RESPIRATORY EFFECTS OF LOW-LEVEL ARSENIC EXPOSURE IN DRINKING WATER

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Arsenic Exposure Overview

• Widespread metalloid toxicant
• Associated with cancer and respiratory effects at >100 ppb
• EPA standard 10 ppb

Respiratory Effects at High Concentrations

• In West Bengal, a 100 ppb increase in arsenic was associated with a 45.0 ml decrease in FEV1.
• In Taiwan, arsenic exposure has been associated with increased mortality from bronchitis.
• In Chile, arsenic exposure was associated with increased mortality from COPD among women and men aged 30-39 years, suggesting harmful effects of arsenic exposure in childhood.
• Also in Chile, children exposed to arsenic with dermatological manifestations had excessive rates of both chronic cough and bronchopulmonary disease.
Interdisciplinary Research on Respiratory Effects of Low-Level Arsenic Exposure

- EPA National Center For Environmental Research (NCER) Science to Achieve Results (STAR) Grant
- *In vitro* studies -- Cell Models to Study Mechanisms
- *In vivo* studies -- Animal Models to Evaluate Lung Biomarkers -- Proteomic Approach
- Human Populations -- Integrate Findings at Human Health Endpoint

Animal Models to Identify Protein Changes

- Mouse model
- Perform bronchiolar lavage
- Proteomic analysis

Protein (spot) changes include:
- Glutathione-S-transferase W-1 (GST W-1) (control 3)
- Phosphatase and tensin homolog (PTEN) (control 19)
- Alpha-1-antitrypsin (control 10)
- Receptor for advanced glycation end products (RAGE) (control 1 and 2)
Airway Remodeling as a Target

- Abnormal airway remodeling is an important step in the development of chronic lung disease.
- Matrix metalloproteinases (MMPs) play essential roles in lung remodeling.
- Tissue inhibitor of metalloproteinase 1 (TIMP-1) inhibits MMPs.
- Decreased receptor for advanced glycation end products (RAGE) may increase RAGE activation and MMP-9 production.
- AAT deficiency is a known risk factor for lung disease.

Ajo Study

- NIEHS Community-Based Prevention/Intervention Research (CBPIR) Grant
- In Ajo, AZ arsenic in tap water is elevated, averaging 20.3 ppb with a range of 10.8-27.6 ppb
- In Tucson arsenic in tap water averages 4.0 ppb with a range of 0.8-9.5 ppb
- Study questions:
  1) Does provision of bottled drinking water reduce urinary arsenic concentrations?
  2) Can we discover biomarkers of low-dose arsenic exposure?

**Ajo Study**

**Subjects**
- 35 households in Ajo
- 30 households in Tucson
- Only subjects ≥18 years old
- Same house for ≥3 years
- Drink untreated tap water
- No occupational arsenic exposure
- Non-smokers

**Sample collection**
- Tap water
- Urine
- Questionnaire
- Buccal swabs
- Induced sputum
- Toenails
Human Sputum Studies

MMP-9/TIMP-1

![Graph showing MMP-9/TIMP-1 regression model]

In MMP-9/TIMP-1 Regression Model

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Coefficient</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Town</td>
<td>0.178</td>
<td>0.673</td>
</tr>
<tr>
<td>Asthma</td>
<td>-0.151</td>
<td>0.696</td>
</tr>
<tr>
<td>Urinary As</td>
<td>0.031</td>
<td>0.005</td>
</tr>
<tr>
<td>MMA/(As³⁺ + As⁵⁺)</td>
<td>0.119</td>
<td>0.136</td>
</tr>
</tbody>
</table>

* Using the natural logarithm and excluding sRAGE outliers

Human Sputum Studies

TIMP-1

![Graph showing TIMP-1 relationship]

Human Sputum Studies

sRAGE

![Graph showing sRAGE relationship]

* Using the natural logarithm and excluding sRAGE outliers
Regression Results for sRAGE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N</th>
<th>R²</th>
<th>Variables</th>
<th>Coef.</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log sRAGE</td>
<td>47</td>
<td>0.2095</td>
<td>Town</td>
<td>0.011</td>
<td>0.973</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetes</td>
<td>0.761</td>
<td>0.079</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BMI</td>
<td>0.091</td>
<td>0.002</td>
</tr>
<tr>
<td>Urinary As</td>
<td></td>
<td></td>
<td></td>
<td>-0.021</td>
<td>0.016</td>
</tr>
</tbody>
</table>

* Excludes outliers

AAT/Total Protein regression model*

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Town</td>
<td>-0.1008</td>
<td>0.753</td>
</tr>
<tr>
<td>Total urinary Inorganic As</td>
<td>-0.0193</td>
<td>0.031</td>
</tr>
<tr>
<td>MMA/(As³⁺ + As⁵⁺)</td>
<td>-0.1436</td>
<td>0.020</td>
</tr>
<tr>
<td>Toenail selenium</td>
<td>0.2761</td>
<td>0.005</td>
</tr>
<tr>
<td>Constant</td>
<td>0.1537</td>
<td>0.794</td>
</tr>
</tbody>
</table>

* N = 51, adjusted R² = 0.2455

Postulated Mechanisms of Toxicity

Study Aims: 1=Aim 1 (In-vitro); 2=Aim 2 (In-vivo); 3=Aim 3 (Human)

Summary

- At high concentrations arsenic causes respiratory disease.
- We have found evidence of delayed wound healing at concentrations as low as 30 ppb in cellular models.
- At low concentrations, arsenic causes alterations in lung protein expression in mice.
- In humans, low-level arsenic exposure (at 20 ppb and below) causes changes in lung proteins associated with development of lung disease.
- Lung injury may exacerbate this process.
Next Steps

• NIEHS Grant Application
• Determine the mechanisms of arsenic-induced alterations in epithelial permeability and wound repair.
• Determine the extent of lung remodeling and physiological changes associated with low-level arsenic exposure.
• Determine the relation between arsenic-induced alterations in pulmonary biomarkers and clinical findings.

Questions?