Arsenic: A Global Public Health Crisis
How Safe is Our Food and Water?

Bruce A. Stanton, Ph.D.
Director, Superfund Research Program and Center for the Environmental Health Sciences

April 9, 2015
Outline of Presentation

• Overview of the Dartmouth Superfund Program

• Arsenic exposure in water and food, a global public health crisis

• Studies on inflammation, arsenic and respiratory disease
Dartmouth Superfund Program
P42 ES007373

The Dartmouth Toxic Metals Superfund Research Program uses an interdisciplinary approach to investigate the ways in which arsenic and mercury in the environment affect ecosystems and human health.
Arsenic Uptake, Transport and Storage in Plants

Project Leader:
Mary Lou Guerinot Ph.D.
Associate Director, Toxic Metals Superfund Research Program
Professor, Biological Sciences
Dartmouth College

Project Co-Leaders:
Tracy Punshon Ph.D.
Research Assistant Professor, Biological Sciences, Dartmouth College
David E. Salt Ph.D.
Professor and 6th Century Chair, University of Aberdeen

PERSPECTIVE

Using membrane transporters to improve crops for sustainable food production

Nature, 2014
Methylmercury Production and Fate in Response to Multiple Environmental Factors

Project Leader:
Celia Y. Chen, Ph.D.
Research Professor
Department of Biological Sciences
Dartmouth College

Project Co-Leaders:
Robert Mason, Ph.D.
Professor of Marine Sciences, University of Connecticut
Nicholas S. Fisher, Ph.D.
Distinguished Professor & Director, Consortium for Inter-Disciplinary Environmental Research, Stony Brook University

Experimental and Natural Warming Elevates Mercury Concentrations in Estuarine Fish

Jennifer A. Dijkstra¹*, Kate L. Buckman², Darren Ward³, David W. Evans⁴, Michele Dionne¹, Celia Y. Chen²
Arsenic and Innate Immune Function of the Lung

Project Leader:
Bruce A. Stanton, Ph.D.
Director, Toxic Metals Superfund Research Program
Professor, Department of Microbiology and Immunology
Andrew C. Vail Professor
Geisel School of Medicine at Dartmouth

Other Research Team Members:
Tom Hampton, M.S.

Natural Selection Canalizes Expression Variation of Environmentally Induced Plasticity-Enabling Genes

Joseph R. Shaw, Thomas H. Hampton, Benjamin L. King, Andrew Whitehead, Fernando Galvez, Robert H. Gross, Nathan Keith, Emily Notch, Dawoon Jung, Stephen P. Gla, Celia Y. Chen, John K. Colbourne, and Bruce A. Stanton

Mol. Biol. Evol., 2015
Arsenic Epidemiology, Biomarkers and Exposure Assessment of Metals

Project Leader:
Margaret R. Karagas, Ph.D.
Professor, Geisel School of Medicine at Dartmouth
Director, Children's Environmental Health and Disease Prevention Research Center at Dartmouth

Project Co-Leaders: Zhigang Li Ph.D., Lisa Chasan-Taber Sc.D., Emily Baker M.D.
Consultants: Susan Korrick Ph.D. (Harvard University), Yu Chen Ph.D. (New York University)
Dartmouth Superfund Program

- **ICP-MS core** - Brian Jackson

- **Research Translation Core** - Stakeholder outreach on As and Hg. Superfund sites. DES, CDC, ATSDR, EPA

- **Training Core** - Alan Alda Communication Workshops, Science Writers Workshop, NE SRP Workshop

Dartmouth Works With Alda Center for Communicating Science
Community Engagement Core Educational Videos

**Mercury: From Source to Seafood**
Explains how mercury enters the seafood we eat, why eating low-mercury fish is important for good health, and the need to keep mercury out of the environment.
12,000+ Views

**In Small Doses: Arsenic**
and learn about the risks of exposure to arsenic in private well water. 6,300+ views

http://www.dartmouth.edu/~toxmetal/
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General Properties of Arsenic

- Group 5 element - “metalloid”

- Most forms of arsenic are odorless and colorless in water

- $\text{As}^{+3}$ (Arsenite) or $\text{As}^{+5}$ (Arsenate) in water, arsenic trioxide (APL)

- Organic forms:
  - MMA, DMA, arsenobetaine, arsenosugars and arsenolipids (fish)
  - Roxarsone and Nitarsone-added to poultry feed. Now banned in the US
WHO, EPA and CDC: Arsenic is the number one agent of concern with regard to public health

40 million Bangladeshis drink water contaminated with arsenic

Arsenic exposure in Bangladesh is the “largest mass poisoning of a population in history!” New York Times, 7/17/05
Global Sources of Human Arsenic Exposure

- ~500 million people are exposed to arsenic in drinking water worldwide.

- ~3 billion people are exposed to arsenic in rice and rice products.

Dartmouth Toxic Metals Research Program
Arsenic Exposure in the US

• 25 million Americans exposed to arsenic in well water (>10 ppb)

• All Americans exposed to arsenic in rice and rice products

• Arsenobetaine, arsenolipids and arsenosugars in seaweed
  Roxarsone and nitarsone in poultry

• No laws or limits on arsenic in well water or food in the US

J. Exp Sci Envir Epi, 2013
>25 Million Americans Drink Well Water Contaminated with Arsenic (>10 ppb)
Arsenic in Rice and Rice Based Products in the US

Rice consumption contributes to arsenic exposure in US women

Diane Gilbert-Diamond\textsuperscript{a,b,1,2}, Kathryn L. Cottingham\textsuperscript{a,c,1}, Joann F. Gruber\textsuperscript{a,b}, Tracy Punshon\textsuperscript{a,c}, Vicki Sayarath\textsuperscript{a,b}, A. Jay Gandolfi\textsuperscript{d}, Emily R. Baker\textsuperscript{b,e}, Brian P. Jackson\textsuperscript{f}, Carol L. Folt\textsuperscript{a,c}, and Margaret R. Karagas\textsuperscript{a,b}

Arsenic, Organic Foods, and Brown Rice Syrup

Brian P. Jackson,\textsuperscript{1} Vivien F. Taylor,\textsuperscript{1} Margaret R. Karagas,\textsuperscript{2} Tracy Punshon,\textsuperscript{3} and Kathryn L. Cottingham\textsuperscript{3}

\textsuperscript{1}Trace Element Analysis Core Laboratory, Department of Earth Sciences, Dartmouth College, Hanover, New Hampshire, USA; \textsuperscript{2}Department of Community and Family Medicine, Section of Biostatistics and Epidemiology, Dartmouth Medical School, Lebanon, New Hampshire, USA; \textsuperscript{3}Department of Biological Sciences, Dartmouth College, Hanover, New Hampshire, USA

Rice Consumption and Urinary Arsenic Concentrations in U.S. Children

Matthew A. Davis,\textsuperscript{1} Todd A. Mackenzie,\textsuperscript{2} Kathryn L. Cottingham,\textsuperscript{3} Diane Gilbert-Diamond,\textsuperscript{2} Tracy Punshon,\textsuperscript{3} and Margaret R. Karagas\textsuperscript{2}

\textsuperscript{1}Institute for Quantitative Biomedical Sciences, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire, USA; \textsuperscript{2}Section of Biostatistics and Epidemiology, Department of Community and Family Medicine, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire, USA; \textsuperscript{3}Department of Biological Sciences, Dartmouth College, Hanover, New Hampshire, USA
<table>
<thead>
<tr>
<th>RICE (45 g, about ¼ cup uncooked)</th>
<th>Total</th>
<th>iAs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>365 Everyday Value Long Grain Brown (Whole Foods)</strong></td>
<td>210 to 282</td>
<td>7.4 to 8.4</td>
</tr>
<tr>
<td><strong>365 Everyday Value Organic Indian Basmati White (Whole Foods)</strong></td>
<td>82.2 to 99.9</td>
<td>2.9 to 3.5</td>
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<tr>
<td><strong>365 Everyday Value Organic Thai Jasmine White (Whole Foods)</strong></td>
<td>104 to 150</td>
<td>2.7 to 3.0</td>
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<tr>
<td><strong>Archer Farms Organic Basmati (Target)</strong></td>
<td>54.7 to 81.7</td>
<td>1.3 to 2.2</td>
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<tr>
<td><strong>Archer Farms Organic Jasmine (Target)</strong></td>
<td>112 to 121</td>
<td>2.7 to 3.9</td>
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<tr>
<td><strong>Cajun Country Enriched Long Grain</strong></td>
<td>328 to 438</td>
<td>4.8 to 5.2</td>
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<tr>
<td><strong>Cajun Country Popcorn Long Grain</strong></td>
<td>350 to 436</td>
<td>3.9 to 5.3</td>
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<tr>
<td><strong>Canilla Extra Long Grain Enriched</strong></td>
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<td><strong>Carolina Enriched Extra Long Grain</strong></td>
<td>144 to 236</td>
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<tr>
<td><strong>Carolina Jasmine Enriched Thai Fragrant Long Grain</strong></td>
<td>119 to 159</td>
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<td><strong>Carolina Whole Grain Brown</strong></td>
<td>277 to 318</td>
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<td><strong>Della Basmati Brown</strong></td>
<td>308 to 568</td>
<td>5.9 to 9.4</td>
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<td><strong>Della Basmati White</strong></td>
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<td><strong>Doguet’s Brown</strong></td>
<td>283 to 342</td>
<td>5.6 to 6.4</td>
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<tr>
<td><strong>Doguet’s Enriched Long Grain</strong></td>
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<td>3.3 to 4.4</td>
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<td><strong>Goya Enriched Medium Grain</strong></td>
<td>196 to 297</td>
<td>3.8 to 5.1</td>
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<td><strong>Great Value Brown (Walmart)</strong></td>
<td>212 to 344</td>
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<tr>
<td><strong>Great Value Parboiled (Walmart)</strong></td>
<td>138 to 239</td>
<td>4.1 to 4.4</td>
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<td><strong>Jazzmen Louisiana Aromatic Brown</strong></td>
<td>237 to 295</td>
<td>4.7 to 8.6</td>
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<tr>
<td><strong>Jazzmen Louisiana Aromatic White</strong></td>
<td>168 to 209</td>
<td>3.2 to 4.1</td>
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<tr>
<td><strong>Lundberg California White Basmati</strong></td>
<td>64.3 to 75.5</td>
<td>1.3 to 1.6</td>
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<td><strong>Lundberg Short Grain Brown</strong></td>
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<td><strong>Mahatma Extra Long Grain Enriched</strong></td>
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<td>3.4 to 4.9</td>
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<tr>
<td><strong>Market Pantry Enriched Long Grain White (Target)</strong></td>
<td>184 to 254</td>
<td>4.0 to 4.6</td>
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<td><strong>Martin Long Grain Brown</strong></td>
<td>113 to 455</td>
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<tr>
<td><strong>Martin Long Grain Enriched</strong></td>
<td>133 to 193</td>
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<td><strong>Rice-Select Organic Texmati White</strong></td>
<td>330 to 917</td>
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<td><strong>Texas Best Organics Long Grain Brown</strong></td>
<td>252 to 287</td>
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<tr>
<td><strong>Texas Best Organics Long Grain White</strong></td>
<td>138 to 226</td>
<td>3.2 to 4.3</td>
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<tr>
<td><strong>Trader Joe’s White Basmati From India</strong></td>
<td>75.9 to 86.0</td>
<td>2.5 to 2.9</td>
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<td><strong>Uncle Ben’s Original Enriched Parboiled Long Grain</strong></td>
<td>220 to 246</td>
<td>5.9 to 6.3</td>
</tr>
<tr>
<td><strong>Uncle Ben’s Whole Grain Brown</strong></td>
<td>209 to 285</td>
<td>5.7 to 6.7</td>
</tr>
</tbody>
</table>
Cereal killers? More than half of rice products including Rice Krispies and Heinz baby rice exceed new EU limits for ARSENIC

- Experts warn some popular rice products contain high levels of arsenic
- Tests found 58% exceeded new recommended arsenic limits for children
- Scientists say high levels over time could lead to cancer or heart disease
- People in Britain consume five times more rice today than 40 years ago

By KEILIGH BAKER FOR MAILONLINE

PUBLISHED: 05:32 EST, 2 November 2014 | UPDATED: 10:11 EST, 3 November 2014

Dartmouth TOXIC METALS Research Program
Arsenic in Wine and Turkeys

Should you be worried about arsenic in California wine?

By Emanuella Grinberg, CNN
Updated 3:47 PM ET, Sun March 29, 2015

FDA withdrawing approval for last remaining food-animal drug containing arsenic

Nitarsone used in turkeys and chickens to prevent blackhead disease

04/01/2015 | ConsumerAffairs | Health

EFSA 2014-Main contributor to dietary exposure to iAs: non rice-based grain, rice, milk and dairy products and water.
Arsenic in Seafood

Arsenic in Seafood

• Seafood ingestion (24 h): Arsenic in urine. Total arsenic in urine (24.5 µg/L), DMA (6.0 µg/L), arsenobetaine (10.2 µg/L). 8.3 µg/L unknown. Navas-Acien, Envir. Res., 2011

• Arsenobetaine and arsenocholine most prevalent arsenic in seafood. 90% arsenobetaine. Non-toxic

• Arsenolipid cytotoxicity. 380 to 3,800 µg/L disrupts development in Drosophila.

• 100 µg/L tAs measured in blood in Bangladesh and 8 µg/LtAs in the U.S.

• Cytotoxic effects of arsenolipids/arsenosugars in humans? Unknown, but unlikely to be prevalent at high enough concentrations.
Arsenic and Disease in the US

• **Epidemiological Studies in the US - Correlations**
  – In utero arsenic increases respiratory infections, dysregulates the fetal immune system and is associated with premature birth (Karagas-Dartmouth 2014)
  – Arsenic in drinking water is associated with a 5-10 point reduction in IQ in Maine children (Wasserman-Columbia 2014)

• **Gaps in our knowledge – Cause and Effect Relationships**
  – Effects of low levels of arsenic relevant to the US?
  – Relative effects of inorganic vs. organic forms of arsenic?
  – Is there a reason to be concerned about organic forms of arsenic (roxarsone and nitarsone in poultry)?
  – **EPA and most scientists state that organic forms are less toxic than inorganic arsenic, but little or no relevant data.**
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Arsenic and Respiratory Disease

• Arsenic increases the incidence of respiratory bacterial and fungal infections, bronchiectasis and COPD (~50-fold).

• Respiratory infections are a significant public health concern and a major cause of morbidity and mortality worldwide

Smith et al (2006) EHP
Innate Immunity in the Lungs

- Airway cells release cytokines in response to pathogens
  - Interleukins are secreted by lung cells and recruit macrophages and neutrophils to the lungs.
  - Macrophages phagocytose pathogens and activate adaptive immunity
  - **Excessive** or **inadequate** cytokine release leads to inappropriate immune cell clearance of bacteria and chronic, irreversible lung damage.
US Relevant Concentrations of Arsenic are Not Cytotoxic to HBE Cells

iAs Has No Effect on PAO1 Stimulated Cytokine Secretion by HBE Cells

Stanton et al., in press, 2015
DMA Has No Effect on PAO1 Stimulated Cytokine Secretion by HBE Cells

Stanton et al., in press, 2015
MMA Increases PAO1 Stimulated Cytokine Secretion by HBE Cells
5 ppb Total Arsenic Has No Effect on PAO1 Stimulated Cytokine Secretion by HBE Cells
10 ppb Total Arsenic Reduces PAO1 Stimulated Cytokine Secretion by HBE Cells

A

B

C

D

Stanton et al, in press, 2015
MMA Stimulates Bacterial (PAO1) Induced IL-10 Secretion in Macrophages

![Graph showing IL-10 cytokine secretion (% PA01) for different treatments: Control, 10ppb MMA, PA01, and 10ppb MMA + PA01. The graph indicates a significant increase in IL-10 secretion with the combination of 10ppb MMA and PA01 compared to other treatments.](graph.png)
MMA (5 ppb) Has No Effect on IL-8, CXCL2 or IL-6 mRNA Levels

Stanton et al, in press, 2015
Total As (10 ppb) has no effect on IL-8, or CXCL1 mRNA levels

Stanton et al, in press, 2015
Summary and Conclusions

- **Organic arsenic** - at levels relevant to US exposure – has adverse effects on the innate immune response of HBE cells and immune cells to *Pseudomonas* infection. Mechanism unknown. 12 million patients with COPD and 85% of CF patients infected with *Pseudomonas*

- The adverse biological effects of organic arsenic on inflammation have important implications for ongoing FDA policy considerations regulating arsenic in food and well water.
Acknowledgements

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