3/02-6/02
150 pairs

Cohort II
3/05-6/05
150 pairs

Cohort III
3/07-6/07
150 pairs

5/2004

March 2002

Downtown, Tongliang City

March 2005
The Air PAHs Levels of Tongliang

Bar chart showing the levels of various PAHs (benzo[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, benzo[e]pyrene) in 2002-3 and 2005-6.
The PAH-DNA adducts level of newborns was 22% lower (p<0.001) after power plant shut down. The analysis is adjusted for ETS during pregnancy.
### Measures of Fetal Growth

<table>
<thead>
<tr>
<th>Measure</th>
<th>2002</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td>3337.5 ± 388.1 (149)</td>
<td>3406.0 ± 399.8 (158)</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>50.34 ± 1.7 (149)</td>
<td>50.30 ± 1.5 (155)</td>
</tr>
<tr>
<td>Head Circumference (cm)$^a$</td>
<td>33.8 ± 1.1 (149)</td>
<td>34.2 ± 1.3 (157)*</td>
</tr>
</tbody>
</table>

*Adjusting for gender, gestational age, maternal head circumference, and caesarian status *p=0.069
Gesell scores in the two prospective cohorts on development Delay (%)

- Motor
- Adaptive
- Language
- Social
- Average

Categories: 2002, 2005
2005 Cohort: No Association between Cord PAH-DNA Adduct Level and Birth Outcomes

(2006 Cohort Collected after Power Plant Shut Down)

<table>
<thead>
<tr>
<th></th>
<th>Continuous</th>
<th></th>
<th>High-low</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>p-value</td>
<td>β</td>
<td>p-value</td>
</tr>
<tr>
<td>Weight</td>
<td>-0.135</td>
<td>0.378</td>
<td>0.012</td>
<td>0.750</td>
</tr>
<tr>
<td>Length</td>
<td>0.048</td>
<td>0.250</td>
<td>0.015</td>
<td>0.135</td>
</tr>
<tr>
<td>HC</td>
<td>0.011</td>
<td>0.795</td>
<td>0.010</td>
<td>0.339</td>
</tr>
</tbody>
</table>

Models included ETS, gender, maternal height, and maternal weight as covariates. Gestational age was additionally considered as a covariate for birth outcome analysis, and maternal head circumference and cesarean status were additionally considered as covariates for all analyses involving head circumference.
Summary

PAH DNA adducts is a good integrated biological dosimeter of PAH exposure.

The air concentration of PAHs in Tongliang were significantly higher before the power plant shut down.

PAH-DNA adduct levels were significantly reduced after the power plant shut down.

Birth outcomes were improved after the power plant shut down.
Next Steps

Complete follow-up of cohort I, II and III children to age 10 yr to confirm neurocognitive function and asthma

Comparison analysis between cohort I, II and III to assess full effects of plant shut-down on body burden and child health

Assess interactions between genes and nutritional factors, respectively, and environmental exposures.

Evaluate the full impact of intervention in terms of health and societal costs and benefits

Help translate the scientific results to policy (publications, briefings, and case study)