Asking the Right Questions:
Are Women of Childbearing-Age at Risk of Exposure to Multiple Pollutants?

Marcella Remer Thompson
PhD, MS, CSP, RN, COHN-S, FAAOHN
State Agencies and Community Liaison
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Superfund Research Program
of Brown University

resolving the complex health, engineering, and community challenges of contaminated environments
http://www.brown.edu/Research/SRP
Are We Really Asking the Right Questions?

- Why are we waiting nine months to find out about maternal and fetal exposures to environmental chemicals?

- Are women of childbearing age at risk of exposure to multiple pollutants?

- To what extent are they exposed?

- Which subgroups are exposure more than others?
Topics

- Concurrent Exposure to Multiple Environmental Chemicals
- Pervasive, Persistent, Co-Occur
- Neurotoxicants
- Mechanistic Studies of Binary Chemical Combinations
- Body Burden
- Human Studies
- Vulnerability

- Research Study
- Implications for Policy
Concurrent Exposure to Multiple Environmental Chemicals

Anthropogenic Chemicals (100,000)
• 6,716 chemicals EPA ChAMP Requirements
• 2,889 each > 1,000,000 pounds per year
• 3,249 each > 25,000 pounds per year

Natural Chemicals
• Elements (90)
• Inorganic Compounds
• Organic Compounds

Michael G. Thompson (2007)
Michael G. Thompson (2005)
Kapono Pa (2008)
Pervasive, Persistent, Co-Occur

• Pervasive
  – Remote Locations
  – Sentinel Species

• Persistent
  – Climate Factors
  – Climate Change

• Co-Occur
  – Common Spatial and Temporal Distributions
Concurrent Exposure to Multiple Environmental Chemicals

Hazardous Waste in U.S. (2011)
4,090,000 pounds Disposed/Released
8% annual increase

Pervasive, Persistent Toxics
36% annual increase
- Lead 35% increase
- Mercury 10% increase
- Dioxins 35% increase
- PCBs 36% increase

Toxic Release Inventory
21,000 facilities
676 chemicals

Superfund Sites (2004)
- 67,000,000 live within 4.0 miles
- 38,000,000 live within 2.5 miles
Neurotoxicants

- Lead (Pb), mercury (Hg), and polychlorinated biphenyls (PCBs) are known neurotoxicants in animal models and human populations.
- Health effects from co-exposure and biologically-effective dose are relatively unknown.
- There is a need to assess chemicals’ cumulative risk for neurotoxicity, even though they may not share the same mode of action.

Meacham et al. (2005); Radio et al. (2010); National Research Council (2008)
# Mechanistic Studies of Binary Chemical Combination (MeHg-PCBs)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Antagonistic</th>
<th>Non-Additive</th>
<th>Additive</th>
<th>Synergistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bemis &amp; Seegal (1999)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Sitarek &amp; Gralewicz (2009)</td>
<td>X</td>
<td></td>
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<tr>
<td>Coccini et al. (2006)</td>
<td>X</td>
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<tr>
<td>Costa et al. (2007)</td>
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<td>X</td>
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<tr>
<td>Roegge et al. (2004)</td>
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<td>X</td>
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</tbody>
</table>

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<thead>
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<th>Additive</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Goldoni et al. (2008)</td>
<td>MeHg then PCB153</td>
<td>PCB153 then MeHg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Radio et al. 2010; Meacham et al. 2005)
Body Burden

- The body burden from past exposures as well as those maternal exposures that occur during gestation can transfer to the fetus via the placenta and to infant and child during lactation.
- Childbearing-aged women in general and not just those who are currently pregnant are of special public health concern.
- Little is known about the prevalence of co-exposures to these chemicals among childbearing-aged women.
## Human Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Outcome</th>
<th>PCBs</th>
<th>Hg</th>
<th>Pb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qin et al. (2010)</td>
<td>uterine leiomyomas</td>
<td>$p&lt;0.05$</td>
<td>$p&lt;0.01$</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td>Denham et al. (2005)</td>
<td>attainment of menses</td>
<td>$p&lt;0.05$</td>
<td>$p=0.08$</td>
<td>$p&lt;0.05$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Percent Detectable PCBs, Hg, Pb</th>
<th>Percent Detectable VOCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woodruff et al. (2011)</td>
<td>pregnant</td>
<td>89% - 100%</td>
<td>38% - 94%</td>
</tr>
<tr>
<td></td>
<td>non-pregnant</td>
<td>96% - 100%</td>
<td>47% - 95%</td>
</tr>
</tbody>
</table>

(National Research Council 2006; Woodruff et al. 2011)
Vulnerability

- Exposure
- Resistance
- Resilience/Recovery

(Turner et al., 2003; Aday, 2001; Kasperson, 2001; Kasperson, Kasperson, Turner, Dow, & Meyer, 1995; Sexton, 1997)
Figure 1. Modified Environmental Health Paradigm. Adapted from Sexton et al., 1993
Aim and Research Questions

The aim of this research was to characterize the body burden and covariates for exposure to three neurotoxicants among childbearing-aged women living in the U.S. 1999 through 2004.

1. What was the percentage of childbearing-aged women who had body burdens at or above the median for lead, mercury, and PCBs?

2. What was the extent of their mixed exposures?

3. What, if any, subsets of these women were disproportionately burdened by two or more of these environmental chemicals based on susceptibility-related attributes, exposure-related attributes, socioeconomic factors, and race-ethnicity?
Methodology

Research Design. Descriptive and Exploratory Study

Data Source. Centers for Disease Control and Prevention National Center for Health Statistics National Health and Nutrition Examination Survey (NHANES)
http://www.cdc.gov/nchs/nhanes.htm

Components. Demographics, Interviews, Physical Examination, Laboratory Tests including Biomonitoring and Environmental Monitoring
Methodology


Dependent Variable. Two or more xenobiotic levels at or above the median. Lead and total mercury were measured in blood. The sum of four PCB congeners (118, 138/158, 153, 180) were measured in serum.

# Study Population

(NHANES unweighted and weighted 1999-2004)

<table>
<thead>
<tr>
<th>Study Criteria</th>
<th>Laboratory Sample (unweighted)</th>
<th>Laboratory Sample (weighted)</th>
<th>All Chemicals and Reliable Dietary Recall (unweighted)</th>
<th>All Chemicals and Reliable Dietary Recall (weighted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-19 years old</td>
<td>1,321</td>
<td>22,209,998</td>
<td>1,085</td>
<td>18,510,469 (14%)</td>
</tr>
<tr>
<td>20-29 years old</td>
<td>994</td>
<td>49,713,270</td>
<td>884</td>
<td>45,347,515 (34%)</td>
</tr>
<tr>
<td>30-39 years old</td>
<td>818</td>
<td>42,250,320</td>
<td>702</td>
<td>36,357,837 (27%)</td>
</tr>
<tr>
<td>40-49 years old</td>
<td>575</td>
<td>39,459,259</td>
<td>502</td>
<td>34,286,213 (25%)</td>
</tr>
<tr>
<td>Race-Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-Hispanic white</td>
<td>1,736</td>
<td>112,166,998</td>
<td>1,493</td>
<td>97,887,544 (73%)</td>
</tr>
<tr>
<td>non-Hispanic black</td>
<td>761</td>
<td>15,494,990</td>
<td>623</td>
<td>12,747,178 (10%)</td>
</tr>
<tr>
<td>Mexican-American</td>
<td>875</td>
<td>9,978,059</td>
<td>745</td>
<td>8,670,576 (6%)</td>
</tr>
<tr>
<td>other Hispanic</td>
<td>192</td>
<td>8,026,759</td>
<td>178</td>
<td>7,525,992 (6%)</td>
</tr>
<tr>
<td>other racial</td>
<td>144</td>
<td>7,966,041</td>
<td>134</td>
<td>7,670,743 (5%)</td>
</tr>
<tr>
<td>Total</td>
<td>3,708</td>
<td>153,632,847</td>
<td>3,173</td>
<td>134,502,033</td>
</tr>
<tr>
<td>lost from sample</td>
<td></td>
<td></td>
<td>535 (14.4%)</td>
<td>19,130,814 (12.4%)</td>
</tr>
</tbody>
</table>
Methodology

- Concatenated and Organized Dataset
- Operationalized Dependent and Independent Variables
- Constructed Software Instructions in 64-bit SAS© and SAS-callable SUDAAN©.

- Levels of Detection (LoD)
  - Each lipid-adjusted PCB congener varied as each sample from each individual had its own limit
  - For Pb and total Hg, values below LoD were imputed by NHANES
Xenobiotic Levels in Childbearing-Aged Women  
(NHANES weighted data 1999-2004)

<table>
<thead>
<tr>
<th>Xenobiotic</th>
<th>LoD</th>
<th>≥ LoD (%)</th>
<th>GM (SE)</th>
<th>50th Percentile</th>
<th>95th Percentile</th>
<th>CV (GSE/GM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead [blood (µg/dl)]</td>
<td>0.3</td>
<td>98.50</td>
<td>0.93 (0.03)</td>
<td><strong>0.89</strong></td>
<td><strong>2.24</strong></td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>Total Mercury [blood (µg/L)]</td>
<td>0.2</td>
<td>95.85</td>
<td>0.94 (0.06)</td>
<td><strong>0.99</strong></td>
<td><strong>5.55</strong></td>
<td><strong>0.06</strong></td>
</tr>
<tr>
<td>PCB 118 [serum (ng/g lipid)]</td>
<td>NA</td>
<td>67.50</td>
<td>5.95 (0.20)</td>
<td>5.14</td>
<td>20.22</td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>PCB 138/158 [serum (ng/g lipid)]</td>
<td>NA</td>
<td>74.12</td>
<td>12.84 (0.52)</td>
<td>13.79</td>
<td>45.38</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>PCB 153 [serum (ng/g lipid)]</td>
<td>NA</td>
<td>78.29</td>
<td>17.09 (0.72)</td>
<td>18.18</td>
<td>60.72</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>PCB 180 [serum (ng/g lipid)]</td>
<td>NA</td>
<td>74.81</td>
<td>10.85 (0.40)</td>
<td>10.38</td>
<td>42.89</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Σ PCBs [serum (ng/g lipid)]</td>
<td>NA</td>
<td>55.50</td>
<td>48.09 (1.82)</td>
<td>51.59</td>
<td>198.75</td>
<td><strong>0.04</strong></td>
</tr>
</tbody>
</table>
Percentage of Childbearing-Aged Women in U.S. burdened by specific xenobiotic combinations at or above the median (NHANES weighted data 1999-2004)

- Pb+THg+PCBs (22.8%)
- Pb only (11.6%)
- THg only (9.7%)
- THg+PCBs (9.6%)
- PCBs only (5.6%)
- PCBs+Pb (12.0%)
- none (17.3%)

Denham et al. (2005); Boucher et al. (2011); Stewart et al. (2006)
Best-Fit Logistic Regression Model
(NHANES weighted data 1999-2004)

Variable Names

- Age
- Fish Consumption
- Alcohol Consumption
- Past Breastfed Child
- Household Size
- Education
- Shellfish Consumption
- Language Spoken at Home
- Race-Ethnicity
- Selenium Intake
- Currently Breastfeeding
- Employment

\[ p \leq 0.05 \]
Odds of childbearing-aged women in U.S. with two or more xenobiotics at or above the median based on age (NHANES weighted data 1999-2004)

Axelrad et al. (2009); Mushak (1998); Caldwell et al. (2009); Laden et al. (2001)
Odds of childbearing-aged women having two or more xenobiotic levels at or above median based on fish consumption

Grandjean et al. (1992); Gunderson (1995); Falco et al. (2006); Tran et al. (2004)
<table>
<thead>
<tr>
<th>Variable Names</th>
<th>df</th>
<th>Wald F</th>
<th>P value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol Consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>never, seldom drinkerR</td>
<td>2</td>
<td>4.01</td>
<td>0.03</td>
<td>1.00</td>
<td>ns</td>
</tr>
<tr>
<td>including 16-19 y/o data restricted drinker</td>
<td></td>
<td></td>
<td></td>
<td>0.63</td>
<td>0.33-1.19</td>
</tr>
<tr>
<td>heavy and/or binge drinker</td>
<td>1.56</td>
<td>0.81</td>
<td>0.33-1.19</td>
<td>3.01</td>
<td></td>
</tr>
<tr>
<td>Variable Names</td>
<td>df</td>
<td>-2LL</td>
<td>Wald F</td>
<td>P value</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----</td>
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<td>--------</td>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>Past Breastfed Child</td>
<td>1</td>
<td>5.09</td>
<td>0.03</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>never breastfed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>breastfed more than one month</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td>Currently Breastfeeding</td>
<td>1</td>
<td>1.20</td>
<td>0.28</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>no</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>currently breastfeeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.97</td>
</tr>
</tbody>
</table>

ATSDR (2004); Gundacker et al. (2002); Arendt (2008); Needham et al. (2011); CDC NCEH (2010)
Study Limitations

- cross-sectional study
  - associations, not causations
- goodness of fit ($R^2 = 0.25$)
  - binary interactions (33% $p < 0.001$)
- limited understanding of exposure covariates
- body burden ≠ identify exposure sources
  - time and place
- generalized to U.S. population of childbearing-aged women only
- population-based study, not individualized risk
- only these three environmental chemicals
Conclusions

• Childbearing-Aged Women in U.S.
• Body Burden for Pb, Hg, PCBs
  – 23% all three xenobiotics at or above median
  – Equally likely to have two as one at or above median
• Covariates
  – increasing age
  – any fish consumption
  – heavy and/or binge drinking alcohol consumption
  – prior history of breastfeeding (lower)
Questions?
Implications for Policy

Is it safe?
Is it safe enough?

Should protecting the next generation by regulating environmental exposures of the current generation be addressed in public and environmental health policy?

Should pregnant and lactating women be protected exclusively?
Guidelines for the Identification and Management of Lead Exposure in Pregnant and Lactating Women

• Does NOT recommend routine prenatal testing
• If prenatal BLL ≥5 µg/dL, institute education and environmental, nutritional, and behavioral interventions
• Does recommend breastfeeding UNLESS breast milk lead level <40 µg/dL.
  • If prenatal BLL ≥10 µg/dL, remove from occupational exposures
• Does NOT address return to work or compensability
• Fetal Protection Policy is neither acceptable nor legal

(NCEH, 2010)
Blood Lead
↑10 µg/dL
IQ
↓5 points

(Needleman 1989, p.643)
Just think how smart we all could have been.