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Topics included: Air Quality, Pesticides, Natural Disasters, BPA, Mold, Lead, Mercury
Old Poison, New Findings: Arsenic’s effect on maternal and child health

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This material was supported by the American College of Medical Toxicology (ACMT) and funded (in part) by the cooperative agreement FAIN: U61TS000238-02 from the Agency for Toxic Substances and Disease Registry (ATSDR).

Acknowledgement: The U.S. Environmental Protection Agency (EPA) supports the PEHSU by providing partial funding to ATSDR under Inter-Agency Agreement number DW-75-95877701. Neither EPA nor ATSDR endorse the purchase of any commercial products or services mentioned in PEHSU publications.

Dr Molly Kile is an Associated Professor at Oregon State University. She has been supported by funding from the US National Institutes of Environmental Health Sciences for studies investigating the health effects associated with chronic arsenic exposure (R01 ES015533, K01 ES017800, P30 ES000210, P30 ES000002, P42 ES016454, and R01 ES023441).
Learning Objectives

• Describe how people can be exposed to arsenic

• Evaluate the epidemiological evidence linking in utero and early life exposure to adverse pregnancy outcomes and children’s health

• Recommend ways to reduce exposure to arsenic
What is arsenic?

- Arsenic is a naturally occurring element

- Exists in different chemical forms and in different valence states
  - Inorganic arsenic forms
    - Arsenite ($\text{As}^3$)
    - Arsenate ($\text{As}^5$)
  - Organic arsenic forms
    - Arsphenamine \([\text{C}_{12}\text{Cl}_2\text{H}_{14}\text{As}_2\text{N}_2\text{O}_2(\text{H}_2\text{O})_2}\]
    - Cacodyl \([\text{As(CH}_3)_2]\]
    - Arsenobetaine \((\text{C}_5\text{H}_{11}\text{AsO}_2)\)
    - Arsenocholine \((\text{C}_5\text{H}_{14}\text{AsO})\)
Old poison and old medical reports

- Case studies and epidemiological studies describing risk of Fowler’s solution
- Increased risk of:
  - Skin cancer (Hutchinson, 1887)
  - Lung cancer (Robson et al, 1963)
  - Angiosarcoma (Lander et al, 1979)
  - Bladder cancer (Cuzick et al, 1992)

Fowler’s Solution
1% Potassium arsenite
General tonic used until 1936

Image from: Toxipedia
Epidemic of neuropathy and skin ailments reported in beer drinkers in England (1900-1901)

“Modern” brewing sugar was made using impure sulfuric acid

Average arsenic concentration in Manchester beer was $1/9^{th}$ grain per gallon ($\approx 1,800 \mu g/L$)
Old poison and newer mass poisonings

British Geological Survey (2001)
Chronic high exposure and human health

- Known human carcinogen
  - Lung
  - Bladder
  - Kidney
  - Liver
- Skin lesions
- Peripheral neuropathy
- Cardiovascular disease
- Type 2 diabetes
Sources of Exposure

- Coal combustion
- Smelting of metal ores
- Soil and dust
  - Insecticides
  - Natural ores
- CCA-preserved wood
- Specialty glass manufacturers
- Semiconductors
- Poultry waste
- Herbal remedies
- Food
- Water
Distribution of arsenic in US soils
Distribution of arsenic in U.S. groundwater

Arsenic concentration in micrograms per liter
- > 50
- >10 to ≤50
- >5 to ≤10
- >3 to ≤5
- ≤3

EXPLANATION
Arsenic concentration, in micrograms per liter

USEPA Arsenic drinking water standard is 10 micrograms per liter
Arsenic levels in common food and water

- **Rice, Rice Products**: 3.5-6.7 µg per cup
- **Meat**: Beef: 0.1 µg per half pound
- **Cooked Spinach**: 1.1 µg per cup
- **Grape Juice**: 2.3 µg per cup
- **Shrimp**: 0.4 µg per half pound
- **Fish**: Has high amounts of organic arsenic that are not as risky to human health as inorganic arsenic.

**Arsenic in water**
- **Well, Spring, Natural Water**
  - Concentration can reach 100-200 ppb (parts per billion) = 200-400 µg per 2 liters of water.

**Public Water**
- Typical concentration: 2-4 ppb = 4-8 µg per 2 liters of water.

**Note**: 10 ppb is the maximum concentration allowed, or 20 µg per 2 liters of water.

Sources: “A Market Basket Survey of Inorganic Arsenic in Food,” Food and Chemical Toxicology 37 (1999), by R.A. Schoof, et. al.
Age- and creatinine-adjusted ln-transformed total urinary arsenic comparing tap water (μg/d) and rice consumption (dry g/d)

Consumption of 0.56 cup/d of cooked rice was comparable to drinking 1 L/d of 10 μg As/L water

Arsenic Exposure in U.S.

Total Urinary Arsenic (not counting seafood)
NHANES 2010-2011
2855 individuals
~90% of ingested inorganic arsenic (arsenate and arsenite) absorbed in GI Tract

Arsenate is reduced in bloodstream

Arsenite

Glutathione S-transferase

Arsenite is methylated in the liver

Monomethylarsonic acid (MMA)

Dimethylarsinic acid (DMA)

10-30% Inorganic Arsenic

10-20% MMA

60-70% DMA

Arsenic metabolites excreted in urine

Arsenite binds to sulfhydryl groups

Germinal Keratin Cells

Inorganic arsenic excreted in hair and nail
Considerations when using biomarkers

- **Blood**
  - Half-life is a few hours
  - Total arsenic will reflect all arsenic species including non-toxic exposures from seafood

- **Urine**
  - Half-life is approximately 3 days
  - Total arsenic will reflect all arsenic species including non-toxic exposures from seafood
  - Monitored by NHANES which provides opportunity for comparison

To avoid mistaking seafood consumption for exposure to inorganic arsenic, determine if person has eaten fish or crustaceans in last 3 days or use analytical instrumentation that measures arsenic speciation.
Considerations when using biomarkers

- **Toenail and Hair**
  - Reflects historical exposures
  - Half-life is dependent on growth rate which creates a temporal delay between exposure and appearance at distal end of matrix

**Hair**: 1.25 cm/month  
**Toenail**: 3 mm/month
• Arsenic crosses the placenta

• Maternal and fetal blood arsenic concentrations similar (Concha et al, 1998)

• High levels of arsenic were related to adverse fetal outcomes (e.g. spontaneous abortion, stillbirth, neonatal death)
Establishing prospective birth cohorts

- Prospective birth cohorts established around the world to examine effects of chronic low dose arsenic exposure on maternal-child health
  - Repeated exposure measurements at critical windows of development
  - Health outcomes at different ages
  - Collect information on confounders
  - Strongest form of epidemiological evidence
Population living near abandoned mine site in U.S. \((n=532)\)

Maternal arsenic exposure measured in blood and hair

Blood glucose (GTT) measured between 24-28 weeks gestation

Women with the highest blood arsenic level had 2.8-fold higher odds of impaired GTT after controlling for other risk factors

Ettinger et al, Environmental Health Perspectives, 2009
Population living in New Hampshire using domestic wells \((n=512)\)

Maternal arsenic exposure measured in urinary arsenic at 24-28 weeks gestation

Repeated blood pressure measurements throughout pregnancy

Every 5 ug/L increase in urinary arsenic was associated with a 0.15 mmHg increase in systolic BP per month and a 0.14 mmHg increase in pulse pressure per month

Farzan et al, Environmental Health Perspectives, 2015
Population in Bangladesh using private wells ($n = 1,458$)

Maternal arsenic exposure measured in drinking water at <16 weeks gestational age

Repeated measures of maternal symptoms (nausea/vomiting, abdominal cramping)

Women with the highest arsenic exposure had a 1.84-fold increase in nausea/vomiting and 1.74-fold increase in abdominal cramping during pregnancy

Kile et al, Environmental Health 2014
• Every unit increase in natural log water arsenic was indirectly associated with decreased birth weight ($\beta = -19.17$ grams, 95% CI: -24.64, -13.69 grams) after adjusting for other risk factors that could contribute to birth weight

Kile et al, Epidemiology 2016
## Relative risk of diagnosed infection in first 4 months of life per ln maternal urinary arsenic (n=214)

<table>
<thead>
<tr>
<th>Infections</th>
<th>At least one infection</th>
<th>Lasting 2 or more days</th>
<th>With a physician visit</th>
<th>Treated with prescription medication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory tract infections (RTI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Any upper RTI</td>
<td>1.1 (0.8, 1.6)</td>
<td>1.2 (0.9, 1.7)</td>
<td>1.1 (0.8, 1.6)</td>
<td>1.6 (1.0, 2.5)</td>
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<tr>
<td></td>
<td>133</td>
<td>111</td>
<td>53</td>
<td>28</td>
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<tr>
<td>Cold, runny or stuffed nose</td>
<td>1.0 (0.8, 1.4)</td>
<td>1.1 (0.8, 1.5)</td>
<td>1.0 (0.7, 1.4)</td>
<td>2.3 (1.0, 5.2)</td>
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<tr>
<td></td>
<td>126</td>
<td>103</td>
<td>39</td>
<td>9</td>
</tr>
<tr>
<td>Any lower RTI</td>
<td>1.4 (0.7, 3.1)</td>
<td>1.4 (0.7, 3.1)</td>
<td>1.4 (0.7, 3.1)</td>
<td>3.3 (1.2, 9.0)</td>
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<tr>
<td></td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>7</td>
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<tr>
<td><strong>Acute symptoms, conditions, illnesses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>1.1 (0.8, 1.6)</td>
<td>1.3 (0.9, 1.9)</td>
<td>1.3 (0.8, 2.0)</td>
<td>4.0 (1.0, 15.9)</td>
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<td></td>
<td>74</td>
<td>57</td>
<td>27</td>
<td>5</td>
</tr>
</tbody>
</table>

Epigenetics – possible mechanism

- Environmental exposures modify epigenetic mechanisms
  - DNA methylation
  - Histone
  - Chromatin
- Modifies gene expression without altering DNA sequence
- Epigenome experiences greatest plasticity during fetal development
- Proposed mechanism for fetal origins of adult disease
Mice exposed to arsenic in utero had increased hepatocellular carcinoma incidence and multiplicity in adulthood (Waalkes et al., 2003)


In vivo evidence that prenatal exposure to arsenic alters epigenetic mechanisms and chronic disease later in life (Tokar et al, 2012; Tokar et al 2011; Tokar et al 2010; Waalkes et al 2007)
In Chile, adults who were exposed to arsenic from drinking water in utero or during their early life exposure had increased risk of:

- Lung cancer (Marshall et al, 2007; Smith et al., 2006)
- Liver cancer (Liaw et al., 2008)
- Kidney cancer (Yuan et al, 2010)
- Decreased lung function (Dauphine et al., 2011)

In Japan, infants exposed to arsenic-contaminated milk powder had increased rates of skin, liver, pancreatic cancer and leukemia (Yorifuji et al, 2010)
In utero arsenic exposure and epigenetic modification LINE-1 methylation in cord blood and maternal blood (N=144)

(A) umbilical cord leukocytes adjusted for average maternal BMI (21.0) and prematurity (≥ 37 weeks gestation)
(B) maternal leukocytes adjusted for average maternal BMI (21.0).

Kile et al (2012) Environmental Health Perspectives
Structural equation model suggests that arsenic exposure is associated with increased placental expression of AQP9 followed by a decreased expression of ENPP2 which results in lower infant birthweight.

Fei et al, Environmental Health, 2013.
How to reduce exposures

- If your household uses a private well it is important to have it tested for arsenic
- Eat a well balanced diet with a variety of grains (quinoa, barley, wheat, etc)
- Limit consumption of rice-milk or processed foods containing rice or rice sweeteners
- Boil rice with excess water and drain it before service which has been shown to reduce arsenic exposure
- Introduce your child to a variety of foods during weaning and teething and limit consumption of rice products and apple juice
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