Cumulative Risk Assessment: Approaches and Case Study

A webinar sponsored by the Risk Assessment Specialty Section of the Society of Toxicology

3 PM–4:30 PM
June 12, 2013

Glenn E. Rice¹, Amanda M. Evans² and Linda K. Teuschler ¹

¹U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH; ²Oak Ridge Institute for Science and Education

The views expressed in these presentations are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA.
Order of Talks

1. Grouping Chemical and Non-chemical Stressors for Cumulative Risk Assessment: Potential Applications to Stressor Combinations Associated with Cardiovascular Disease
   Glenn Rice  3:10–3:30

2. Adapting Chemical Mixture Risk Assessment Methods to Assess Chemical and Non-Chemical Stressor Combinations
   Linda Teuschler 3:30–3:50

   Amanda Evans 3:50–4:10

4. Questions 4:10–4:30
Grouping Chemical and Non-chemical Stressors for Cumulative Risk Assessment: Potential Applications to Stressor Combinations Associated with Cardiovascular Disease

Glenn Rice
National Center for Environmental Assessment
U.S. EPA
June 12, 2013

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Talk Outline

1. Grouping stressors to simplify and focus cumulative chemical mixture risk assessments
   a) Forming chemical groups based on exposure data
   b) Forming chemical groups based on toxicity data
   c) Forming integrated chemical exposure and toxicity groups

2. Extending grouping approaches to non-chemical stressors

3. Preliminary application of grouping approaches to non-chemical stressors associated with cardiovascular diseases
Goals of EPA’s “Cumulative Risk Resources Document”
- Provide simplifying methods for conducting cumulative risk assessments (CRAs) increases feasibility of conducting CRAs

Grouping chemicals by potential for co-occurrence and joint toxic action simplifies conduct of CRAs & increases feasibility
- Helps focus what could be overwhelming effort
Analytic Steps in Chemical Cumulative Risk Assessment (U.S. EPA, 2007)

1. Generate chemical list
2. Identify links between chemicals and population
3. Quantify population exposures and form exposure groups
4. Quantify dose-response relationships and form toxicity groups
5. Integrate exposure and dose-response groups, refining exposure and toxicity assessments

Adapted from U.S. EPA (2007)
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5. Integrate exposure and dose-response groups, refining exposure and toxicity assessments

Adapted from U.S. EPA (2007)
Forming Chemical Exposure Groups

- Simple approach
- Classify all chemicals of concern into initial groups by their potential to occur in the same or different media and at the same or different time

\[
\begin{array}{|c|c|c|}
\hline
\text{Exposure} & \text{Medium} \\
\hline
\text{Time} & \text{Same} & \text{Different} \\
\hline
\text{Same} & \text{Group 1} & \text{Group 3} \\
\hline
\text{Different} & \text{Group 2} & \text{Group 4} \\
\hline
\end{array}
\]

Adapted from U.S. EPA, 2007
Forming Chemical Exposure Groups

Same Medium/Same Time

- Example: PCBs & Methyl mercury (MeHg) co-occur in local fish, consumed by population.
- Likely co-exposures to chemicals occurring in the same medium at the same time; likely place into same chemical exposure group.
- Importance of knowing populations’ consumption habits (e.g., parts of fish eaten); MeHg accumulates in muscle tissue, but PCBs in fat.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Same</td>
</tr>
<tr>
<td>Same</td>
<td>Group 1 PCBs and MeHg in local fish</td>
</tr>
<tr>
<td>Different</td>
<td>Group 2</td>
</tr>
</tbody>
</table>
Refining Chemical Exposure Groupings: Different Media/Same or Different Time

• To form exposure groups for other situations must examine:
  – Timing of pollutant occurrence in the different contaminated media
  – Timing of associated exposure events (including the time between temporally separated exposures), and
  – Frequency and duration of encountering contaminated exposure media
Refining Chemical Exposure Groupings: Different Media/Same or Different Time II

• Ideally, consider internal doses when forming groups:
  – Half-life of chemicals inside the body
  – Some highly persistent pollutants may always be present

• Ideally, consider whether tissue changes persist after chemical exposure ends
  – Induction of metabolism
  – Altered tissue sensitivity (e.g., liver induction persists after chemical eliminated)

• Does order in which the exposures occur affect outcome?
  – E.g., tumor initiators and promoters
Pharmacokinetic Interaction: Two Chemicals

Hypothetical pharmacokinetic interaction: compound B increases the persistence of both compound A and biologic effect.

This illustrates only one of many possibilities.
**Additivity: Two Chemicals**

**Hypothetical additivity:**
*toxicity of compounds A + B increases persistence and severity of toxicity*

This illustrates only one of many possibilities.
The exposure grouping concept can be extended to chemical buffers.

For example, fish consumption also source of fish fatty acids (e.g., omega-3 fatty acids) that might enhance cognitive development.

Fish fatty acid intake may confound MeHg-IQ relationship, biasing downward observed regression coefficient estimates from epi studies.
Forming Toxicity Groups

• For each individual chemical collect all relevant toxicological data:
  – Identify primary effect (adverse effect observed at lowest dose [LOAEL]) and secondary/tertiary effects (effects above LOAEL)
  – Form groups initially by tissue or organ systems affected

• Refine groups based on the following:
  – Examine mode of action information
  – Identify effects (e.g., continuous responses) not adverse alone, could lead to adverse effect in combination with other factors (e.g., other chemical exposures, nutritional status)
  – Collect pharmacokinetic information including metabolic pathways

• Example: Group: MeHg, Pb, and PCBs as neurodevelopmental toxicants and omega-3 fatty acid (FA) as a possible chemical buffer
  – MeHg, Pb, omega-3 FA, and PCBs exposures may result from contact with different sources
  – Could refine group further with additional PK or PD information
Integrating Exposure and Toxicity Groups

• Exposure Group Results:
  • MeHg
  • PCBs
  • Omega-3 fatty acids

• Toxicity Group Results:
  • MeHg
  • PCBs
  • Pb
  • Omega-3 fatty acid

• Integrated Group:
  • MeHg
  • PCBs
  • Omega-3 fatty acids
  • No Pb because not in exposure group in this population
Part 2. Extending Grouping Approaches to Non-chemical Stressors

- EPA’s Cume Risk Resources Doc does not address this directly
- Feasible
- Some non-chemical stressors considered in existing EPA methods, but not necessarily called “Cume Risk”
  - EPA’s RfD methodology: $U_{F_H}$ for susceptible human populations
  - EPA’s exposure assessment methods address vulnerable populations that are differentially exposed
Extending Grouping Approaches to Non-chemical Stressors: Preliminary Considerations for Identifying Non-chemical Stressors that Could be Grouped with Chemical Stressors

1. Ongoing or previous Health Conditions and Disease States causing effects similar to those associated with a chemical’s effect
   - Pharmacokinetic or pharmacodynamic changes due to ongoing or previous health conditions or disease states that change or exacerbate a chemical’s effect or body’s response (includes buffering)

2. Lifestages that may contribute to or buffer against a chemical’s effect

3. Genetic Factors that may contribute to or buffer against a chemical’s effect

4. Lifestyle Factors, Occupational Factors, Physical Stressors, and Biological stressors that may contribute to or buffer against a chemical’s effect

- My intent: “further the dialogue”
- I make no claim that these considerations constitute a complete set
- Overlaps in these categories
- Likely additional categories/Alternative Approaches to Categorizing
- Different approaches could be used to organize data
Part 3. Example

Illustrate non-chemical stressor groupings using examples from ambient particulate matter (PM) literature (where possible) and cardiovascular disease literature.

Several large U.S. cohort studies have associated elevated short-term and long-term PM$_{10}$ and PM$_{2.5}$ exposures with cardiovascular morbidities and mortality.

It is not known whether Ambient PM exposures cause cardiovascular morbidities and mortality or accelerate these outcomes that are caused by other stressors.
Systemic Inflammation Pathway

- Pulmonary Oxidative Stress and Inflammation
- Liver Acute Phase Response
- Pro-coagulation Effects
- Thrombosis
- Systemic Inflammation/Oxidative Stress
- Atherosclerosis
- Plaque Destabilization or Rupture
- Endothelial Cell Activation/Dysfunction
- Altered Vasoreactivity of Coronary Vessels
- Myocardial Ischemia
- Potential Pathways: PM & Cardiovascular Diseases

Autonomic Nervous System Pathway

- Pulmonary Reflexes
- Altered Sympathetic/Parasympathetic Tone
- Altered Conduction/Repolarization
- Arrhythmia

Myocardial Infarction

Adapted from U.S. EPA, 2009
Ongoing or Previous Health Conditions and Disease States Causing Effects Similar to Those Associated with a Chemical’s Effect

• Diabetes—EPA (2009) judged collective evidence: susceptibility factor
  – Basis included positive epi studies quantifying increased risks of the following outcomes among diabetics exposed to PM relative to non-diabetic populations:
    • Cardiovascular disease-related emergency room visits
    • Hospitalization for cardiac diseases
    • All cause mortality
    • Sources: (Zanobetti & Schwartz, 2002; Peel et al. 2007; Zeka et al., 2006; Goldberg et al., 2006)
  – Some epi studies did not observe effect modification in diabetic populations following PM exposures (Pope et al., 2006; Wellenius et al., 2006; Zanobetti and Schwartz, 2005)
• Additional basis: pathophysiologic evidence of inflammatory outcomes associated with diabetes; also observed following PM exposure
Lifestages That May Contribute to or Buffer Against a Chemical’s Effect

• Lifestages - distinguishable time frames in individuals’ lives characterized by unique and relatively stable behavioral or physiological characteristics, associated with development, growth, and aging (e.g., fetus, birth to <1 month...elderly)

• EPA (2009) concludes: older adults = a susceptible population, possibly due to higher prevalence of pre-existing cardiovascular diseases and gradual decline in physiological processes compared to younger lifestages
  – Overlaps exist between potentially susceptible older adults and populations with pre-existing diseases (Kan et al., 2008)
  – Barnett (2006) and Host (2007) quantified increased risk of cardiovascular disease-related hospital admissions among >65 yr compared to <65 yr after short-term PM exposures

• Youth/middle-aged lifestages could be a buffer
Potential Revision Analytic Steps in Chemical Cumulative Risk Assessment

Suggested additional steps in Cume Risk Methods:
1. After forming chemical groups, identify stressors that plausibly increase or decrease specific disease risks and include these in the appropriate chemical groups.
2. Seek quantitative data to support quantitative estimate of risk associated with stressors
   - Epidemiology or toxicology data (encourage publishing such data! Ranges are important).
3. If data not available to quantify change in risk, qualitative analyses of multiple related stressors still useful for cumulative risk assessment and risk managers
   - Provide opportunities to highlight important uncertainties (stressors that co-occur); needed research.
Acknowledgments

- Linda Teuschler
- Michael Wright
- Rick Hertzberg
- Amanda Evans
- Jane Ellen Simmons
- Jason Lambert
- Gino Scarano
Adapting Chemical Mixture Risk Assessment Methods to Assess Chemical and Non-Chemical Stressor Combinations

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Society of Toxicology
Risk Assessment Specialty Section
Webinar, June 12, 2013

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Mixtures Risk Assessment (MRA) Methods Proposed for Extension to Cumulative Risk Assessment (CRA)

- MRA methods generally use simple models to estimate risks/hazards for complex exposures
- Component based approaches are suggested for application to CRA for chemical and nonchemical stressor combinations
  - Response Addition
  - Effects Addition
  - Hazard Index (HI)
  - Weight of Evidence (WOE*) for Toxicological Interactions
- Tiering is important concept to optimize use of resources

*Mumtaz & Durkin. 1992.*
General Schematic of Toxic Events

- **Exposure**

  - Event – Mechanism of Action
    - Detailed understanding at biochemical and molecular level
  
  - Key Event – Mode of Action
    - Identification of key and required steps

- **Toxicity**

  - Outcome – Observable adverse effect

Graphic used with permission of Jason Lambert
Response Addition & Effects Addition

Response Addition
Assumes Statistical and Toxicological Independence of Toxic Action

\[ R_m = f_1(D_1) + f_2(D_2) + f_3(D_3) = R_1 + R_2 + R_3 , \]
where the \( R_i \) are probabilities of adverse effects

Effects Addition
Assumes Toxicological Independence of Toxic Action

\[ E_m = f_1(D_1) + f_2(D_2) + f_3(D_3) = E_1 + E_2 + E_3 , \]
where the \( E_i \) are biological measurements of an adverse effect

- For a common health outcome, assumes the toxicity caused by the first chemical has no impact on the toxicity caused by the second chemical (and so on).
- Use at levels/exposures where joint toxic action is not expected to occur.
- For effects addition, constrained by the biological limit of the effect measurement.

\( R_m = \) mixture probabilistic risk; \( E_m = \) total effect measurement for the mixture; \( D_i = \) dose of ith stressor; \( f_i = \) dose response function of the ith stressor
Response Addition and Effects Addition via Independent Toxic Action

Exposure to Stressors 4, 5, 6

Assumes same type of adverse effect is caused via independent toxic modes of action

Stressor 4 Toxic Action
Stressor 5 Toxic Action
Stressor 6 Toxic Action

Event – Mechanism of Action
Key Event – Mode of Action
Outcome – Adverse Effect

Office of Research and Development
National Center for Environmental Assessment
Response Addition- Statistical Law of Independent Events

$r_1 = 0.01$, risk of heart attack for chemical 1
$r_2 = 0.02$, risk of heart attack for nonchemical stressor 2
then $r_1 \times r_2 = 0.0002$, and we get,
$$R_m = 0.01 + 0.02 - 0.0002 = 0.0298 \text{ or } \sim 0.03$$

For small risks, the risk intersection (not an interaction term) has virtually no impact.
Effects Addition – Biological Upper Limit to Consider

Diastolic Blood Pressure (DP) Space, Upper Limit of 110 mmHg = E*

\[ e_1 = \text{incremental increase in DP (4 mmHg) caused by chemical 1} \]
\[ e_2 = \text{incremental increase in DP (3 mmHg) caused by nonchemical stressor 2} \]

So, \( E^* \) (mmHg) ≥ baseline DP + \( e_1 \) + \( e_2 \) (constrained by biological upper limit)

e.g., DP in presence of chemical 1 and nonchemical stressor 2

\[ = 88 + 4 + 3 = 95 \text{ (mmHg)} \]
Extension of Response & Effects Addition Methods to CRA

• Given independence of toxicological action
  – Response Addition: For some stressors, it may be reasonable to sum probabilistic risks of the same effect across diverse stressors – subtract off risk intersections
  – Effects addition: May be possible to sum biological effects – need estimate of “normal levels” and a way to account for biological limits of the effect
• Assumption of independence of toxic action may be difficult to show; no established criteria for doing this
• Need to evaluate data on potential toxicological interactions that may preclude additivity assumption
MRA Hazard Index (HI)

\[ HI = \sum_{i=1}^{n} \frac{E_i}{RfV_i} \]

Based on dose addition, assuming toxicological similarity
Interpreted as an indication of potential risk when HI > 1

- Scaling factor = ( 1 / RfV_i ) for each stressor i
- \( n \) = total number of stressors causing the same effect
- RfV_i is a Reference Value, representing an allowable level/intake of stressor i
- \( E_i \) is estimated Intake or exposure (in same units as the RfV_i)
- Use at levels/exposures where interaction effects are unlikely
Dose Addition via Common Mode of Action

Exposure to Stressors 1,2,3

Same toxic effect via a “Shared set of Key Events”

Stressor 1 Toxic Action
Stressor 2 Toxic Action
Stressor 3 Toxic Action

Event – Mechanism of Action
Key Event – Mode of Action
Outcome – Adverse Effect
Dose Addition via Common Mode of Action

Exposure to Stressors 1,2,3

Same toxic effect via a “Shared set of Key Events”

Not Likely Scenario for Diverse Stressors

Event – Mechanism of Action
Key Event – Mode of Action
Outcome – Adverse Effect
More Likely: Dose Addition via Toxicological Similarity

Exposure to Stressors 1, 2, 3

Common target organ, tissue or system affected; may use Common adverse outcomes

Event – Mechanism of Action
Key Event – Mode of Action
Outcome – Adverse Effect

Stressor 1 Toxic Action
Stressor 2 Toxic Action
Stressor 3 Toxic Action
Example CRA HI

\[
HI(\text{Hypertension}) = \frac{E_{PM}}{RfV_{PM}} + \frac{E_{Pb}}{RfV_{Pb}} - \frac{E_{O3}}{RfV_{O3}} + \frac{E_{AL}}{RfV_{AL}}
\]

- **RfV_{PM}** = allowable intake of particulate matter (PM)
- **E_{PM}** = exposure intake of PM
- **RfV_{Pb}** = allowable intake of Lead (Pb)
- **E_{Pb}** = exposure intake of Pb
- **RfV_{O3}** = minimum recommended intake of Omega 3 Fatty Acids (O3)
- **E_{O3}** = exposure intake of O3, limited by an effective dose upper bound
- **RfV_{AL}** = allowable number (3) of Allostatic Load (AL) markers of psychological stress out of 10 cardiovascular, metabolic, immune system markers [AL=0, low stress; AL=1,2; intermediate stress; AL= 3-10; high stress]
- **E_{AL}** = number of AL markers in exposed population

Interpreted as an indication of potential risk when \( HI > 1 \)

Is “dose” addition still a realistic/valid assumption?
• Given similarity of toxicological action
  – HI: For some stressors, it may be reasonable to sum hazard quotients for the same effect across diverse stressors
• Similar mode of action may not be easy to show; example criteria for the dioxin-like compounds and for some pesticide classes
• Similarity of toxicological action can be a very conservative assumption
• Population vulnerabilities can be accommodated
  – Intakes can be estimated for differential exposures
  – RfVs and PODs can be estimated for susceptible populations
• Need to evaluate data on potential toxicological interactions that may preclude additivity assumption
Weight of Evidence (WOE*) Method for Considering Toxicological Interactions of Chemicals

- Systematic, consistent method for expressing the WOE* for toxicological interactions
- Reflects what we know about mechanisms of action and how they can or may apply to interactions
- Applicable using available data, typically found on binary combinations of chemicals
- Can be used to express uncertainty of, or qualitatively alter a mixtures risk assessment (e.g., modify the interpretation of a HI)
- Subject to evaluation with experimental data

Slides used with permission of Moiz Mumtaz.
*Citation: Mumtaz, MM; Durkin, PR. (1992) A weight-of-evidence scheme for assessing interactions in chemical mixtures. Toxicol Ind Health 8:377-406.
Slide shows only 3 of the 6 criteria used to evaluate interactions data on binary combinations of chemicals:


*Mumtaz & Durkin. 1992.*
Type of Joint Toxic Action - Chemicals

<IIA

= Evidence of Additivity

< Evidence of Toxicological Interactions Less than Additive (e.g., antagonism)

> Evidence of Toxicological Interactions Greater than Additive (e.g., synergism)

? Inconclusive Evidence or No Data
Toxicological Significance – Chemicals

A. Directly demonstrated
   • Change in toxicity observed as a result of the interaction.

B. Inferred from related compounds.
   • Interaction observed in related compounds.

C. Unclear
   • No reliable data.
**Effect of Zinc on Lead**

- **<IA (less than additive action)**
  - *in vivo and in vitro*
  - Lead inhibits ALAD, a zinc-containing enzyme in the heme synthesis pathway
  - Zinc protects against the inactivation.
  - Zinc induces metallothionein
  - Zinc protects against lead absorption in GI tract

A oral zinc supplement protective of lead-induced hematopoietic effects in children

*Mumtaz & Durkin. 1992.*
## Example Evaluation of Nonchemical Stressors Effects on Chemical Toxicity

<table>
<thead>
<tr>
<th>EFFECT OF</th>
<th>ON CARDIOVASCULAR TOXICITY OF</th>
<th>Ambient PM</th>
<th>Methyl Mercury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological Stress</td>
<td>+ I</td>
<td>+ I</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>+ A ER Visits</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Elderly (≥ 65)</td>
<td>+ A Hosp Admissions</td>
<td>+ A</td>
<td>Coronary Heart Disease</td>
</tr>
<tr>
<td>Omega 3 Oils</td>
<td>- I</td>
<td></td>
<td>- B Coronary Heart Disease</td>
</tr>
</tbody>
</table>

**Nomenclature:** + increases, - decreases  
**Evidence:** A strong, B weak, I Inferred, ? none
Extension of WOE* Methodology to Cumulative Risk Assessment

• Evaluation of the effect of nonchemical stressors/buffers on chemical toxicity
  – Not a sequential evaluation
  – Need to articulate criteria/nomenclature for important nonchemical stressors/buffers
    – Add epidemiological study input for associations, effect modification
    – Add strength of collective data; inferred associations
  – Categories of nomenclature may differ for various stressors/buffers
• Use to qualitatively modify a cumulative risk assessment
  – For e.g., say whether a HI combining both chemical and nonchemical stressors would under or overestimate hazard

Uncertainties in Chemical MRA may Apply to CRA for Combined Stressors

• Professional judgment is an important element
  – Ensure results biologically defensible, present transparently
  – Confirm assumptions whenever possible

• Uncertainty/sensitivity analyses are important
  – Discuss data gaps, data quality differences among stressors
  – Describe exposure range(s) for which assessment is valid
  – Analyze influence of variables quantitatively

• Data needs from CRA researchers
  – Test environmentally-relevant doses and stressor proportions
  – Ensure sufficient statistical power to detect effects
  – Publish raw data if possible, otherwise include variance estimates/standard errors/confidence intervals
  – Characterize chemical and nonchemical exposure ranges
Cumulative Exposure to Neurodevelopmental Stressors in Women of Reproductive Age: 2003–2004 NHANES

Amanda M. Evans*, Glenn E. Rice, Linda K. Teuschler, J. Michael Wright

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Why perform a Cumulative Risk Assessment: Differential Exposures and Effects

- Multi-chemical body burdens (Woodruff et al., 2011)

- Differential vulnerability to chemical stressors by non-chemical stressors:
  - Socioeconomic status (Nelson et al., 2012)
  - Gender (Cory-Slechta et al., 2004)
  - Psychological stress (Clougherty et al., 2007)
  - Lifestage (Host et al., 2008)
Cumulative Exposure Case Study: Neurodevelopmental Toxicity (NDT)

- Fetal neurodevelopment is a critical window of vulnerability to many stressors.
- Neurodevelopmental stressors
  - Chemical
    - Lead (Pb) (Lanphear et al., 2005)
    - Methyl mercury (MeHg) (Grandjean et al., 2012)
  - Non-chemical
    - Maternal stress (Bergman et al., 2010)
- Maternal stress modifies lead-induced NDT (Cory-Slechta et al., 2004)
Study Aims

1. Characterize cumulative exposure to chronic stress and neurodevelopmental toxicants, including Pb and MeHg

2. Identify potential maternal populations that may be at increased risk of NDT hazard
Quantifying Chronic Stress: Allostatic Load (AL)

- **Allostasis** is defined as “maintaining stability through change” (Sterling & Eyer, 1988)

- **Chronic stress** may result in physiological dysregulation (McEwen & Wingfield, 2003)
  - Physiological dysregulation **taxes the body** and has been measured using the concept of allostatic load (AL)

- AL has been operationalized as the **sum of “elevated” physiological parameters**
  - Elevated physiological parameters are **secondary mediators** to elevated cortisol in response to stress
Methods: Dataset

2003–2004 National Health and Nutrition Examination Surveys (NHANES) (all women, n = 5,152)

Inclusion Criteria:
- Reproductive age (15 to 44 years) (n = 3,331 excluded)
- Completed both questionnaire and physical examination (n = 64 excluded)
- Not pregnant (n = 347 excluded)
- Self-identified as Non-Hispanic White or Black, or Mexican American (n = 100 excluded)
- Measurements for all biomarkers/biometrics (n = 1,310 analytical sample)
  - Neurodevelopmental Toxicants
    - Blood Pb (µg/dL) and blood MeHg (µg/L)
  - 10 biomarkers/biometrics for AL
Methods: Allostatic Load

**AL is an indicator of chronic stress exposure**

- AL biomarkers were dichotomized as high or low based on clinical criteria (Bird et al., 2010)
- **AL score** = Sum of high-risk biomarkers
  - AL scores ≥3 ≈ high chronic stress exposure (Juster et al., 2010)
  - AL scores 1-2 ≈ intermediate chronic stress exposure
  - AL score = 0 ≈ low chronic stress exposure

### Allostatic Load Biomarkers by System

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Cut-point</th>
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<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Mean Systolic BP (mm Hg)</td>
<td>&gt;130</td>
</tr>
<tr>
<td>Mean Diastolic BP (mm Hg)</td>
<td>&gt;85</td>
</tr>
<tr>
<td>Homocysteine (umol/L)</td>
<td>&gt;15</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>&gt;25</td>
</tr>
<tr>
<td>HDL-Cholesterol (mg/dL)</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Glycohemoglobin (%)</td>
<td>&gt;6.5</td>
</tr>
<tr>
<td><strong>Immune</strong></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>&gt;1.0</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&lt;3.4</td>
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Methods: Hazard Measures

The Hazard Index (HI) is used here as an indicator of NDT

1. **Calculate Hazard quotients (HQs)**
   - Individual blood concentration (E) divided by metal-specific health reference value (HRV)
     - \( HRV_{\text{Pb}} = 1.76 \ \mu g/dL \) (Jedrychowski et al., 2009)
     - \( HRV_{\text{MeHg}} = 5.8 \ \mu g/L \) (USEPA, 2001)

\[
HQ = \frac{E}{HRV}
\]

2. **Calculate the HI: Sum HQs**

\[
HI-NDT = HQ_{\text{Pb}} + HQ_{\text{MeHg}}
\]

- HI-NDT > 1 \( \approx \) higher NDT hazard
- HI-NDT \( \leq 1 \) \( \approx \) lower NDT hazard

*Dose-addition is assumed for the HI calculation because Pb and MeHg have similar neurodevelopmental endpoints*
# Methods:
## Sociodemographic and Lifestyle Variables

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Head of Household highest educational attainment</th>
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<tbody>
<tr>
<td>• Non-Hispanic White (White)                                                  • Less than high school graduate</td>
<td></td>
</tr>
<tr>
<td>• Non-Hispanic Black (Black)                                                   • High School/GED or some college/AA degree</td>
<td></td>
</tr>
<tr>
<td>• Mexican American                                                            • College graduate or more</td>
<td></td>
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<table>
<thead>
<tr>
<th>Age (years)</th>
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<tbody>
<tr>
<td>• 15-19, 20-26, 27-36, 37-44</td>
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<tr>
<th>Income ($1,000)</th>
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<tr>
<td>• &lt;15, 15-55, &gt;55</td>
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</tbody>
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<tr>
<th>Poverty-to-income Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>• &lt;2 or ≥2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking status (serum cotinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Non-smoker (&lt;10 ng/mL)</td>
</tr>
<tr>
<td>• Smoker (≥10 ng/mL)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No or Yes</td>
</tr>
</tbody>
</table>
Methods: Data Analysis

The association between race/ethnicity and higher NDT hazard (HI >1) was examined using logistic regression

- Sampling weights were used to account for complex survey design and to produce unbiased, national estimates

- Covariates that changed the odds ratio (OR) between race/ethnicity and higher NDT hazard by ≥10% were included in the final model

- The final model was stratified by AL groups (0, 1–2, ≥3)
RESULTS
Population Characteristics

<table>
<thead>
<tr>
<th>More likely to have chronic stress (AL≥3)</th>
<th>More concern with NDT hazard (HI-NDT&gt;1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Blacks</td>
<td>• Blacks, Mexican Americans</td>
</tr>
<tr>
<td>• Women 20-44 years of age (compared with those 15-19 years of age)</td>
<td>• Women 20-44 years of age (compared with those 15-19 years of age)</td>
</tr>
<tr>
<td>• Lower socioeconomic status</td>
<td>• Lower socioeconomic status</td>
</tr>
<tr>
<td>• Smokers</td>
<td>• Smokers</td>
</tr>
</tbody>
</table>
| • No physical activity                                     | }
Percentage of population by NDT Hazard

- HQ-PB >1
  - All Women: 11
  - White: 9
  - Black: 14
  - Mexican Americans: 22

- HQ-MeHg >1
  - All Women: 22
  - White: 2
  - Black: 2
  - Mexican Americans: 1

- HI >1
  - All Women: 26
  - White: 32
  - Black: 36
  - Mexican Americans: 36

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Association between race/ethnicity and odds of having an HI >1 among women ages 15-44 years in NHANES 2003-04

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1.7 (1.0, 2.6)</td>
<td>1.7 (1.0, 2.6)</td>
</tr>
<tr>
<td>Black</td>
<td>2.0 (1.3, 3.0)</td>
<td>2.0 (1.3, 3.0)</td>
</tr>
<tr>
<td>Mexican American</td>
<td>2.2 (1.5, 3.4)</td>
<td>2.2 (1.5, 3.4)</td>
</tr>
<tr>
<td>White</td>
<td>1.4 (0.8, 2.5)</td>
<td>1.4 (0.8, 2.5)</td>
</tr>
<tr>
<td>Black</td>
<td>1.4 (0.8, 2.5)</td>
<td>1.4 (0.8, 2.5)</td>
</tr>
<tr>
<td>Mexican American</td>
<td>1.4 (0.8, 2.5)</td>
<td>1.4 (0.8, 2.5)</td>
</tr>
</tbody>
</table>

*Adjusted for country of birth, age, education, and smoking
Adjusted association between race/ethnicity and odds of having an elevated HI-NDT among non-pregnant reproductive-aged women in the 2003–2004 NHANES stratified by chronic stress

Possible effect measure modification of race/ethnicity and HI-NDT association by chronic stress

*Adjusted for age, head of household education, and smoking
Summary

- **Pb** was the main contributor to the HI-NDT
  - Mean HQ$_{Pb}$ **3-fold higher** than the mean HQ$_{MeHg}$ (0.6 vs. 0.2)

- Independent of country of birth, age, education, and smoking, **Blacks were more likely than Whites to have an elevated HI-NDT**

- Chronic stress modified the association between NDT hazard and race/ethnicity
Discussion: Limitations

- Use of exposures in non-pregnant women of reproductive age as surrogates of potential maternal/fetal exposures may not be representative of exposures during pregnancy.

- Other stressors that may be associated with neurodevelopmental outcomes were not included.

- Cross sectional data—One-time measurements performed on all stressors (AL biomarkers, Pb, MeHg).

- Used HI to examine higher joint Pb and MeHg exposures:
  - May not reflect underlying mode of action.
  - Uncertainty in using dose-addition for similar endpoint.
Conclusions

- Chronic stress, a non-chemical stressor, was found to modify the association between race/ethnicity and likelihood NDT hazard.

- This research highlights the importance of evaluating co-exposures (chemical and non-chemical) with a common endpoint.

- Results from these analyses could identify potentially susceptible populations for future epidemiological studies or be used by risk managers.
Thank you!

Questions . . .

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