

Sources and Protracted Effects of Early Life Exposure to Arsenic and Mercury

Bruce A. Stanton, Ph.D.
Director

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Associate Director



GEISEL
— SCHOOL OF —
MEDICINE
AT DARTMOUTH

<http://www.dartmouth.edu/~toxmetal/>

Dartmouth Superfund Program

- The Dartmouth Superfund Research Program uses an interdisciplinary approach to investigate the ways in which arsenic and mercury in the environment affect ecosystems and human health.
- Our research is highly relevant to the mission of the SRP because **arsenic and mercury are two of the top three environmental chemicals of concern regarding human health in the US.**
- Work with our stakeholders to: (1) Reduce exposure to arsenic in well water, rice and rice products, and (2) Reduce exposure to mercury (eating low mercury fish and reduce coal burning emissions of mercury).

Arsenic Uptake, Transport and Storage in Plants



Project Leader:

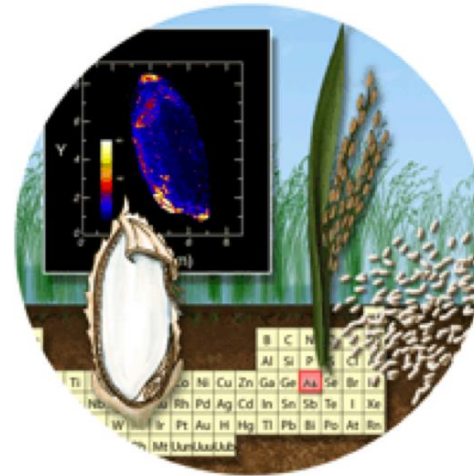
[Mary Lou Guerinot Ph.D.](#)

Associate Director, Toxic Metals Superfund

Research Program

Professor, Biological Sciences

Dartmouth College



Project Co-Leader:

[David E. Salt Ph.D.](#)

Professor and 6th Century Chair, University of Aberdeen

PERSPECTIVE

doi:10.1038/nature11909

Using membrane transporters to improve crops for sustainable food production

Julian I. Schroeder¹, Emmanuel Delhaize², Wolf B. Frommer³, Mary Lou Guerinot⁴, Maria J. Harrison⁵, Luis Herrera-Estrella⁶, Tomoaki Horie⁷, Leon V. Kochian⁸, Rana Munns^{2,9}, Naoko K. Nishizawa¹⁰, Yi-Fang Tsay¹¹ & Dale Sanders¹²

<http://www.ncbi.nlm.nih.gov/pubmed/23636397>

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

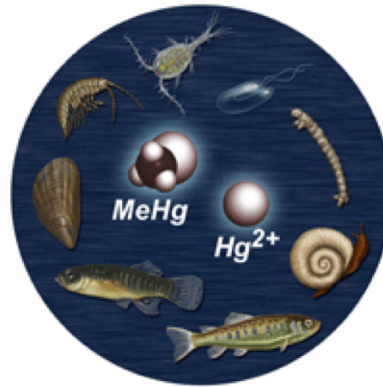
Project Co-Leaders:

[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



OPEN ACCESS Freely available online

PLOS ONE

Experimental and Natural Warming Elevates Mercury Concentrations in Estuarine Fish

Jennifer A. Dijkstra^{1*}, Kate L. Buckman², Darren Ward³, David W. Evans⁴, Michele Dionne¹, Celia Y. Chen²

<http://www.ncbi.nlm.nih.gov/pubmed/23554891>

Arsenic and Innate Immune Function of the Lung

Project Leader:

[Bruce A. Stanton, Ph.D.](#)

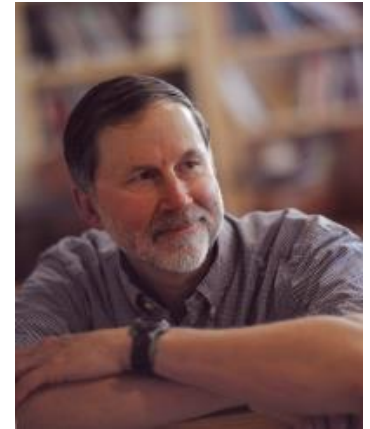
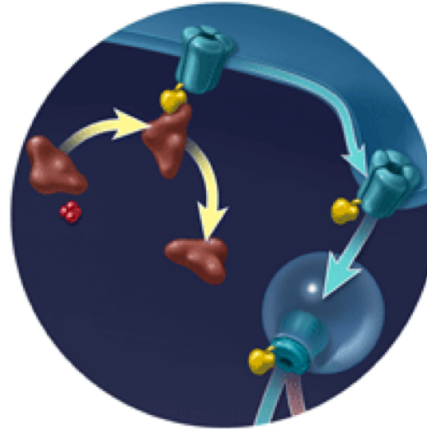
Director, Toxic Metals

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.](#)

Approaches to Limiting Human Exposure to Arsenic. The Arsenic Prevention and Control Consortium.

Current Environmental Health Reports,
in press, 2015

Arsenic Epidemiology, Biomarkers and Exposure Assessment of Metals

Project Leader:

Margaret R. Karagas, Ph.D.

James W. Squires Professor
Professor and Chair
Department of Epidemiology
Geisel School of Medicine 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)



Blood Pressure Changes in Relation to Arsenic Exposure
in a U.S. Pregnancy Cohort

Shohreh F. Farzan, Yu Chen, Fen Wu, Jieying Jiang, Mengling
Liu, Emily Baker, Susan A. Korrick, Margaret R. Karagas

<http://dx.doi.org/10.1289/ehp.1408472>

Received: 25 March 2014
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Advance Publication: 20 March 2015

<http://www.ncbi.nlm.nih.gov/pubmed/25793356>

Dartmouth Superfund Program Cores

- **Trace Element Analysis Core:** Brian Jackson, Ph.D.

TECHNICAL NOTE

[View Article Online](#)
[View Journal](#)



Cite this: DOI: 10.1039/c5ja00049a

Fast ion chromatography-ICP-QQQ for arsenic speciation

Brian P. Jackson*



- **Training Core:** Bruce Stanton, Ph.D.

Alan Alda Communication Workshops, Science Writers Workshop, NE Regional SRP Workshop

Dartmouth Works With Alda Center for Communicating Science



Dartmouth Superfund Program Cores

- **Research Translation Core:** Laurie Rardin and Celia Chen, Ph.D.

Stakeholder outreach on arsenic, mercury and Superfund sites to DES, CDC, ATSDR, EPA and 27 others.



- **Community Engagement Core:** Kathrin Lawlor and Mark Borsuk, Ph.D.

DES Grant: Private well outreach in 6 NH communities
EPA Environmental Education Grant: to engage school children and teachers to monitor private wells for arsenic

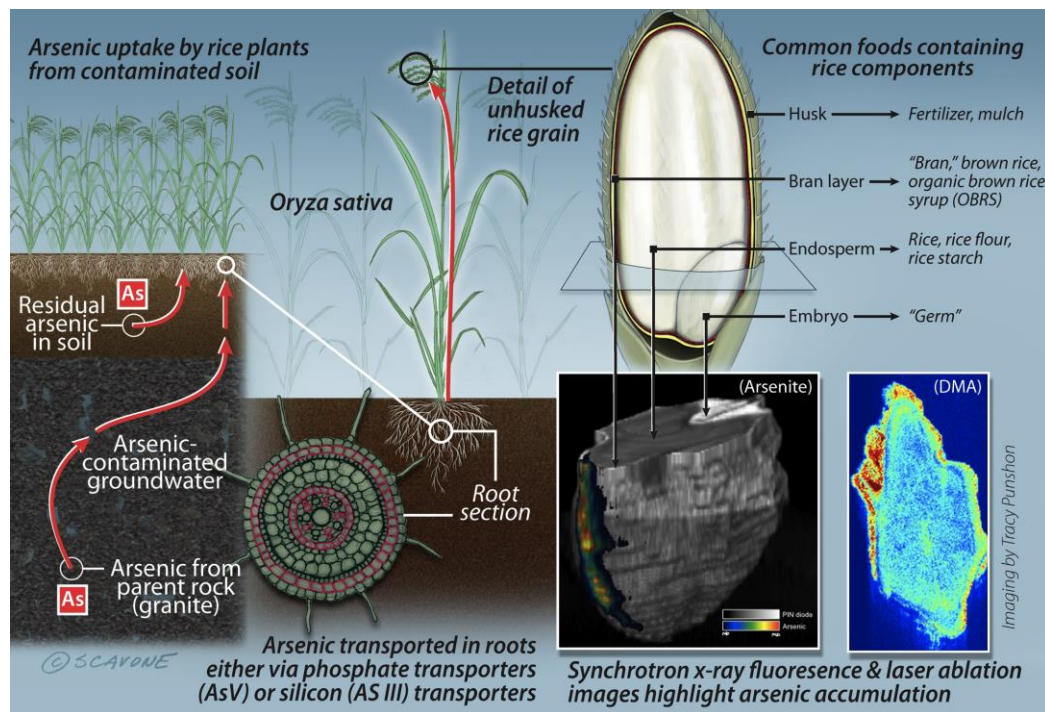


Solutions to the Problem

Through our research, training, translation and community engagement we will provide relevant information to empower our stakeholders and the communities with whom we engage to make informed decisions to reduce their exposure to arsenic and mercury and, thereby, improve public health.

Project 1: Arsenic Uptake, Transport and Storage in Plants

Project Leader: Mary Lou Guerinot, Ph.D.
Associate Director and Professor of Biological Sciences



Arsenic in Rice

Importance of the problem:



Arsenic, a Class I non-threshold carcinogen, is being found in rice, a staple food eaten by half the world every day

Many rice-based foods are on the market, including infant rice cereals and formula



People with allergies to gluten (Celiac disease) consume many rice-based products





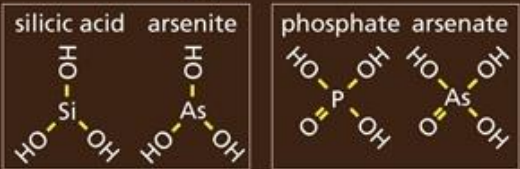
- Arsenic occurs naturally in soil and ground water and was used for many years in pesticides.

- Several factors contribute to rice being an efficient accumulator of arsenic relative to other cereals:

- Cultivation in flooded paddies that leads to arsenite [As(III)] mobilization

- Inadvertent uptake and transport of As(III) through the silicon (Si) pathway which is highly efficient in rice

- Inadvertent uptake and transport of arsenate [As(V)] through phosphate transporters



- There are currently no statutory limits for the arsenic content of food sold in the United States and the European Union.
- To protect consumers from excessive exposure, the Codex Alimentarius Commission (FAO/WHO) recommends that the level of arsenic in rice should not exceed 0.2 mg/kg (issued April 2014).
- A study by our SRP group (Project 4) calculated that consumption of 0.56 cup/day of cooked rice was comparable to drinking 1 L/d of 10 μg As/L water, the current US maximum contaminant limit. (Gilbert-Diamond et al. 2011 PNAS 108: 20656)
- To put this number in perspective, US rice consumption averages \sim 0.5 cup/day, with Asian Americans consuming an average of >2 cups/day.

Consumer Reports January 2015

The New Rice Rules: 7 Points per Week

We used our new data and analysis to assign a point value to types of rice foods. On average, we recommend getting no more than 7 points per week. Risk analysis is based on weight, so a serving of any food will give children more points than adults.

Products	Serving Size	Child Points ¹	Adult Points ¹
Infant Rice Cereal	¼ cup uncooked	1¼	NA
Rice Cereal, Hot	¼ cup uncooked	8¼	3½
Rice Cereal, Ready to Eat	1 cup	4½	2¼
Rice Drinks	1 cup	4	2
White Basmati ² or Sushi Rice	¼ cup uncooked	2½	1½
All Other Rice	¼ cup uncooked	5½	3½
Rice Pasta	2 ounces uncooked	7¼	3
Rice Cakes	1 to 3 rice cakes	6¼	2½
Rice Crackers	16 to 18 crackers	2¾	1¼

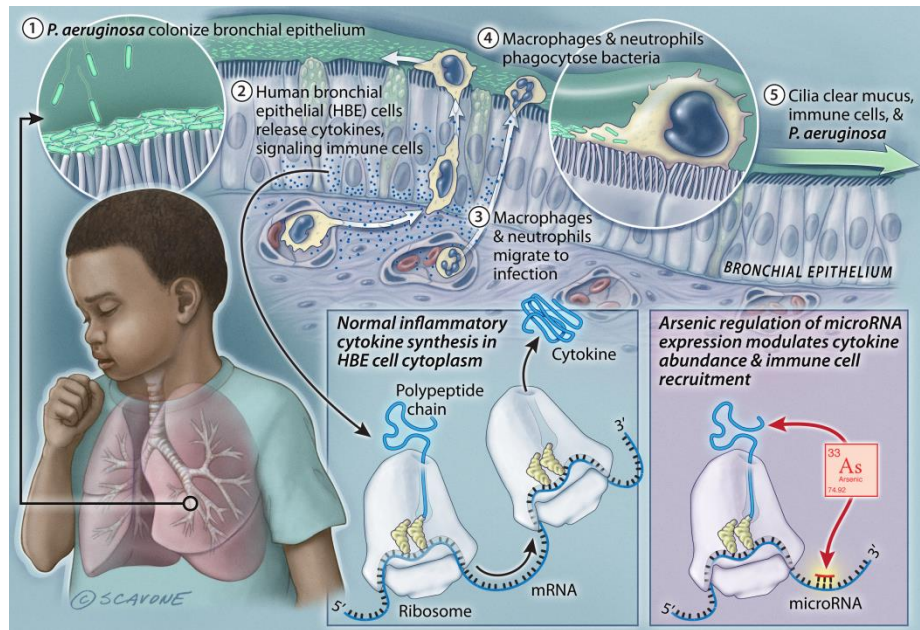
Solutions to the Problem

- Rice cultivars that restrict arsenic accumulation in the grain offer one of the simplest, fastest and most cost effective approaches to solving the problem of arsenic contamination of rice and rice-based products.
- Such cultivars could immediately be used in arsenic-rich soils and can also be used as genetic stock for breeding programs to introduce low grain arsenic traits into agronomically-improved varieties suitable for modern commercial rice production.



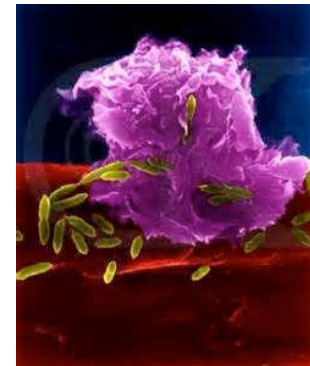
Project 3: Arsenic and Innate Immune Function of the Lung

Project Leader: Bruce A. Stanton, Ph.D.
Director and Professor of Microbiology and Immunology



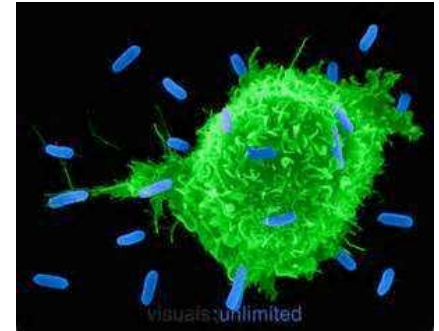
Arsenic and Respiratory Disease

- Arsenic ingestion increases the incidence of respiratory (lung) bacterial and fungal infections.
- Respiratory infections are the third most frequent cause of death worldwide (6.2 million/year-World Health Organization).
- *In utero* arsenic exposure increases respiratory infections and dysregulates the fetal immune system (Project 4 - Karagas - 2014)



Innate Immunity

- Bacterial infections increase the secretion of interleukins, which recruit macrophages and neutrophils to the lungs
- Macrophages and neutrophils kill bacteria
- *Excessive* or *inadequate* cytokine release leads to inappropriate immune cell clearance of bacteria and chronic, irreversible lung damage and death.
- Studies in Project 3 have observed that low levels of arsenic, typical of US exposure, disrupt interleukin secretion and the ability of macrophages to kill bacteria in the lung.



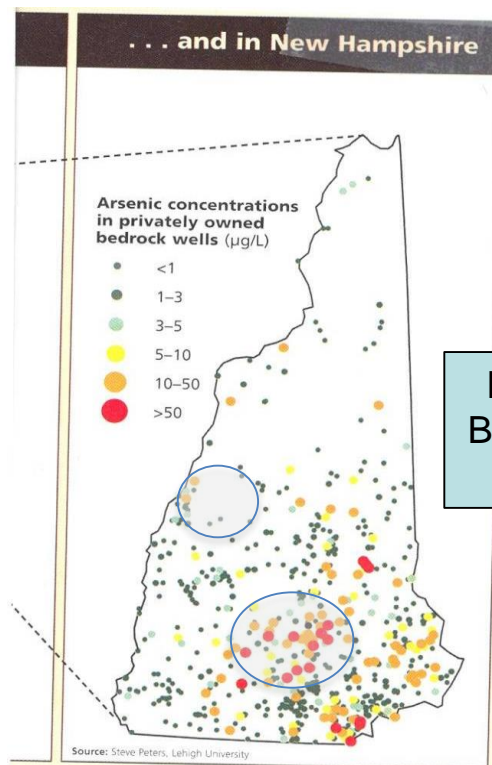
Solutions to the Problem

- Educate and work with state legislators, journalists and public advocacy groups to increase awareness. Project 3 has worked with NH and Maine state legislators to pass bills to inform new home owners of arsenic in well water.
- Work with the FDA to establish regulations for arsenic in food and in well water.



Project 4: Epidemiology, Biomarkers and Exposure Assessment of Metals

Project Leader: Margaret Karagas, Ph.D.
Professor and Chair, Department of Epidemiology



New Hampshire
Birth Cohort Study
Areas





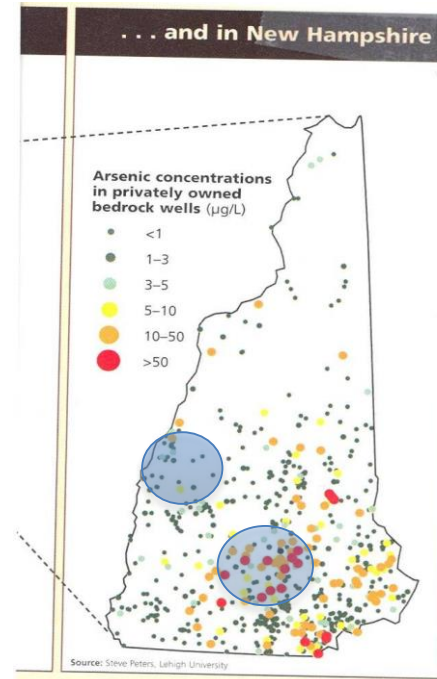
Project 4 Goals

- I. To investigate whether higher arsenic exposure influences cardiovascular disease risk factors in pregnant women i.e., alters glucose metabolism, blood pressure and markers of systemic inflammation and vascular endothelial cell dysfunction.

- II. To investigate whether in utero arsenic exposure is related to cardiometabolic factors (i.e., glucose metabolism, inflammatory and vascular endothelial cell markers) in the newborn.

The New Hampshire Birth Cohort

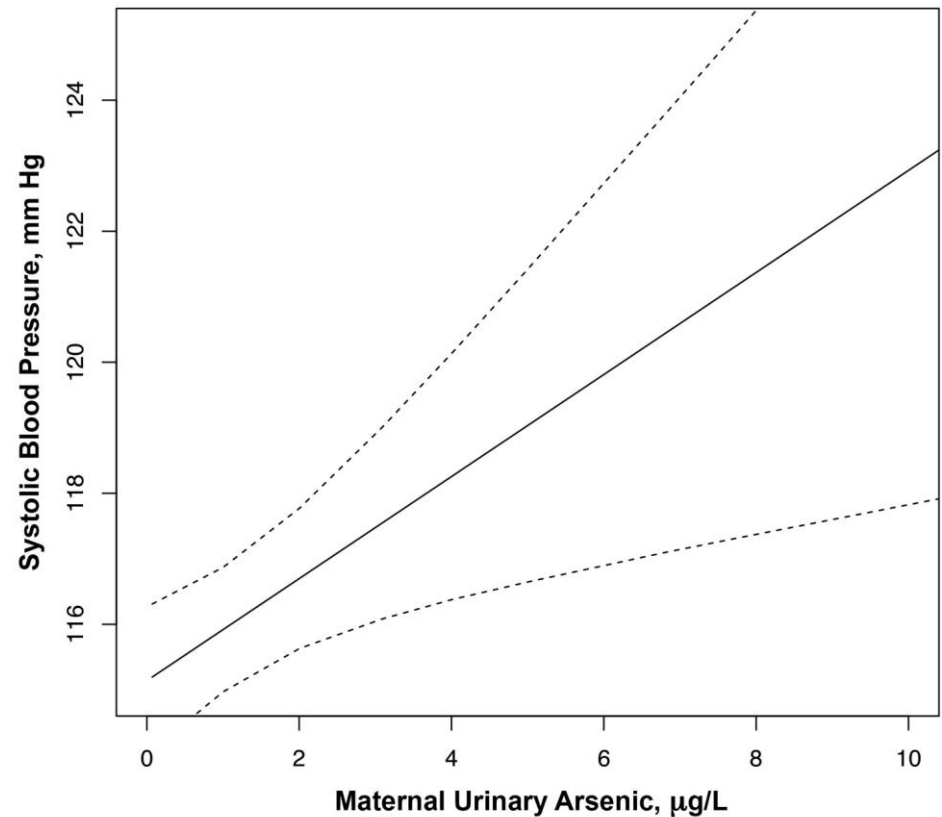
Pregnancy as susceptible window for As exposure



- **Private well users**
- **1,200+ mother-infant pairs**
- **75% response rate**
- **100% urinary arsenic**

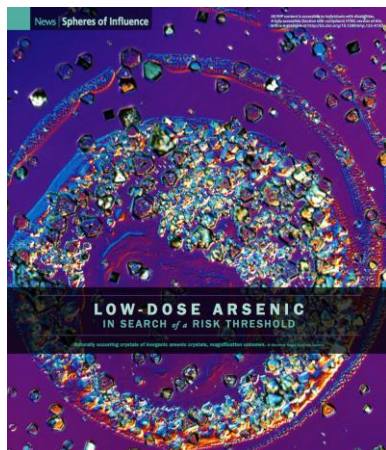
Arsenic is Related to Greater BP Increases Over the Course of Pregnancy

- Over the course of pregnancy, each **10 $\mu\text{g/L}$** increase in urinary As was associated with:
 - **0.31 mmHg** (95% CI: 0.04, 0.57, $p = 0.022$) greater increase in systolic blood pressure per month
 - **0.28 mmHg** (95% CI: 0.05, 0.52; $p=0.018$) greater increase in pulse pressure per month



Solutions to the Problem

- Our work is determining the effects of low level arsenic exposure during pregnancy and contributing to the scientific communication of the health impacts, through:
 - Publications/media releases, including primary research and other reports
 - Participation in lay publications (e.g., Consumer Reports), consensus panels and committees e.g., the NRC committee to evaluate the EPA IRIS
 - Co-leading C-Farr initiative



Annals of Internal Medicine | EDITORIAL

Arsenic and Cardiovascular Disease: New Evidence From the United States

Mounting evidence suggests that exposure to chemical and other environmental substances, such as arsenic, can have a profound effect on cardiovascular disease (CVD) risk. Inorganic arsenic, a known carcinogen, occurs naturally in groundwater, exposing millions of people in the United States and worldwide. Epidemiologic studies in villages of southwestern Taiwan with high levels of arsenic in groundwater (median, 700 µg/L) provided early evidence of a dose-response relationship of water arsenic concentrations at less than 300 µg/L, 300 to 700 µg/L, and greater than 700 µg/L with CVD mortality (1). Arsenic exposure has also been related to increased mortality from acute myocardial infarction (AMI), when annual concentrations in drinking water increased from 95 to 870 µg/L between 1976 and 1978 (2). Recent prospective studies from Bangladesh (median arsenic concentration of 10 to 100 µg/L) (3, 4) and urinary creatinine-adjusted arsenic concentrations of 10 to 64 µg/L creatinine (5), although estimates for lower arsenic levels were less precise, in the same. Most and colleagues (3) report results from a U.S. study of American Indians from the Strong Heart Study. Study participants with a urinary arsenic concentration greater than 15 µg/L creatinine were 1.63, 1.71, and 3.03 times more likely to die of CVD, coronary heart disease, and stroke, respectively, than their counterparts with urinary arsenic levels less than > 8 µg/L creatinine (6). The risk for incident CVD associated with urinary arsenic, although lower than that for CVD mortality, was also elevated.

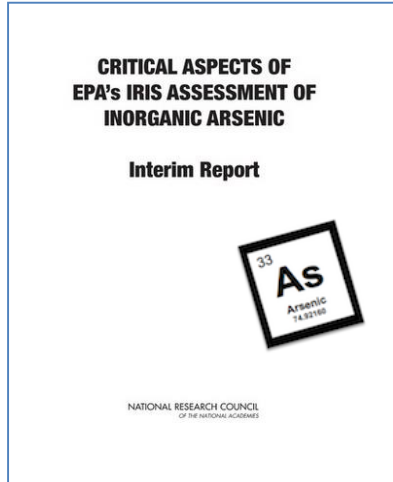
In the first prospective study to our knowledge in a U.S. population that assessed effects of arsenic exposure on CVD in aging, urinary arsenic as a biomarker measured on each participant, the study by Moon and colleagues provides critical data. To our knowledge, the Strong Heart Study also is the largest, longest longitudinal study in the United States on CVD in a population with a high prevalence of diabetes and has the additional strength of comprehensive and repeated follow-up data on both lipid and modified CVD and CVD risk factors. Moreover, participants who could measure arsenite/arsenate, an organic chemical found in water that is not considered to be toxic, levels were very low (median, 6.7 µg/L creatinine), which somewhat concerns about potential confounding by arsenite. Further, although they measured arsenic only 1 time, temporal representativeness, which refers to the consistency of measurements from the same person at different times, was a factor with repeated urinary arsenic measured over 10 years was 0.64. This is within the acceptable limits

of the reproducibility of biomarkers with observed disease associations from significant exposure in epidemiologic studies. The study has several noteworthy points, and the findings raise new questions. Given that urinary arsenic also captures inorganic arsenic exposure from sources other than drinking water, it is difficult to judge the extent to which the observed association was due to arsenic from drinking water versus dietary arsenic. Detailed analyses showed that the association between urinary arsenic and CVD risk was strongest in Indians, whose drinking water was probably the main source of arsenic exposure (7). Yet, recent data indicate that dietary arsenic, such as rice, can be a major source of exposure for many persons (8).

The Strong Heart Study revealed American Indians, a population that has a high prevalence of both diabetes and obesity and, consequently, an especially high risk for CVD. Detailed analyses showed that the association between urinary arsenic and CVD risk was strongest in persons with diabetes at baseline, which indicated that diabetes or risk factors associated with diabetes may modify the cardiovascular effects of arsenic exposure. Alternatively, prevalent cases of diabetes have lower levels of creatinine, which would result in difference in urinary creatinine-adjusted arsenic concentration. The authors conducted sensitivity analyses adjusting urinary arsenic using specific gravity instead and found similar results. Thus, the findings do not fully answer the question of whether the relationship between arsenic and CVD is generalizable to other U.S. populations, especially in persons without diabetes.

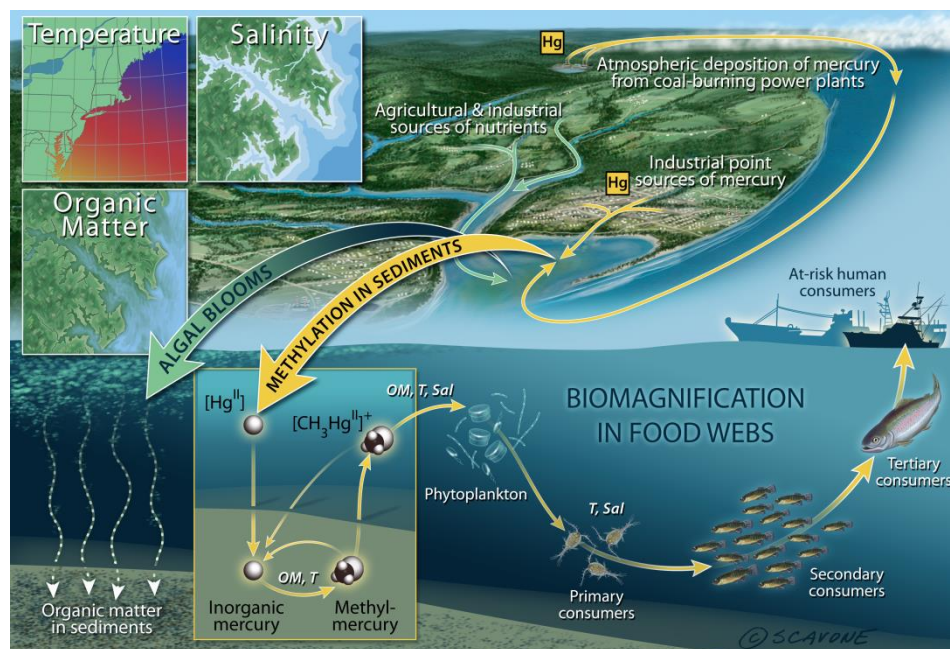
Another issue regarding the generalizability of the study population is that the percentage of urinary monomethylarsonic acid, a biomarker for arsenic metabolism that is in part genetically driven (9), is not related to CVD risk in the Strong Heart Study. The percentage of urinary monomethylarsonic acid has been positively related to health effects of arsenic, including cancer and CVD-related end points, in recent data from Bangladesh (3). Lack of an association in the Strong Heart Study may question about whether differences in arsenic metabolism influence susceptibility to arsenic-associated CVD in populations with lower exposure levels, such as in the United States.

The association with risk that is not dose-effect adjustment for potentially confounding factors, with effect measures based on urine (3), and Bangladesh (3) in populations with higher exposure levels showed stronger associations with coronary heart disease than stroke. With longer follow-up, the Strong Heart Study may offer insights on subtypes of CVD that may be affected by arsenic.



Project 2: Methylmercury Production and Fate in Response to Multiple Environmental Factors

Project Leader: Celia Chen, Ph.D.
Professor of Biological Sciences



Climate Change Effects on Marine Mercury

- *Increased temperatures:*

- Increased methylation rates and uptake of mercury and methylmercury by biota

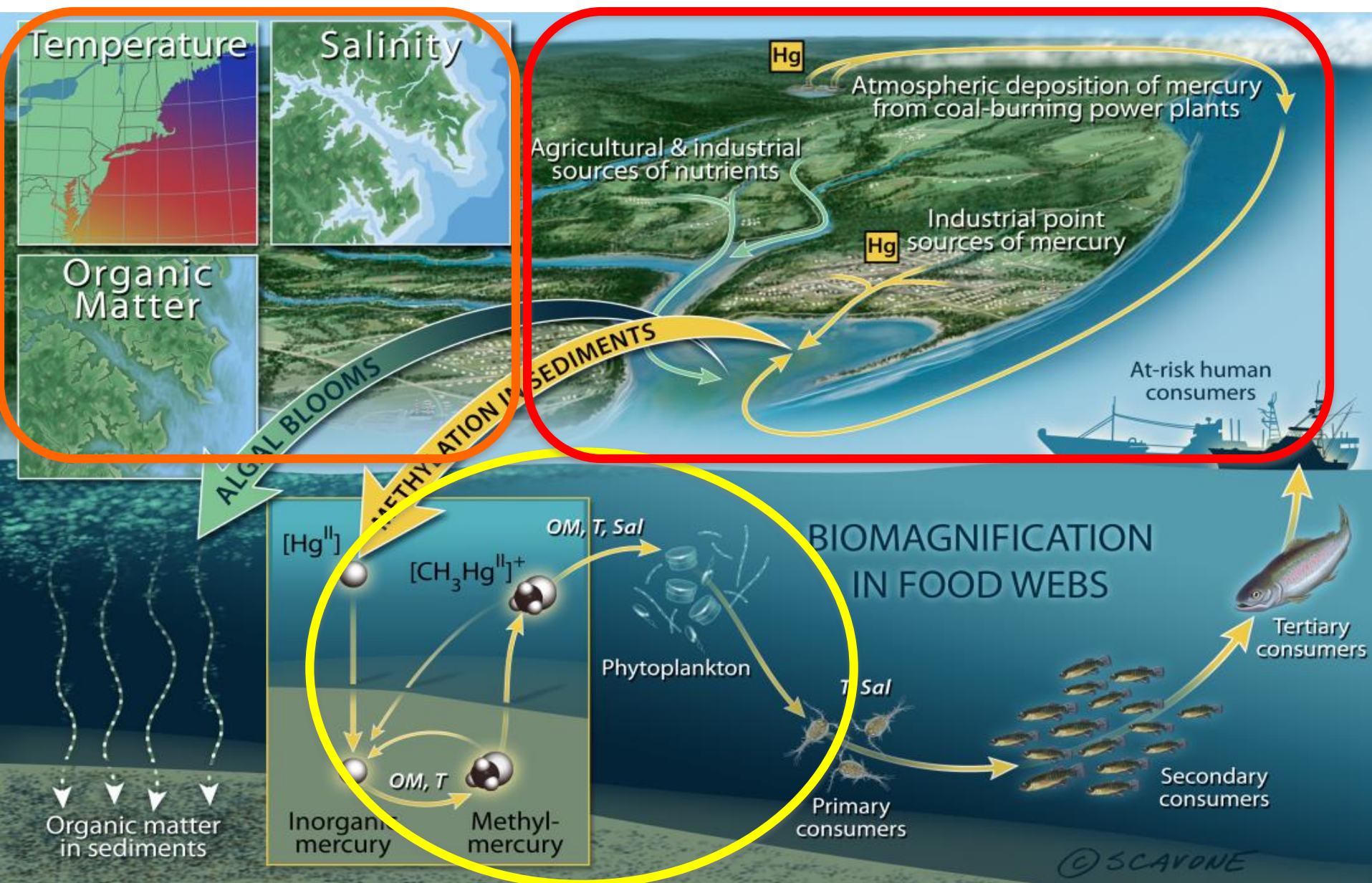
- *Increased rainfall, runoff and stream flow:*

- Increased loading of nutrients and mercury from watershed
- Increased productivity and biomass dilution
- Increased carbon flux to sediments and water column
- Decreases in salinity downstream

- *Sea level rise:*

- Increased salinity upstream
- Increased submergence of soils and mercury methylation

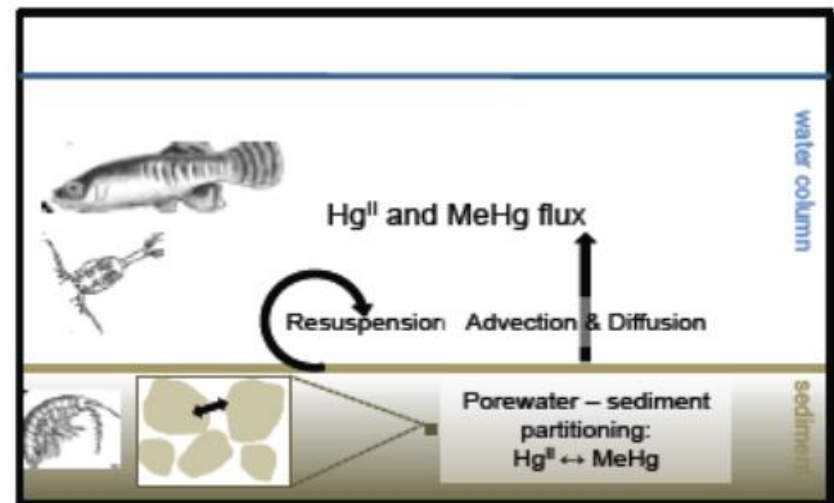
Climate Change Effects on Marine Mercury



Research Goals

To examine individual and combined effects of three climate-induced factors, **temperature**, **salinity** and **organic carbon (OC)** inputs on:

- Methylmercury production in estuarine sediments and flux to water column
- Bioaccumulation by lower trophic levels of the estuarine food web



Solutions to the Problem

- Global, national, and local policies to reduce mercury emissions and discharges to the atmosphere (e.g., Minamata Treaty, U.S. Mercury Rule, Coastal and Marine Mercury Research Consortium-C-MERC)
- Global policies to evaluate the effectiveness of the Minamata Treaty (UNEP Fate and Transport Partnership)
- Educating the public about the *risks and benefits* of consuming seafood

Trace Element Analysis Core

PI: Brian Jackson, Ph.D., Co-I Tracy Punshon, Ph.D.

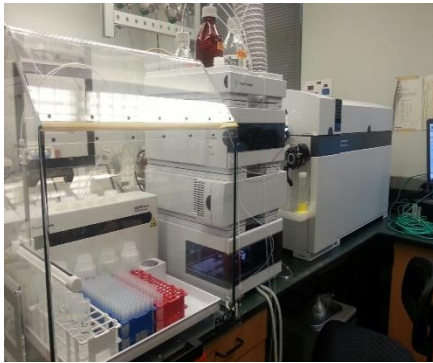
- **Core service center supporting Dartmouth SRP**
- **Services**
 - Trace metal analysis
 - Mercury speciation
 - Arsenic speciation
 - Method development
 - LC-ICP-MS speciation methods
 - LA-ICP-MS for elemental (bio)imaging
- Training
 - Vivien Taylor;
2014 KC Donnelly fellowship



Trace Element Analysis Core

State of the art instrumentation

- New reaction Cell triple quad-ICP-MS



8800 QQQ-ICP-MS

High sensitivity

Low detection limits

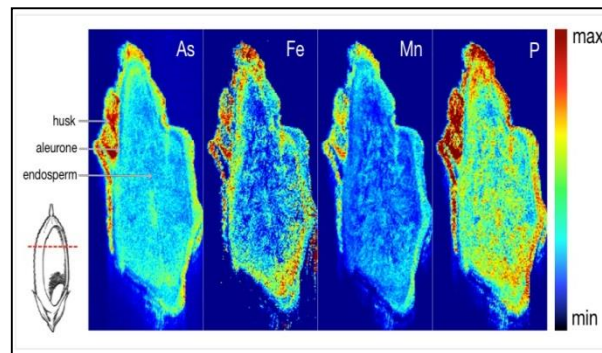
(< 5 PPT: parts per trillion for As)

Elemental speciation and bio-imaging

Laser ablation-ICP-MS

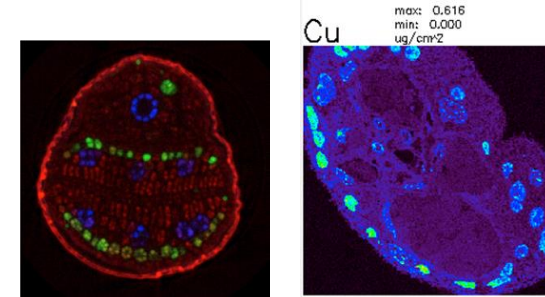


LA-ICP-MS images of arsenic distribution in rice grain



Synchrotron XRF imaging

Collaborations with three US synchrotrons: methods for a range of tissue from plants (Arabidopsis seed, left) and animals (Human placenta, right)



Trace Element Analysis Core Collaboration

Analysis of arsenic in GF-foods in support of CEC



Trace metal analysis of toenails
Support for Project 4 and collaboration with:
National Cancer Institute
Spanish National Cancer Research Center

Pancreatic cancer



ORIGINAL ARTICLE

Pancreatic cancer risk and levels of trace elements

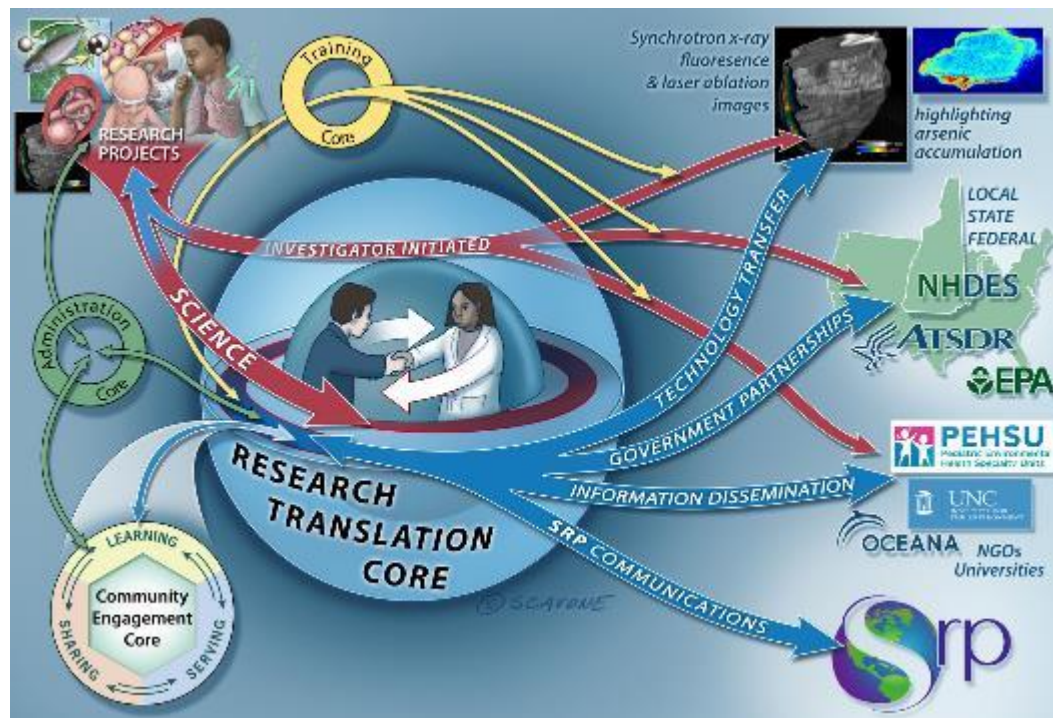
André F S Amaral,¹ Miquel Porta,^{2,3} Debra T Silverman,⁴ Roger L Milne,¹ Manolis Kogevinas,⁵ Nathaniel Rothman,⁴ Kenneth P Cantor,⁶ Brian P Jackson,⁷ José A Pumarega,^{2,3} Tomàs López,^{2,3} Alfredo Carrato,^{8,9} Luisa Guarner,¹⁰ Francisco X Real,^{11,12} Núria Malats¹

Gut;
2011

Research Translation Core

Core Leader: Celia Chen, Ph.D.

Coordinator: Laurie Rardin, M.S.



Research Translation Core Aims

1. Assist U.S. Environmental Protection Agency (EPA) at Superfund sites: Callahan Mine, ME, Berlin, NH, Berry' s Creek, NJ, Penobscot River, ME
2. Share innovative methods: low-level detection, speciation, imaging of metals
3. Facilitate dialogue between scientists and policy-makers on sources and effects of arsenic exposure
4. Collaborate with the Agency for Toxic Substances and Disease Registry, EPA, New England Pediatric Environmental Health Specialty Unit on risk decisions on Arsenic in food and water and Mercury in fish
5. Provide opportunities for researchers and trainees to communicate research and develop relationships
6. Develop a centralized website on Arsenic and Mercury



Alan Alda Center for Communicating Science



AT STONY BROOK UNIVERSITY



Dartmouth Workshop

Attendees from multiple institutions and agencies throughout New England

NAC-SETAC 2015 Annual Meeting

Communicating Chemical and Environmental Risk

Session on Research Translation and Community Engagement ● collaboration with Brown SRP



NH Arsenic Consortium 2014 Annual Meeting

● 24 stakeholder groups represented

Next Meeting February 2016



Arsenic in Private Wells in NH

Working with our Community Engagement Core to evaluate rate of and barriers to treatment and testing and evaluate interventions.



C-FARR Collaborative on Food with Arsenic & associated Risk & Regulation

Bringing together an interdisciplinary group of scientists and policy stakeholders to synthesize the science and identify knowledge gaps relevant to policy on arsenic in food to produce peer reviewed synthesis papers for a special journal issue.



Arsenic in Food and Water Website

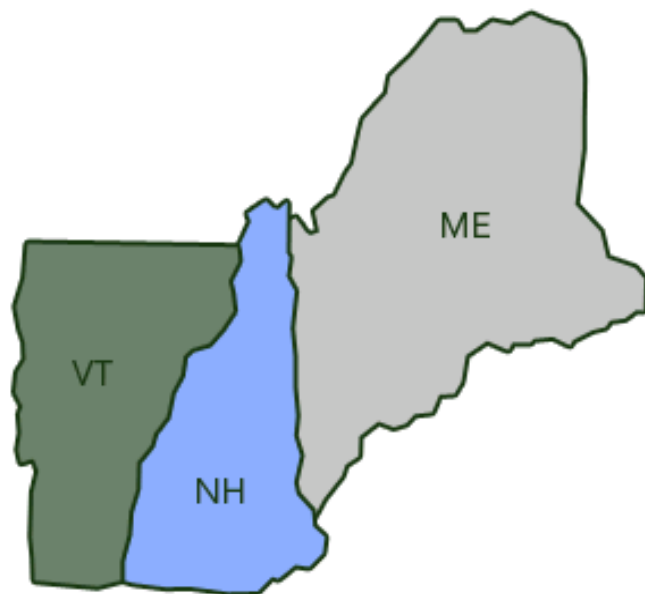
The website will allow visitors to understand cumulative arsenic exposure to make informed lifestyle decisions to reduce their exposure to arsenic and improve their long-term health.



Community Engagement Core

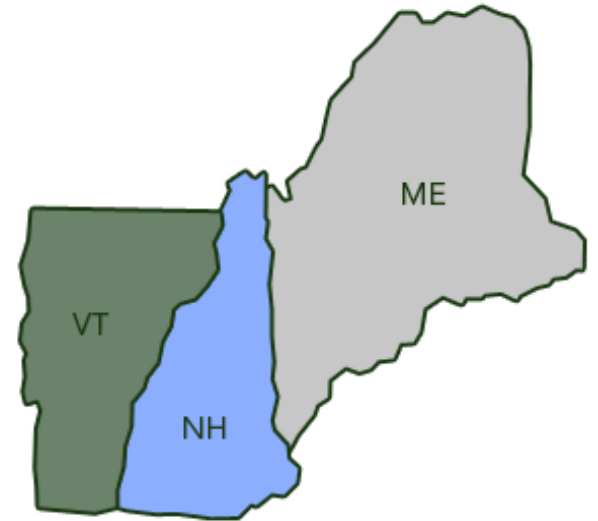
Core Leader: Mark Borsuk, Ph.D.

Coordinator: Kathrin Lawlor, B.A.



Community Engagement Core Aims

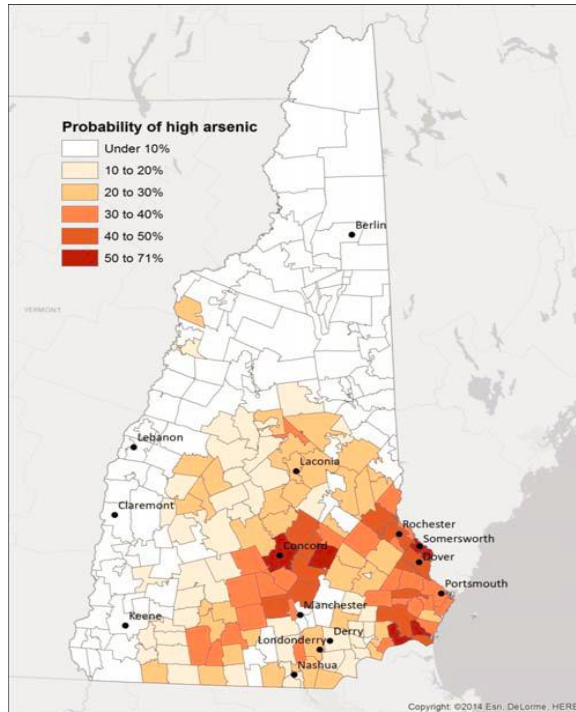
Aim 1: To sustain engagement with community partners in Northern New England to better understand and support healthy decision-making



Aim 2: Cultivate opportunities for Dartmouth to serve community partners by providing resources, information, communications, and expertise.

Aim 3: Foster collaborative community-engaged research.

Arsenic in Private Well Water in NH



Geographic distribution by ZIP code of the probability of arsenic in well water exceeding 10 parts per billion, as estimated by the US Geological Survey model.

Prepared by J. Chipman.

Year One Activities

- Community Focus Groups
- Statewide Survey
- Intervention Selection and Design

Year Two Activities

- Data Storage System for NH Lab Testing Results
- Town Selection Process
- Intervention Planning and Implementation
- Communication Materials Development
- Evaluation
- Toolbox Creation

The Dragonfly Project

- Four High Schools in Vermont and New Hampshire
 - 9 classes total
- Instruction from Trainee Kate Buckman
- Annual Student Symposium at Dartmouth, January 2015.
- Local press coverage of event, including The Valley News, The Berlin Daily Sun, WCAX Channel 3 News



Project Specific RTC and CEC Activities

- **Projects 1, 2 and 4:** C-FARR: Collaborative on Food with Arsenic and Associated Risk and Regulation
- **Project 2:** International mercury policy and Dragonfly Project
- **Project 3:** Arsenic legislation in ME & NH and Arsenic Summit



Stakeholders and Collaborators

- USDA, FDA, EPA, WHO, EFSA (European Food Safety Authority), NH DES, NH DHHS, CT State Legislature, ME State Legislature, Academic Community, California EPA, CT Dept. of Health, US House of Representatives (Rosa DeLauro), USGS, ATSDR, CDC, National Groundwater Association, American Groundwater Trust, Toxics Action Center, Private Water Testing Labs, Water Treatment Companies, Realtors, Local Town Government, Conservation Commissions, Communities in Southeastern NH, and International Mercury Community
- Nick Fisher (SUNY Stony Brook), David Salt (Univ. of Aberdeen), Robert Mason (UCONN), Susan Korrick (Harvard), Yu Chen (NYU)



Sources and Protracted Effects of Early Life Exposure to Arsenic and Mercury

“Working together with the NIEHS, our collaborators and stakeholders, we look forward to continuing to provide cutting edge research to inform policy decisions and community actions that will lead to reduced human exposure to mercury and arsenic and improved public health.”



GEISEL
— SCHOOL OF —
MEDICINE
AT DARTMOUTH

For more information about our program
please go to:
<http://www.dartmouth.edu/~toxmetal/>