Arsenic as a Human Health Hazard: Highlights of Recent Epidemiologic Findings

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Arsenic in Groundwater: An International Problem

- Taiwan
- China
- Chile
- Argentina
- Mexico
- United States

- India
- Bangladesh
- Nepal
- Vietnam
- Cambodia
- Mongolia
Arsenic metabolism: detoxification(?) by mono- and dimethylation.

**Arsenate**
\[ \text{As}^V - \text{O} - \text{H} \]
\[ \text{O} = \text{As}^V - \text{OH} \]
\[ \text{O}^- \]

**Arsenite**
\[ \text{HO} - \text{As}^{III} - \text{OH} \]

\[ \text{GSH} \quad \text{GSSG} \]

**Dimethylarsonous acid (MMA^{III})**
\[ \text{O} = \text{As}^V - \text{CH}_3 \]
\[ \text{OH} \]

**Dimethylarsinic acid (DMA^{V})**
\[ \text{CH}_3 \]
\[ \text{As}^{III} - \text{CH}_3 \]
\[ \text{OH} \]

\[ \text{GSSG} \quad \text{GSH} \]

**Methy larsonic acid (MMA^{V})**
\[ \text{CH}_3 \]
\[ \text{As}^{III} - \text{CH}_3 \]
\[ \text{OH} \]

\[ \text{GSSG} \quad \text{GSH} \]

**Methy larsonous acid (MMA^{III})**
\[ \text{As}^{III} - \text{CH}_3 \]
\[ \text{OH} \]

\[ \text{SAH} \quad \text{SAM} \]
### Arsenic Metabolites in Human Urine

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Toxicity (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{As}^{+3}$ Arsenite</td>
<td>8</td>
</tr>
<tr>
<td>$\text{As}^{+5}$ Arsenate</td>
<td>22</td>
</tr>
</tbody>
</table>

#### LD$_{50}$ (Toxicity)

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Toxicity (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMA$^{+3}$ Monomethylarsonous Acid</td>
<td>2</td>
</tr>
<tr>
<td>MMA$^{+5}$ Monomethylarsonic Acid</td>
<td>916</td>
</tr>
<tr>
<td>DMA$^{+5}$ Dimethylarsinic Acid</td>
<td>648</td>
</tr>
</tbody>
</table>

#### Mammalian Metabolites

- MMA$^{+3}$ Monomethylarsonous Acid: 2 mg/kg
- MMA$^{+5}$ Monomethylarsonic Acid: 916 mg/kg
- DMA$^{+5}$ Dimethylarsinic Acid: 648 mg/kg

#### Fish Metabolites

- AsB Arsenobetaine: ~10,000 mg/kg
- AsC Arsenocholine

*Hughes, M.F. Toxicology Letters, 2002*
Arsenic Metabolites in Human Urine

LD$_{50}$ (Toxicity)

- As$^{+3}$ Arsenite 8 mg/kg
- As$^{+5}$ Arsenate 22 mg/kg

Mammalian Metabolites
- MMA$^{+3}$ Monomethylarsonous Acid 2 mg/kg
- MMA$^{+5}$ Monomethylarsonic Acid 916 mg/kg
- DMA$^{+5}$ Dimethylarsinic Acid 648 mg/kg

Fish Metabolites
- AsB Arsenobetaine ~10,000 mg/kg
- AsC Arsenocholine

Hughes, M.F. Toxicology Letters, 2002
Recent Findings from Taiwan

- People with a relatively high proportion of MMA in urine had ~5-fold higher risk for skin and bladder cancer (Yu et al, 2000).

- There is a dose-response relationship between the ratio of MMA/DMA in urine and the risk for skin and bladder cancer (Chen et al, 2003).

- Those with very heavy As exposure (> 20 mg/L-yrs) had a 3-fold higher risk for carotid atherosclerosis (Wang et al, 2002), as well EKG findings of a prolongation of the QT interval (Wang et al, 2003).
As in the United States

Arsenic concentrations in at least 25% of samples exceed:
- 50 µg/L
- 10
- 5
- 3
- 1

Insufficient data

USGS
Recent Findings from New Hampshire

• Among smokers, an elevated odds ratio for bladder cancer was observed for those in the upper quartile of As exposure (toenail As) (Karagas et al, 2004).

• Arsenic exposure is associated with decreased DNA repair *in vitro* and in people residing in New Hampshire and Mexico (Andrew et al, 2006).

• Bladder cancer mortality, long known to be particularly high in northern New England, is associated with the use of private wells (Ayotte et al, 2006).
Recent Findings from Chile

For those born in Antofagasta, during the high arsenic exposure period (1958-1971) with probable exposure *in utero* and early childhood, the standardized mortality ratios were 6.1 for lung cancer (CI 3.5-9.9, \( p<0.001 \)) and 46.2 for bronchiectasis (CI 21.1-87.7, \( p<0.001 \)) (Smith et al, 2006).
Transplacental carcinogenicity of inorganic arsenic in the drinking water: induction of hepatic, ovarian, pulmonary, and adrenal tumors in mice

Michael P. Waalkes, Jerrold M. Ward, Jie Liu, and Bhalchandra A. Diwan

Inorganic Carcinogenesis Section, Laboratory of Comparative Carcinogenesis, National Cancer Institute at the National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709, USA
Veterinary and Tumor Pathology Section, Office of Laboratory Animal Science, National Cancer Institute-Frederick, Frederick, MD 21702, USA
Intramural Research Support Program, Science Applications International Corp.-Frederick, National Cancer Institute at Frederick, Frederick, MD 21702, USA

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ArSENic Contamination in Bangladesh

Map showing the percentage of tubewell contamination in Bangladesh.
Dose-Response Relationship Between Water As Concentration and Risk for Skin Lesions

Ahsan et al, AJE, 2006
Influence of Sun Exposure on Effect of Arsenic on Risk of Skin Lesion in Men

Adjusted Odds Ratio

Chen et al, Epidemiol, 2006
Influence of Body Mass Index on Effect of Arsenic on Risk of Skin Lesions
Other Recent Findings from Bangladesh

• Blood folate concentrations are associated with the ability to methylate arsenic. Those who are folate deficient are poor methylators and are at increased risk for arsenic-induced skin lesions (Gamble et al, EHP, 2005).

• Folate supplementation decreases the proportion of MMA and inorganic As in urine, and increases the proportion of DMA (Gamble et al, AJCN, 2006).

• People with a higher proportion of MMA in their urine are at increased risk for skin lesions (Ahsan et al, in review).
Blood Selenium Level and Risk of Skin Lesions

<table>
<thead>
<tr>
<th>Blood Selenium Level (µg/L)</th>
<th>Total N</th>
<th>Adjusted Hazard Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 131.8</td>
<td>222</td>
<td>1.0</td>
</tr>
<tr>
<td>131.9-144.3</td>
<td>222</td>
<td>0.71 (0.42-1.21)</td>
</tr>
<tr>
<td>144.5-156.3</td>
<td>221</td>
<td>0.54 (0.32-0.91)</td>
</tr>
<tr>
<td>156.4-169.8</td>
<td>222</td>
<td>0.54 (0.31-0.93)</td>
</tr>
<tr>
<td>169.9-262.6</td>
<td>221</td>
<td>0.53 (0.31-0.90)</td>
</tr>
</tbody>
</table>

*RRs were controlled for age, gender, BMI, and smoking status.

Chen et al, in review
## Blood Arsenic and Risk of Skin Lesions

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<thead>
<tr>
<th>Blood Arsenic Level (µg/L)</th>
<th>Total N</th>
<th>Adjusted Hazard Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5.8</td>
<td>222</td>
<td>1.0</td>
</tr>
<tr>
<td>5.8-7.9</td>
<td>225</td>
<td>1.24 (0.64-2.38)</td>
</tr>
<tr>
<td>8.0-10.9</td>
<td>218</td>
<td>1.94 (1.02-3.69)</td>
</tr>
<tr>
<td>11-15.9</td>
<td>221</td>
<td>2.37 (1.26-4.49)</td>
</tr>
<tr>
<td>16.0-63.9</td>
<td>222</td>
<td>3.71 (1.94-7.09)</td>
</tr>
</tbody>
</table>

*RRs were controlled for age, gender, BMI, and smoking status.

Hall et al, Toxicol, 2006
A Cross-Sectional Study of 10 year-old Children Exposed to a Wide Range of Arsenic Concentration in Drinking Water: The Relationship Between Arsenic and Children Intelligence
Relationship Between Water Arsenic Concentrations and Intellectual Function