Global environmental epidemiology research in action: recent arsenic findings

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and

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Wellington, New Zealand
July 18, 2013
### Periodic Table

**Atomic Properties of the Elements**

<table>
<thead>
<tr>
<th>Group</th>
<th>Period</th>
<th>Symbol</th>
<th>Name</th>
<th>Atomic Number</th>
<th>Atomic Weight</th>
<th>Ground-state Configuration</th>
<th>Ionization Energy (eV)</th>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>H</td>
<td>Hydrogen</td>
<td>1</td>
<td>1.00794</td>
<td>1s0</td>
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<td>2</td>
<td>2</td>
<td>Li</td>
<td>Lithium</td>
<td>3</td>
<td>6.94102</td>
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<td>3</td>
<td>3</td>
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<td>Sodium</td>
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<td>5</td>
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<td>Phosphorus</td>
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<td>8</td>
<td>8</td>
<td>S</td>
<td>Sulfur</td>
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<td>32.064</td>
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<tr>
<td>9</td>
<td>9</td>
<td>Cl</td>
<td>Chlorine</td>
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<td>Argon</td>
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<td>21.20</td>
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</tbody>
</table>

**Frequently used fundamental physical constants**

- Speed of light in vacuum, c = 299,792,458 m/s
- Planck constant, h = 6.626 × 10^-34 Js
- Elementary charge, e = 1.602 × 10^-19 C
- Proton mass, m_p = 1.6726 × 10^-27 kg
- Fine-structure constant, α = 1/137.036
- Rydberg constant, R = 1.09737 × 10^7 m^-1

**Notes**

- For a description of the data, visit physics.nist.gov/data
- NIST SP 966 (September 2003)
The Berkeley Arsenic Health Effects Research Group (ASRG)

Arsenic Research Group
Not
Allan Smith’s Research Group

Associate Director: Craig Steinmaus
The Berkeley Arsenic Health Effects Research Program

Our focus is on highly exposed populations, with a range of exposure usually including some with more than 500 ug/L in water, in order to have good statistical power to detect real effects, with scientific plausibility.

Populations in which we conduct studies include:

- **USA: California and Nevada**
- **Argentina (Cordoba)**
- **Chile (Northern)**
- **India (West Bengal)**
- **Bangladesh (Matlab)**
What does arsenic in water cause?

When I was asked by the State of California in 1989 to assess the risks from arsenic in drinking water the only established outcomes were skin lesions and skin cancer.
Lung cancer and arsenic in Taiwan
adapted from CJ Chen et al 1988

- Comparison population, all of Taiwan
- vertical axis: age adjusted rate ratios (relative risk)
Bias  You got the wrong answer
So, look before you leap

And in epidemiology, to stay alive,

consider bias before you squeak
It is surprising that arsenic in drinking water would have major effects in the lungs.
Known causes of lung cancer involve inhalation

- smoking
- passive smoking
- asbestos
- radon
- silica
- chromium

- diesel exhaust
- coke oven PAHs
- bischloromethyl ether
- nickel
- arsenic
Lung cancer and arsenic in Taiwan
adapted from CJ Chen et al 1988

- Comparison population, all of Taiwan
- Vertical axis: age adjusted rate ratios (relative risk)
Bladder cancer mortality associated with arsenic in drinking water in Argentina

Claudia Hopenhayn, Mary Lou Biggs, Analia Fuchs, Remo Bergoglio, Enrique E. Tello, Hugo Nicolli, Smith AH

Epidemiology 1996; 7: 117-124
Unos de los Primeros Estudios y Publicaciones del Arsénico en el Agua en Córdoba

CHILE

Region II

Region V
### Lung Cancer Mortality Region II Chile, 1989-1993

<table>
<thead>
<tr>
<th>Age Group</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
<th>SMR</th>
<th>p value</th>
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<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Observed</td>
<td>5</td>
<td>23</td>
<td>21</td>
<td>41</td>
<td>47</td>
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<tr>
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<td>8.0</td>
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<tr>
<td>O/E</td>
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<td>7.7</td>
<td>2.6</td>
<td>2.6</td>
<td>3.5</td>
<td>3.1</td>
<td>p&lt;0.001</td>
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<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed</td>
<td>14</td>
<td>48</td>
<td>142</td>
<td>177</td>
<td>129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expected</td>
<td>1.2</td>
<td>8.1</td>
<td>28.5</td>
<td>61.8</td>
<td>32.1</td>
<td></td>
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<tr>
<td>O/E</td>
<td>11.7</td>
<td>5.9</td>
<td>4.9</td>
<td>2.9</td>
<td>4.0</td>
<td>3.8</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>


Mario Goycolea
Lung Cancer and Inhalation of Arsenic

Lung cancer relative risk estimates from a case-contol study in Chile (Ferreccio et al, *Epidemiology*, 2000)
Increased lung cancer risks are similar whether arsenic is ingested or inhaled.

IARC classification, 2002

Arsenic in drinking-water was evaluated as carcinogenic to humans (Group 1) on the basis of sufficient evidence for an increased risk for cancer of the urinary bladder, lung and skin.
Cancer risks from arsenic in drinking water

At the current standard of 50 ug/L, the lifetime risk of dying from cancer from drinking 1 L/day of water could be as high as 13 per 1000 persons.

Environmental Health Perspectives 97:259-267, 1992

Martyn Smith
The estimated cancer risk at the drinking water standard of 50 µg/L for arsenic is more than 100 times greater than that for any other drinking water contaminant.

Cancer risk from contaminants in drinking water other than arsenic

Per 100,000

Top of the list:
Ethylene dibromide
Cancer risks from arsenic at the old drinking water standard were >100 times higher than the next highest risk contaminant.
Cancer risks from arsenic in drinking water

Lung cancer and smoking

- 10 ug/L  1 in 500 die
- 50 ug/L  1 in 100 die  married to a smoker
- 500 ug/L 1 in 10  die  active smoker
- 5000 ug/L all die

And arsenic in water looks good, does not smell and has no taste. So the risks are unbelievable
Arsenic in drinking water results in the highest known toxic substance disease risks and mortality from any environmental exposure.
End Stage Lung Disease

Obstruction, Infection, Hemoptysis, Bronchiectasis
Non-malignant pulmonary effects

We believe that the first evidence of arsenic in drinking water causing non-malignant pulmonary effects came from Antofagasta in Chile, when river water with a high concentration (about 850 µg/L) of naturally occurring arsenic was first diverted to the city for use as municipal water supply in 1958.

Beginning in 1962, patients (including children) with arsenic-caused skin lesions and bronchopulmonary effects, including chronic cough and bronchiectasis, were identified. (Borgono et al, 1977)
High resolution computed tomography (HRCT) with readings in India and the United States without knowing who had arsenic skin lesions.
Study design, x-ray (HRCT) study in West Bengal, India

7600 surveyed

108 selected with skin lesions and high arsenic exposure
- 27 had chronic cough more than 2 years
- 18 had evidence of bronchiectasis

150 selected with no skin lesions and low arsenic exposure
- 11 had chronic cough More than 2 years
- 3 had evidence of bronchiectasis

Assessed in this study

Referred for HRCT

10-fold increased prevalence of bronchiectasis  OR=10.1,  p<0.01
Epidemiology 2005
Lung function findings of reduced FEV1 adjusted for age and height

- For all men combined $P=0.007$
- Among men in this population, arsenic-caused skin lesions were associated with a greater FEV1 reduction (-256ml) than from smoking (-156ml)

Cardiovascular disease

The first evidence of a link between cardiovascular disease and arsenic in drinking water came in 1980 from Antofagasta, Chile, with a report of 17 deaths from myocardial infarction in people under the age of 40. (Zaldívar, 1980).

Later, a comprehensive body of evidence from a series of studies in Taiwan starting in 1988 found that arsenic in water was associated with increased mortality from cardiovascular disease.

In 2007, cardiac effects including QT prolongation were shown to be associated with arsenic in drinking water in China.
Arsenic water concentrations for the city of Antofagasta (population 125,000 in 1970)

- Highly contaminated river water used for drinking
- Arsenic treatment plant installed
- Treatment plant improved

Year
- 1950-57
- 1958-70
- 1971-80
- 1981-90
- 1991-2000
Excess deaths among men in Region II of Chile from acute MI, lung cancer and bladder cancer.

At the peak more than 1 in 10 of all deaths were due to arsenic
Effect of early life exposure

In *utero*

and in the first few years of childhood
Arsenic water concentrations for the city of Antofagasta (population 125,000 in 1970)

- Highly contaminated river water used for drinking
- Arsenic treatment plant installed
- Treatment plant improved

Year:
- 1950-57
- 1958-70
- 1971-80
- 1981-90
- 1991-2000
Lung cancer mortality in men according to exposure in childhood

(SMR = standardized mortality ratio = observed/expected deaths)
Lung cancer mortality in men according to exposure in childhood
(SMR = standardized mortality ratio = observed/expected deaths)

- Age at death: 30 – 34

- SMR
  - rest Chile
  - exposed
  - p < 0.001
Mortality (SMRs) from Chronic Obstructive Pulmonary Disease, age 30-49, for those born in the very high exposure period (in utero exposure) or just before (child).

\[ p < 0.001 \ \text{except other COPD} \quad p = 0.004 \]
Ecologic study of mortality of young adults aged 30-49 following exposure to high concentrations of arsenic in drinking water in early life

(Environmental Health Perspectives, November 2012)
In 1996 I was asked by WHO to investigate the newly discovered arsenic in drinking water problem in Bangladesh.


No. No! Professor Smith. We will not declare it a public health emergency. It might alarm the people.
Studies in other countries where the population has had long-term exposure to arsenic in groundwater indicate that **1 in 10 people who drink water containing 500 mg of arsenic per litre may ultimately die** from cancers caused by arsenic, including lung, bladder and skin cancers.

The rapid allocation of funding and prompt expansion of current interventions to address this contamination should be facilitated.

It was a public health emergency

No. No! Professor Smith. We will not declare it a public health emergency. It might alarm the people.
Relative Risk of Mortality from **all nonaccidental deaths** in a Bangladesh study (from Sohel N et al, Epidemiology, 2009)
Figure 6: Multivariate adjusted Hazard Ratios for all-cause mortality in a Bangladesh study (from Argos M et al, Lancet, 2010)
Project Well

Clean drinking water for West Bengal

Photography by Rudi Dundas and Chris Majors
The water crisis is not just about scarcity. India has a lot of water, but so much of it we cannot drink...
Project Well has developed an innovative system using PVC pipes to bore up to 27 feet into the earth.
80% of all Project Well funds go directly to the villages and the rest goes to our local partner staff.
$1000 is the cost of a bore-dugwell that will provide drinking water for more than 100 people…
**Intervention program in West Bengal**  
**Director: Meera HiraSmith**

- Modern design dugwell program to provide arsenic free water in West Bengal
- Funded by private donors
- for more information
  http://www.projectwellusa.org
First findings concerning arsenic and drinking water and child intellectual function were obtained by Thailand investigators.

Siripitayakunkit U. Association between chronic arsenic exposure and schoolchildren's growth and ability at Ronpiboon District, Nakorn Si Thammarat Province. abstract. Epidemiology 8:S69, 1997; and also Proceedings of the 3rd International Conference on Arsenic Exposure and Health Effects, San Diego, 1998

Because of the Thailand findings, in 2000 we were asked by UNICEF to conduct studies of intellectual function in children in West Bengal, India, who were exposed to arsenic in drinking water.


Distribution of Children’s Arsenic Exposure (ug/L) In Utero

Number of Subjects (total=571)

Arsenic Categories

- 0-9
- 10-99
- 100-299
- 300-499
- 500-699
- 700-899
- 900-1099
- 1100+

The graph shows the distribution of children's arsenic exposure in utero, categorized by levels of arsenic exposure in micrograms per liter (ug/L). The highest number of subjects (approximately 280) are in the 0-9 category, indicating the most prevalent exposure level. The number of subjects decreases as the arsenic category increases, with fewer subjects in categories such as 100-299, 500-699, and above 900 ug/L.
Chronic respiratory symptoms in children following in utero and early life exposure to arsenic in drinking water in Bangladesh

Allan H Smith¹, Mohammad Yunus², Al Fazal Khan², Ayse Ercumen¹, Yan Yuan¹, Meera Hira Smith¹, Jane Liaw¹, John Balmes¹,³, Ondine von Ehrenstein¹,⁴, Rubhana Raqib², David Kalman⁵, Dewan S Alam², Kim Streatfield² and Craig Steinmaus¹,⁶

Respiratory Symptoms for Which Adjusted* Odds Ratios for Highly Exposed Compared with Never Exposed In Utero are Greater Than 2

* Adjusted for age, gender, mother's education, father's education, father's smoking status and rooms in the house
Case-control Study of Arsenic in Drinking Water and Kidney Cancer in Uniquely Exposed Northern Chile

122 kidney cancer cases and 640 population-based controls

Catterina Ferreccio, Allan Smith … Craig Steinmaus
Am J Epidemiol on- line June 2013
Cases were ascertained from all pathologists and radiologists in the study area, and included people who: 1. had primary kidney or ureter cancer diagnosed between October 2007 and December 2010.

Controls without cancer were randomly selected from the Chile Electoral Registry for the study area, frequency matched by gender and five-year age group.
Renal pelvis plus ureter cancer odds ratios with increasing arsenic concentrations up to OR=19.3 (95% CI 2.4-154)

\[ p \text{ for trend} = 0.006 \]
Although the IARC has concluded that there is sufficient evidence that arsenic in drinking water causes lung, bladder, and skin cancer, a similar determination has not been made for kidney cancer since “no studies have reported dose-response relationships on the basis of individual exposure data.”

With these new findings, including evidence of dose-response, we believe there is now sufficient evidence in humans that drinking-water arsenic causes transitional cell renal pelvis and ureter cancer.
Arsenic, Tobacco Smoke, and Occupation: Associations of Multiple Agents with Lung and Bladder Cancer Risks

Catterina Ferreccio, Yan Yuan, Jacqueline Calle, Hugo Benítez, Roxana L Parra, Allan H. Smith, Jane Liaw, Craig Steinmaus

In Press: Epidemiology
Table 3. Odds Ratios for Bladder Cancer in Relation to Arsenic Concentrations in Water, by Smoking Status, Northern Chile, 2007-2010

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<thead>
<tr>
<th></th>
<th>Arsenic &lt; 11 µg/L&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Arsenic &gt; 335 µg/L&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OR&lt;sup&gt;b&lt;/sup&gt; (95% CI) for smoking within arsenic strata</th>
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<tr>
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<td>Cases/controls</td>
<td>OR&lt;sup&gt;b&lt;/sup&gt; (95% CI)</td>
<td>Cases/controls</td>
</tr>
<tr>
<td>Never smoker</td>
<td>6/79</td>
<td>1.00</td>
<td>19/34</td>
</tr>
<tr>
<td>Smoker</td>
<td>14/45</td>
<td>4.12 (1.30-13.0)</td>
<td>33/18</td>
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<tr>
<td>OR&lt;sup&gt;b&lt;/sup&gt; (95% CI) for smoking within arsenic strata</td>
<td>4.12 (1.30-13.0)</td>
<td>3.20 (1.28-7.97)</td>
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</table>
Bladder cancer, synergy of smoking with arsenic going up to OR=23.2 (95% CI 8.2-66)
Latency

Fifty-year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water.


Mortality data were already available computerized for 1971-2000.

For the years 1950-1971, 200,000 death certificates were digitally photographed and coded for this study.
Mortality from lung cancer among men, Region II Chile


Peak exposure started stopped

Rate Ratios

Year

Rate ratios Lower 95% CI Upper 95% CI
Drinking Water Arsenic in Northern Chile: High Cancer Risks 40 Years after Exposure Cessation

Craig Steinmaus, Catterina Ferreccio, Johanna Acevedo Romo, Yan Yuan, Sandra Cortes, Guillermo Marshall, Lee E Moore, John R Balmes, Jane Liaw, Todd Golden, Allan H Smith

Figure 2. Bladder and lung cancer odds ratios* including only cases with histologic confirmation, in non-proxy subjects, and in males and females comparing subjects in the upper to lower quartiles of average lifetime arsenic concentration prior to 1971.

*Odds ratios are adjusted for age, sex, smoking, mining work, race, body-mass index, and socioeconomic status. For display purposes, the bladder cancer odds ratio in females of 23.6 (95% CI, 4.14 to 135.3) is truncated.
Drinking Water Arsenic in Northern Chile: High Cancer Risks 40 Years after Exposure Cessation

Bladder and lung cancer odds ratios in those highly exposed in Antofagasta during 1958-70 but not thereafter were 6.88 (3.84 to 12.32) and 4.35 (2.57 to 7.36), respectively.

p<0.001

The only other known cause of cancer with a long latency like this after cessation of exposure is between asbestos and mesothelioma
So what do we now think arsenic in drinking water causes?

- **Respiratory** Cancers of the lung and larynx, reduced lung function, bronchiectasis, chronic cough and shortness of breath. Tuberculosis mortality increased?
- **Renal tract** Bladder and kidney cancer, chronic renal failure
- **Cardiovascular** Myocardial infarction, cerebrovascular effects, hypertension.
- **Neurological** Peripheral neuropathy, reduced cognitive function in children
- **Other** Skin pigmentation changes, skin cancer, liver cancer, diabetes
Once we asked what arsenic might cause; now we ask, what does it not cause?