Advancing Research on Chemical Mixtures: Epidemiology

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We are surrounded by
• hills
• mountains
• sea
• trees,
• and toxicants...
Environmental Mixtures: A Disaster

Filled with mining waste toxic mixtures:
• lead
• manganese
• cadmium,
• and others

TAR CREEK, Oklahoma Superfund Site
Environmental Mixtures

• The combination exposure to two or more environmental agents.

• Interactions may occur between toxicants on many levels that, in some cases, have the potential to greatly magnify toxicity. (Hu et al. Pediatr Clin North Am. 2007)

• A challenge for epidemiologic studies.
Epidemiology of Mixtures

• Approach has often been to find populations (US, overseas) that have a predominant exposure of interest (e.g., occupational exposures to benzene; community exposure to Arsenic in drinking water).

• And/or to treat the secondary exposures invariably present as potential confounders or effect modifiers.
Fundamental Questions I
(Sexton and Hattis. EHP 2007)

- Which environmental mixtures are most important?
  - Type of mixture
    - Similar mixtures (e.g., organophosphate pesticides)
    - Defined mixtures (e.g., tobacco smoke, coke oven emissions, diesel exhaust)
    - Coincidental mixtures (e.g., urban air pollution) : most complex
  - Identifying high-priority mixtures
    - Scope of exposure
    - Nature of exposure (magnitude/duration/frequency/timing)
    - Severity of health effect
    - Likelihood of interactions
What is the nature and magnitude of cumulative exposure?

- Increased vulnerability to disease (s)
Fundamental Questions III
(Sexton and Hattis. EHP 2007)

What is the mechanism and consequence of interactive effects?

- Developing better understanding of mechanisms of interaction in (cumulative) risk assessment

- Type of Interactive effects
  - Independence
  - Additivity
  - Synergism (multiplicative)
  - Antagonism
  - Other pattern?
Examples of Epidemiologic Studies of Mixed Exposures to Date: Metals
Synergistic: Prenatal Tobacco and Current Lead Exposures on ADHD

- 2001–2004 NHANES
- 8 to 15 years of age ($N=2,588$)

<table>
<thead>
<tr>
<th></th>
<th>ORs (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal tobacco</td>
<td>2.4 (1.5 to 3.7)</td>
</tr>
<tr>
<td>Blood lead</td>
<td>2.3 (1.5 to 3.8)</td>
</tr>
<tr>
<td>Tobacco and third tertile lead</td>
<td>8.1 (3.5 to 18.7)</td>
</tr>
</tbody>
</table>

(Froehlich et al. *Pediatrics* 2009)
Interactive Effects of Stress and Bone Lead on Hypertension

- VA-Normative Aging Study (NAS)
  - 513 hypertensives
  - 237 nonhypertensives
- In prospective analyses, high stress modified the effect of tibia lead and patella lead on the risk of developing hypertension.

(Peters et al. EHP 2007)
Child Development and Exposure to Metals

- Mixed metal exposures (Lead, As, Mn)
- Gene-environment interaction
- Site characterization
- Effects of timing and duration of human activities on metal bioaccessibility in water and soil

http://www.srphsph.harvard.edu/projects.html
Mexico City: Air Pollution
Bangladesh: Ground Water Arsenic Contamination
Tar Creek, OK, Superfund Site

- Mining activity began in 1891
- EPA’s Superfund National Priority List
- 1 million people live within a 4-mile radius
- Child development and cognitive function are among the most important outcomes in public health
- Little is yet known of metal mixture’s health effects.
Three Birth Cohorts
Manganese and Neurodevelopment

- 448 children, Mexico City from 1997 through 2000.
- Possible biphasic dose-response relationship between early-life Mn exposure at lower exposure levels and infant neurodevelopment.
- Mn as both an essential nutrient and a toxicant; (also seen in other trace compounds).

(Claus Henn et al. *Epidemiology* 2010)
Mixed Metal Exposures: Manganese and Lead Co-exposure with Neurodevelopment

- 486 children, Mexico
  - 12 months (n = 296)
  - 24 months (n = 475)

- Outcome
  - Mental Development Index (MDI)
  - Psychomotor Development Index (PDI)

(Claus Henn et al. EHP 2011)
Examples of Air Pollution Studies
Combined Particulate and Gaseous Air Pollutants and Mortality

- Inchon, South Korea, 1995-1996.
- A combined index of PM$_{10}$, NO$_2$, SO$_2$, and CO seemed to better explain the exposure-response relationship with total mortality than an individual air pollutant.
- Pollutants should be considered together in the risk assessment of air pollution.

(Hong et al. *EHP* 1999)
Interactive Effects of Air Pollutants on the Risk of Stroke Mortality

- Seoul, South Korea, 1995-1998

Table 3. Percent increase of the estimated relative risk of stroke mortality for each interquartile range increase in PM$_{10}$ in the single-pollutant model and change of the estimated percentage increases of relative risk when stratified by the median concentration of the gaseous pollutants.

<table>
<thead>
<tr>
<th>Single-pollutant model for PM$_{10}$</th>
<th>Percent change of relative risk for PM$_{10}$ stratified by gaseous pollutant concentrations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO$_2$</td>
<td>SO$_2$</td>
</tr>
<tr>
<td>1.5 (1.3-1.8)</td>
<td>4.8</td>
<td>-1.5</td>
</tr>
</tbody>
</table>

Med, median. Same-day concentrations are used for PM$_{10}$ and O$_3$, whereas the 2-day lagged concentrations are used for NO$_2$, SO$_2$, and CO.

Table 4. Percent increase of the estimated relative risk of stroke mortality for each interquartile range increase in gaseous pollutants in the single-pollutant model and change of the estimated percentage increases of relative risk when stratified by the median concentration of PM$_{10}$.

<table>
<thead>
<tr>
<th>Single-pollutant model for gaseous pollutants</th>
<th>Percent change of relative risk for gaseous pollutants stratified by PM$_{10}$ concentration</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 (1.1-5.1)</td>
<td>2.8</td>
<td>3.2</td>
</tr>
<tr>
<td>SO$_2$</td>
<td>2.9 (0.8-5.0)</td>
<td>2.2 (0.4-4.1)</td>
</tr>
<tr>
<td>CO</td>
<td>2.2 (0.4-4.1)</td>
<td>2.9 (0.3-5.5)</td>
</tr>
<tr>
<td>O$_3$</td>
<td>2.9 (0.3-5.5)</td>
<td>2.9 (0.3-5.5)</td>
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Med, median. Same-day concentrations are used for PM$_{10}$ and O$_3$, whereas the 2-day lagged concentrations are used for NO$_2$, SO$_2$, and CO.

(Hong et al. *EHP* 2002)
Air Pollution and Low Birth Weight

- Positive correlations of CO, NO₂, SO₂, and TSP: $0.67 < r < 0.83$.
- And secondary particles are formed in the atmosphere by chemical reactions involving NO₂ and SO gases.

$\rightarrow$ Need to consider these pollutants together rather than separately.

(Ha et al. *Epidemiology* 2001)
Maternal SHS Exposure, Genetic Susceptibility, and Oxidative Damage in Newborns

• **Second Hand Smoke (SHS):**
  Complex mixture of volatiles and PM comprising numerous compounds, including **PAHs**, which cause oxidative damage.

• 81 mothers and 20 of their newborns in South Korea (01/1999-06/1999).

• Significant difference in 8-OHdG (µg/L) levels between SHS-non-exposed and exposed groups (0.93 versus 4.03 µg/L).

• **Biomarker, not disease, outcome.**

(Hong et al. *JNCI* 2001)
Key Issues

• Are joint exposures more toxic?
  Precise characteristics of such interaction(s)

• What genetic and acquired susceptibility factors increase or decrease mixture toxicity?

• What environmental conditions increase human exposure to environmental mixtures?
  > Pointing the way to exposure elimination/control.
Key Issues

• “Interaction” concept is used differently in toxicology vs. epidemiology.

• Not a conflict inherently, but we must be clear in the definition.
Key Issues

• Interaction in **toxicology** refers to effect measured are greater than that predicted by each compound individually. Additivity most commonly observed.

• Interaction in **epidemiology** *usually* refers to “super additivity, i.e., synergism (multiplicity) in risk and hence removal of either exposure prevents risk.
Key Issues (cont.)

- Epidemiology is not a “stand alone” discipline. It is very dependent upon:
  - 1. Accurate exposure measurements.
  - 2. Appropriate power (size of study).
  - 3. Appropriate statistical methods.
  - 4. Supportive toxicology/biologic plausibility.

*In addition to solid study design!*
Key Issues (cont.)

• Of the above, the most important part, often missing, is **ACCURATE EXPOSURE ASSESSMENT** that can measure the compounds of interest, properly sum over time, and assign individuals a cumulative exposure value over the time period (s) of interest.
Environmental Sampling Equipment
Key Issues: Design

• Standard designs continue to be important: cohort, case-control, case-cohort, etc.

• The need for larger sample sizes – in genetic studies, investigators have combined studies, even those with different designs. There are pitfalls in doing this.

• Multi-center studies important to increase size.
The study of intermediate outcomes, quantitative traits, using physiologic and biologic markers improves power; may improve prevention.

Examples: urinary 8-OHdG, blood pressure, lung function, protein adducts, DNA adducts, neurodevelopmental tests, etc.
Key Issues: What to Study?

1. What are populations exposed to?

2. What is known about toxicity of these exposures?

3. Are there analytic methods to quantify exposure (short-term and long-term) in the population (s) under study.
Key Issues: toxicology and epidemiology

1. Toxicology and epidemiology should be complementary in their goals.

2. Each does not have all the answers to the question of mixed exposures.

3. Each needs to inform the other: e.g., weighting exposure by toxicity potential.
Ultimate Goals

1. To clarify the environmental causes of common diseases (e.g., Case-Control Study).

2. To evaluate exposure-response relationships for known toxicants so as to set safety standards.

3. To evaluate suspected toxicants in the population (e.g. flame retardants, pesticides).
Epidemiology of Mixtures