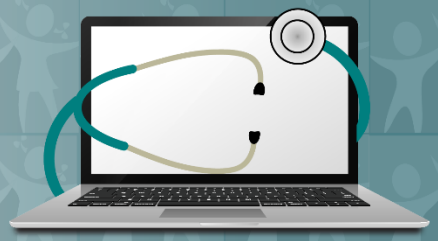
PEHSU NATIONAL CLASSROOM

Pediatric Environmental Health Specialty Units



www.pehsu.net/nationalclassroom.html

Webinars

- Series of scientific webinars that provide a forum for discourse on scientific issues.
- Live and On-Demand
- Case Conferences
  Journal Clubs
  Grand Rounds
- CE Available

Online Courses

- Evidence-based online courses on a variety of children's environmental health topics.
- Interactive and Self-Paced
- CE Available

Resource Catalog

- Fact sheets, journal publications, reports, and other resources for parents, community members, patients and healthcare professionals
- Topics included:
  Air Quality, Pesticides, Natural Disasters, BPA, Mold, Lead, Mercury

Old Poison, New Findings: Arsenic's effect on maternal and child health

Molly Kile, ScD
Associate Professor
Environmental & Occupational Health

PEHSU
Pediatric Environmental Health Specialty Units

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

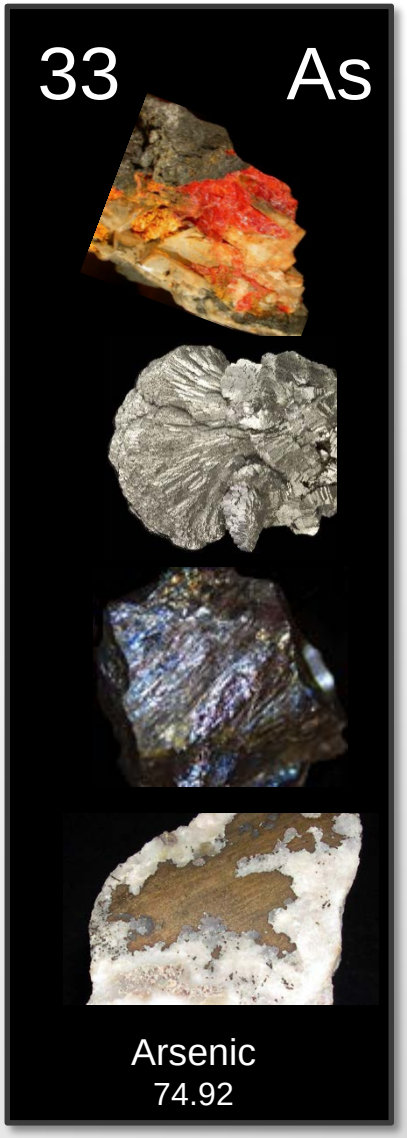
Dr Molly Kile is an Associated Professor at Oregon State University. She has been supported by funding from the US National Institutes of Environmental Health Sciences for studies investigating the health effects associated with chronic arsenic exposure (R01 ES015533, K01 ES017800, P30 ES000210, P30 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 (As^3)
    - Arsenate (As^5)
  - Organic arsenic forms
    - Arsphenamine [$C_{12}Cl_2H_{14}As_2N_2O_2(H_20)_2$]
    - Cacodyl [$As(CH_3)_2$]
    - Arsenobetaine ($C_5H_{11}AsO_2$)
    - Arsenocholine ($C_5H_{14}AsO$)



Old poison and old medical reports

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

- 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)

Image from: Toxipedia

Old poison and old mass poisonings

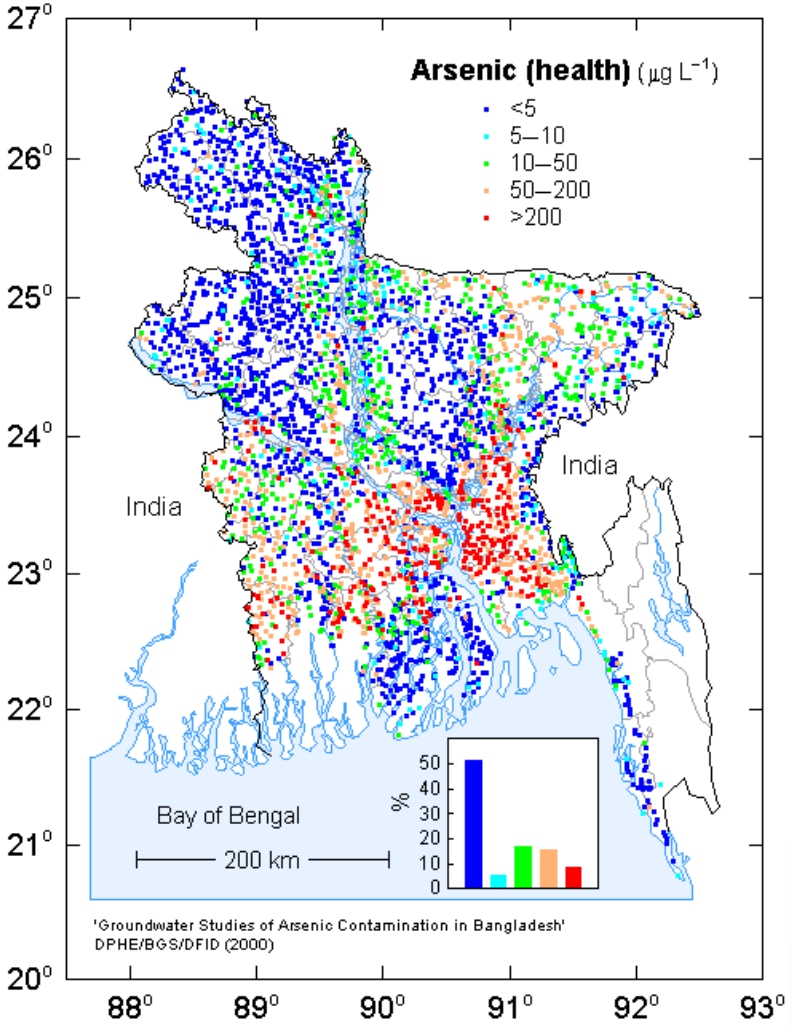
- Epidemic of neuropathy and skin ailments reported in beer drinkers in England (1900-1901)
- “Modern” brewing sugar was made using impure sulfuric acid
- Average arsenic concentration in Manchester beer was 1/9th grain per gallon (≈ 1,800 µg/L)

FIG. 1.
Lamellar and nodular hyperkeratosis of palms.

FIG. 2.
Hyperkeratosis of feet.

British Journal of Dermatology, 1902

Old poison and newer mass poisonings



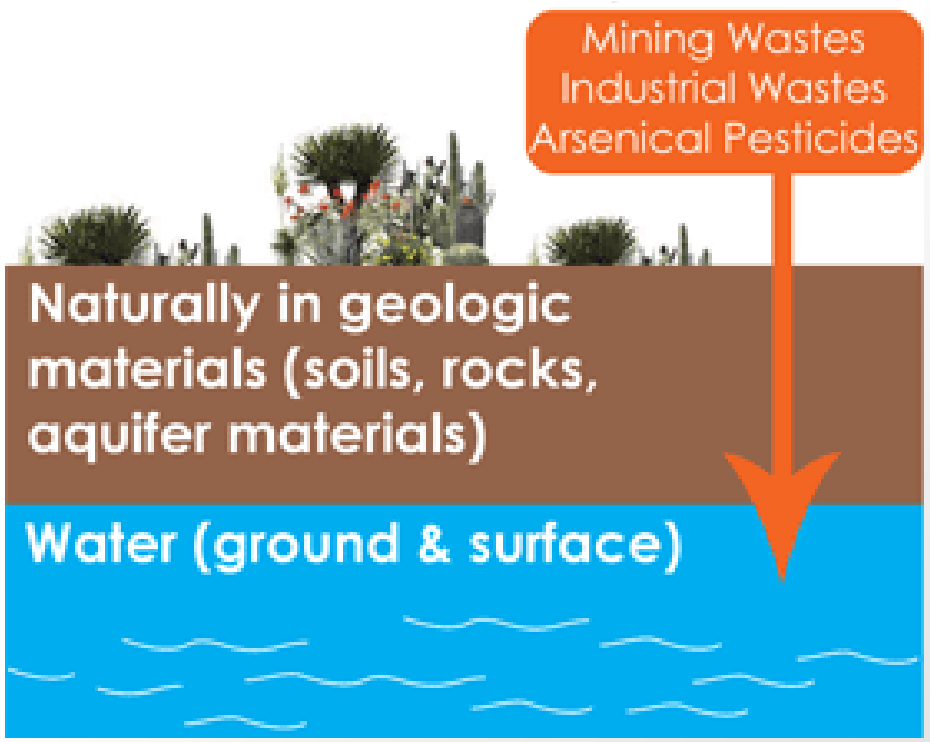
British Geological Survey (2001)

Chronic high exposure and human health

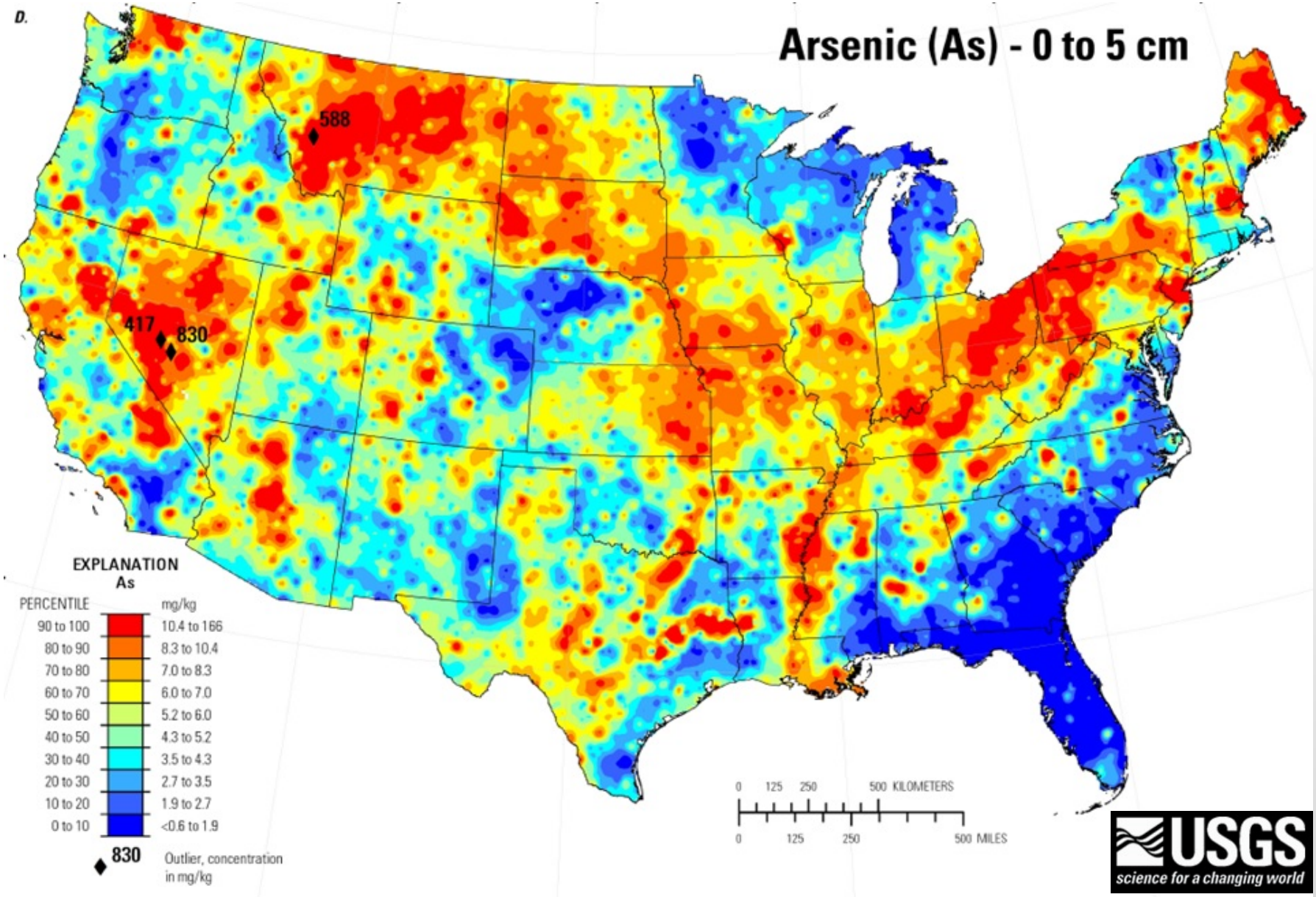
- Known human carcinogen
  - Lung
  - Bladder
  - Kidney
  - Liver
- Skin lesions
- Peripheral neuropathy
- Cardiovascular disease
- Type 2 diabetes

Sources of Exposure

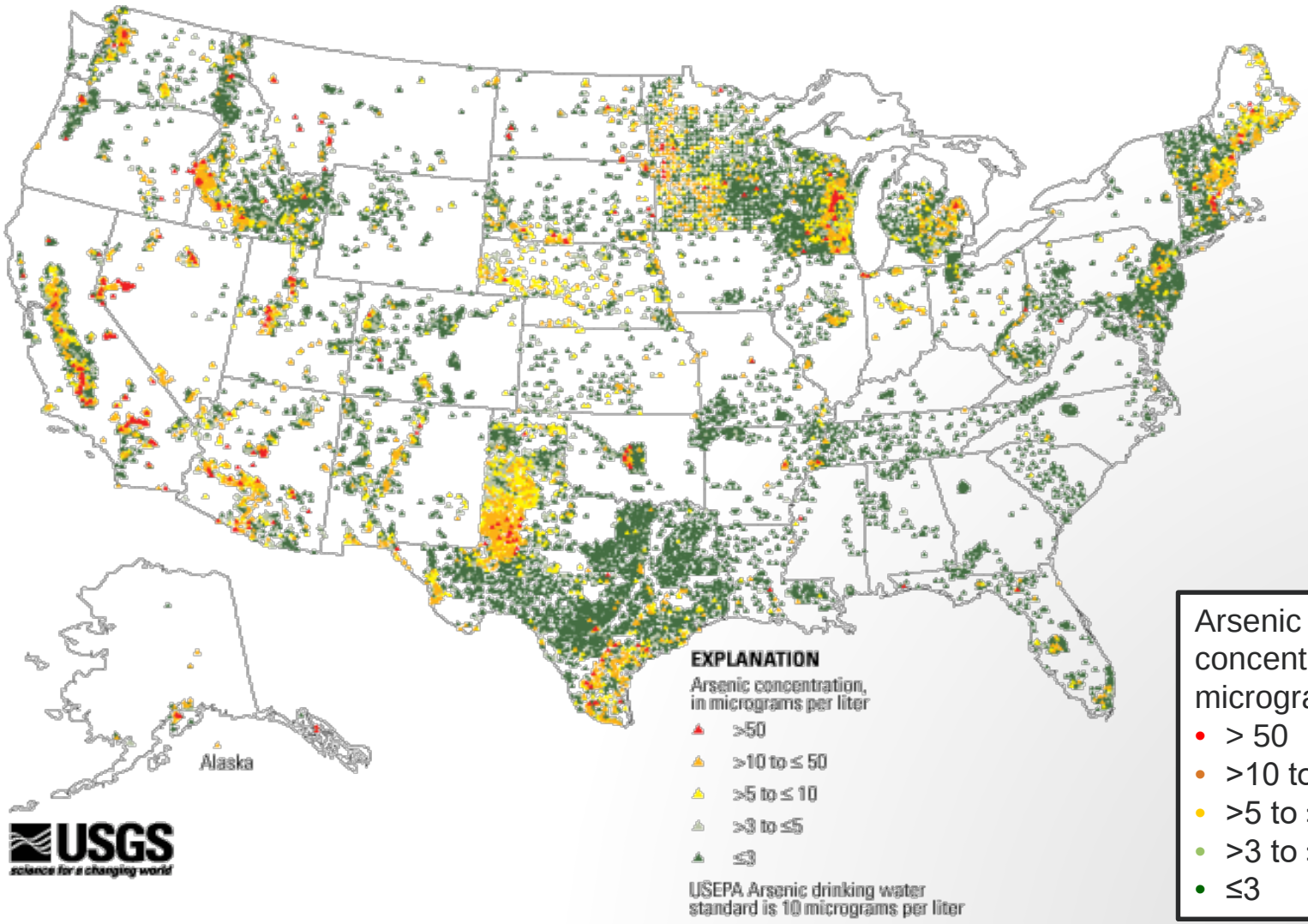
- Coal combustion
- Smelting of metal ores
- Soil and dust
  - Insecticides
  - Natural ores
- CCA-preserved wood
- Specialty glass manufacturers
- Semiconductors
- Poultry waste
- Herbal remedies
- Food
- Water



Distribution of arsenic in US soils



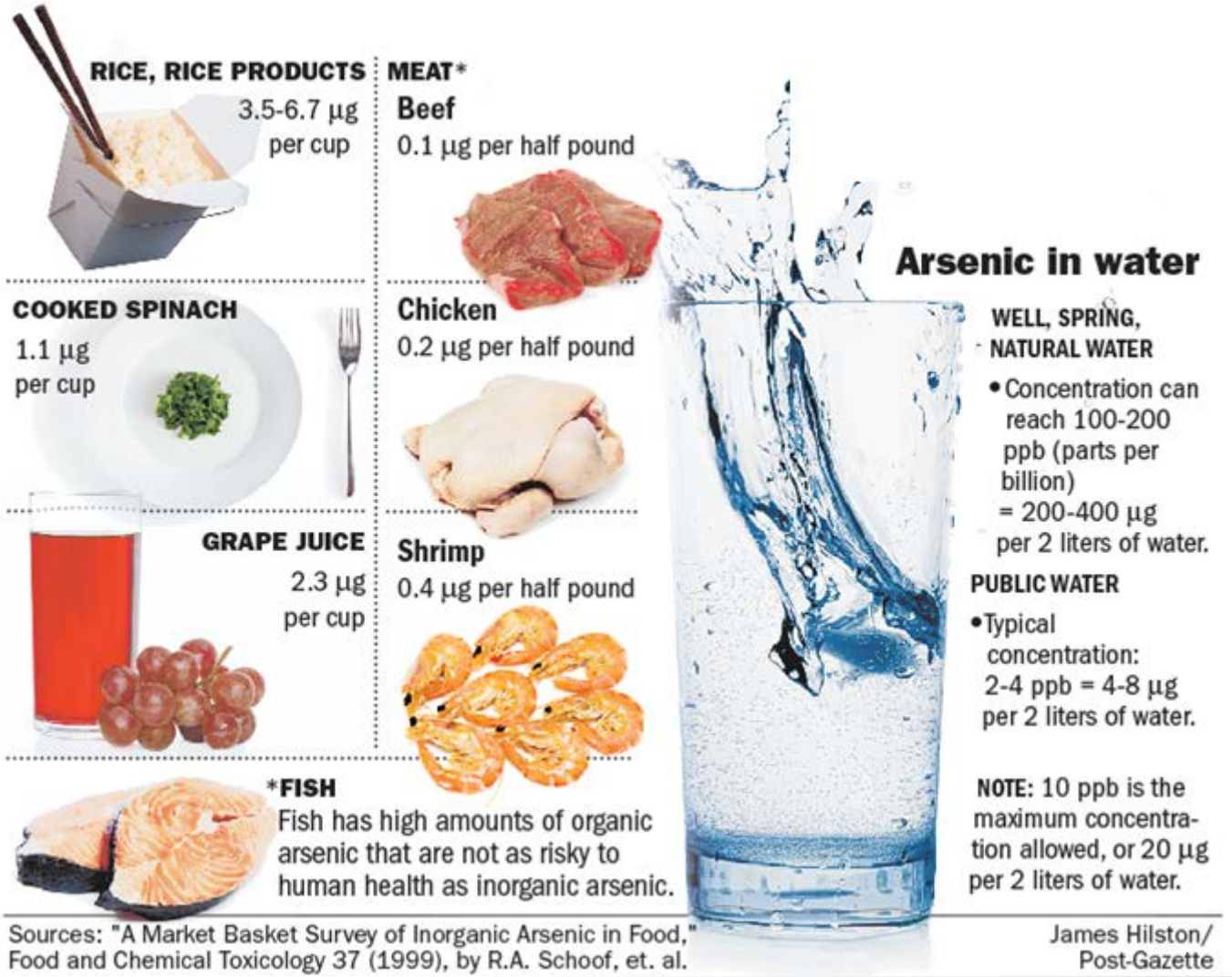
Distribution of arsenic in U.S. groundwater



Arsenic concentration in micrograms per liter

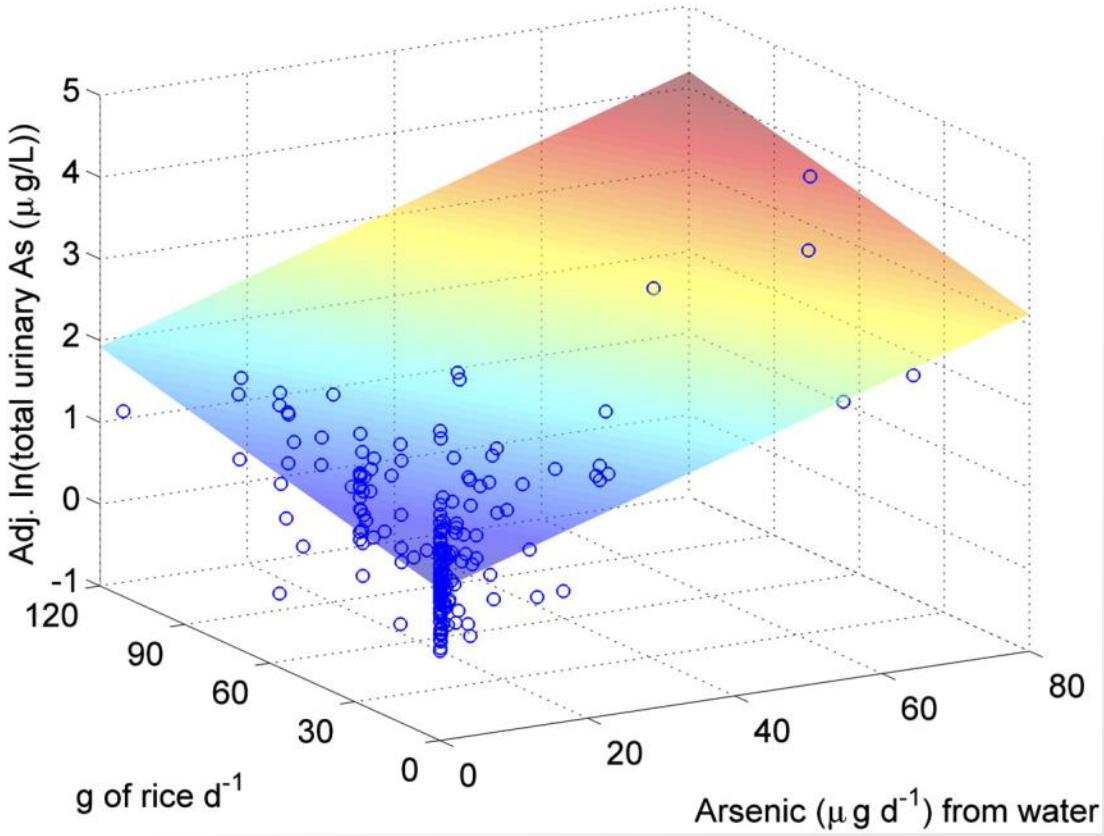
- > 50
- >10 to ≤50
- >5 to ≤10
- >3 to ≤5
- ≤3

Arsenic levels in common food and water



Source: Pittsburg Post-Gazette

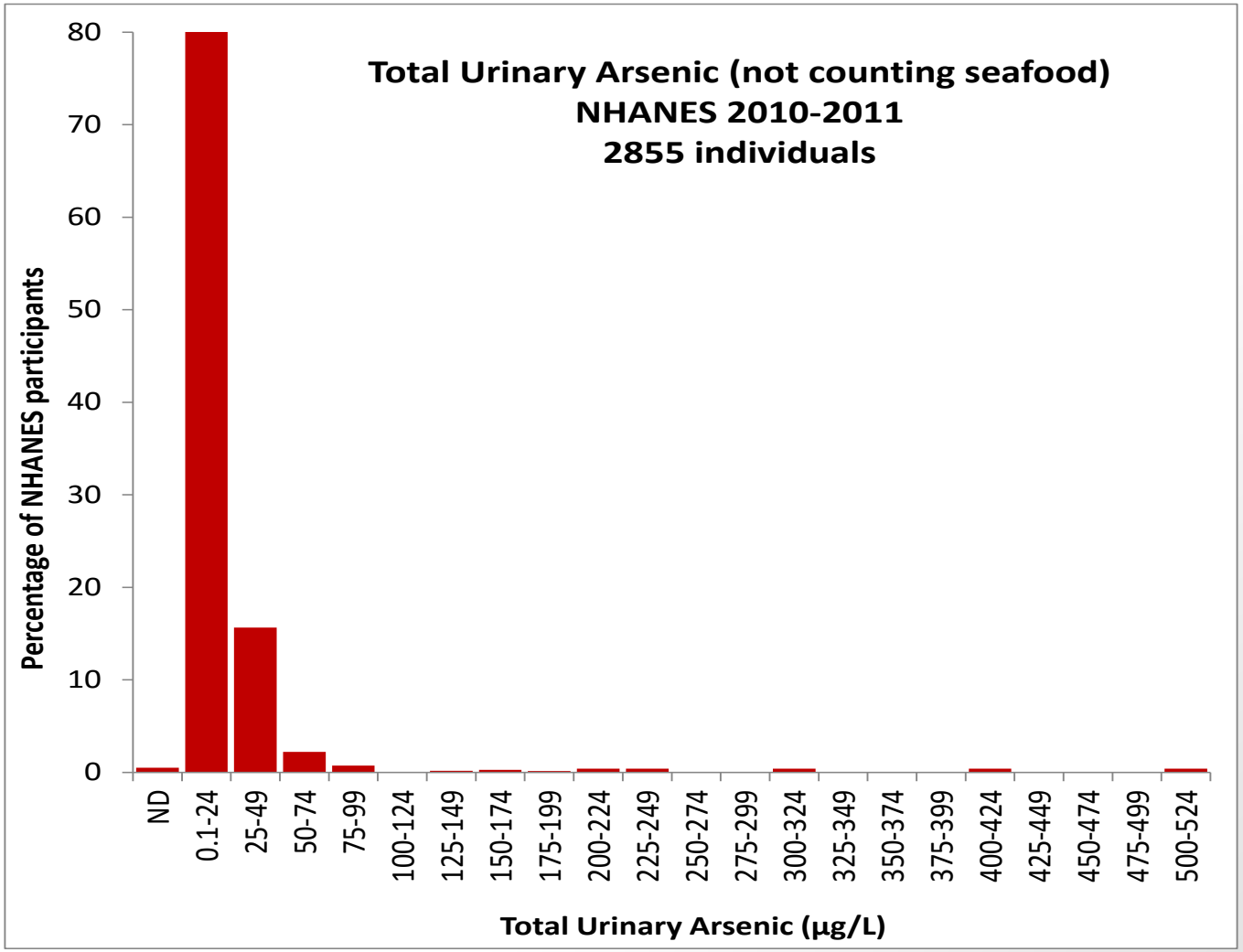
Age- and creatinine-adjusted ln-transformed total urinary arsenic comparing tap water (µg/d) and rice consumption (dry g/d)



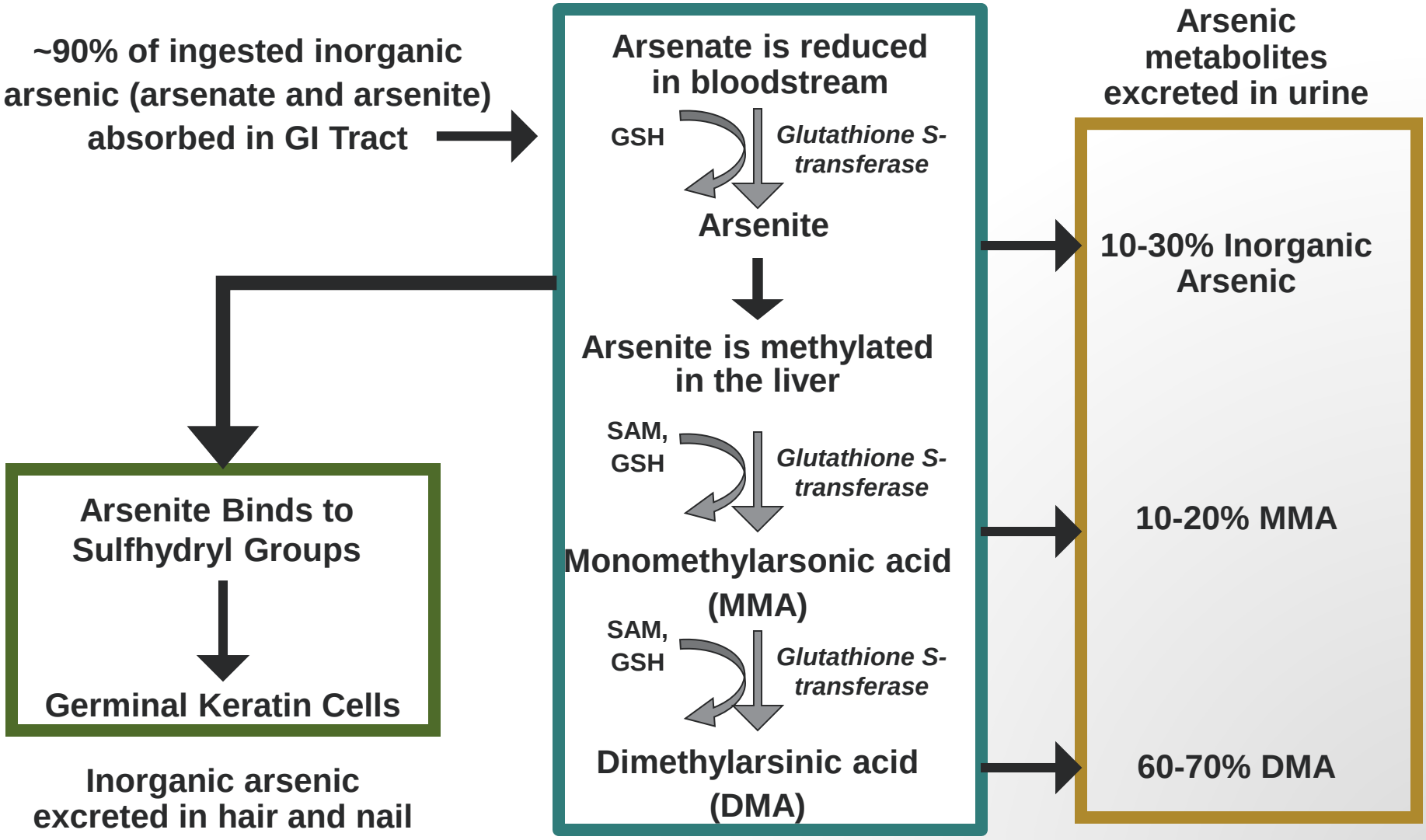
Consumption of 0.56 cup/d of cooked rice was comparable to drinking 1 L/d of 10 µg As/L water

Gilbert-Diamond et al (2011) PNAS, 108:20656-20660

Arsenic Exposure in U.S.



Arsenic Metabolism and Biomarkers



Considerations when using biomarkers

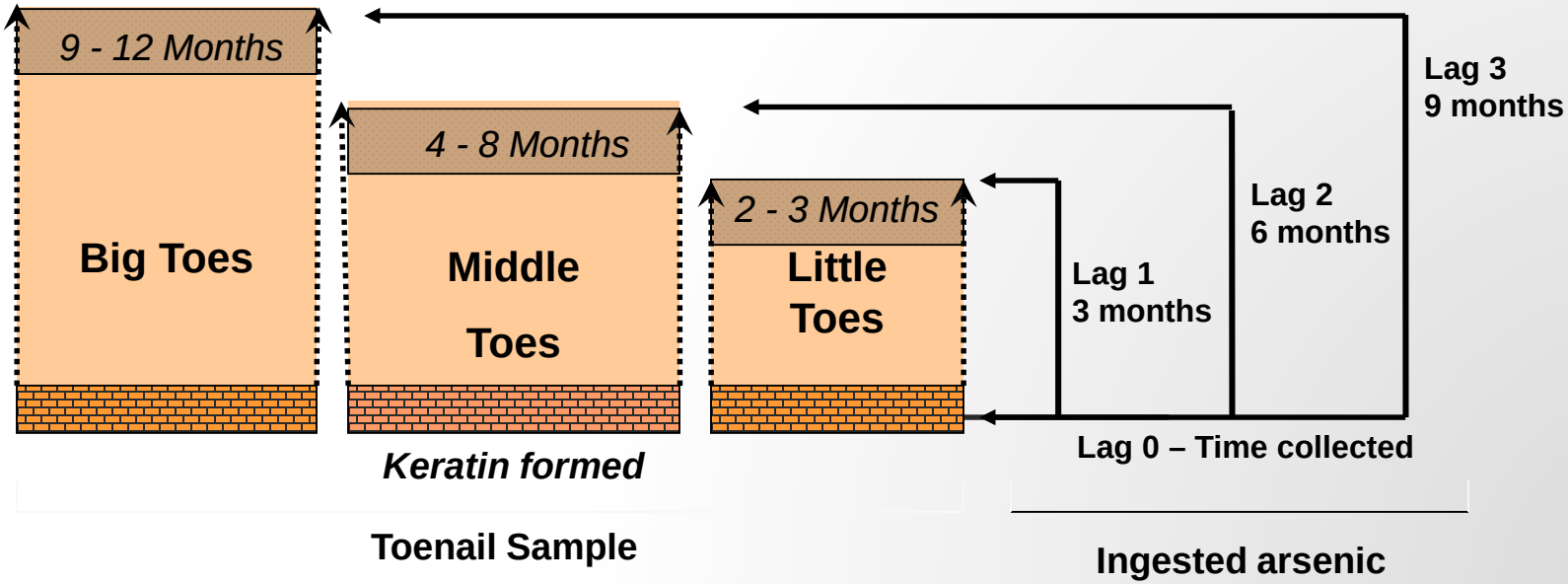
- Blood
  - Half-life is a few hours
  - Total arsenic will reflect all arsenic species including non-toxic exposures from seafood
- Urine
  - Half-life is approximately 3 days
  - Total arsenic will reflect all arsenic species including non-toxic exposures from seafood
  - Monitored by NHANES which 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



Maternal – Child Health

- 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)

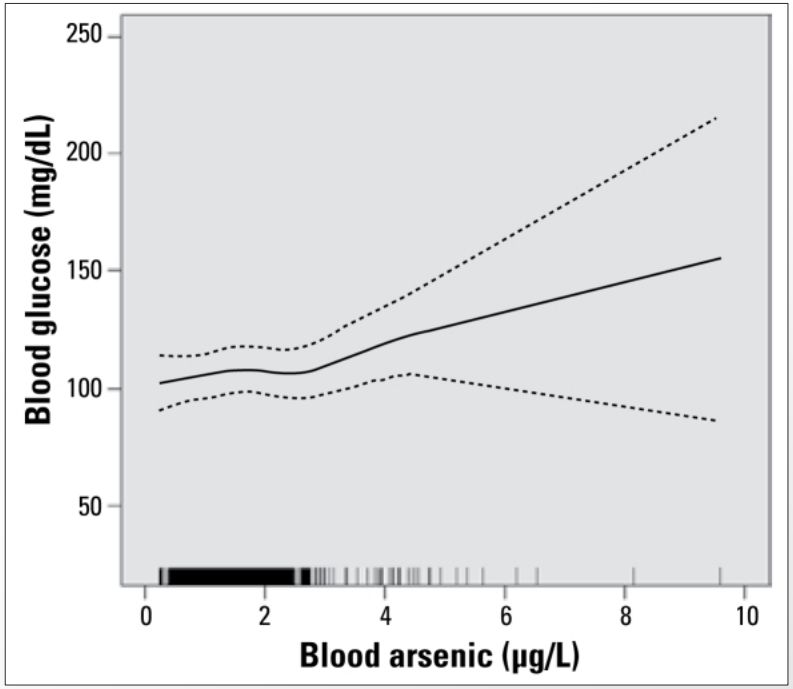
Photo: National Geographic, In the Womb

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

Arsenic and Maternal Glucose Tolerance

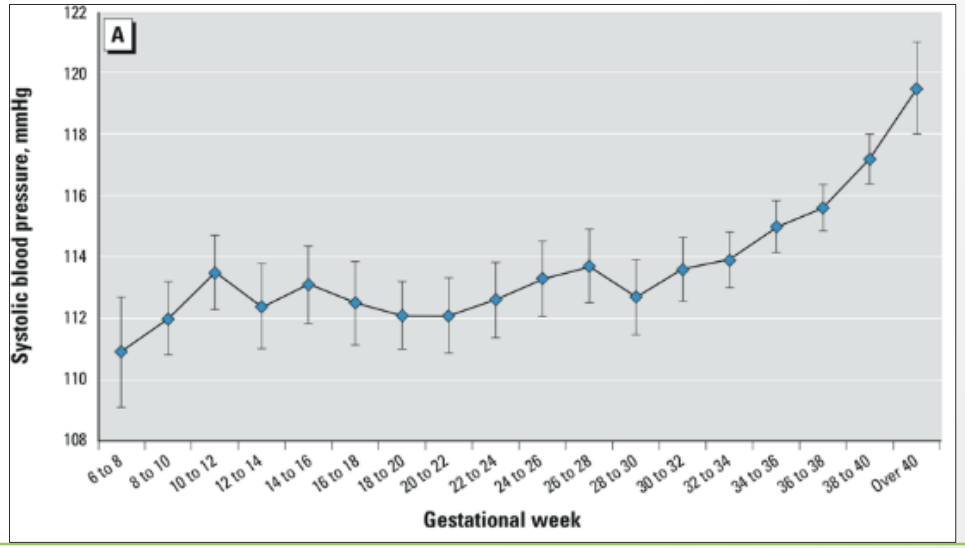
- Population living near abandoned mine site in U.S. (*n=532*)
- Maternal arsenic exposure measured in blood and hair
- Blood glucose (GTT) measured between 24-28 weeks gestation
- Women with the highest blood arsenic level had 2.8-fold higher odds of impaired GTT after controlling for other risk factors



Ettinger et al, Environmental Health Perspectives, 2009

Arsenic and Maternal Blood Pressure

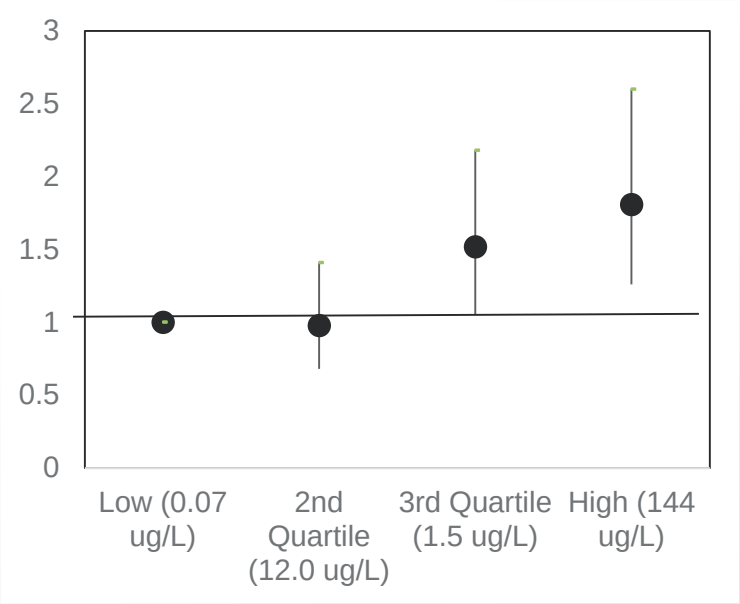
- Population living in New Hampshire using domestic wells (*n=512*)
- Maternal arsenic exposure measured in urinary arsenic at 24-28 weeks gestation
- Repeated blood pressure measurements throughout pregnancy
- Every 5 ug/L increase in urinary arsenic was associated with a 0.15 mmgHg increase in systolic BP per month and a 0.14 mmHg increase in pulse pressure per month



Farzan et al, Environmental Health Perspectives, 2015

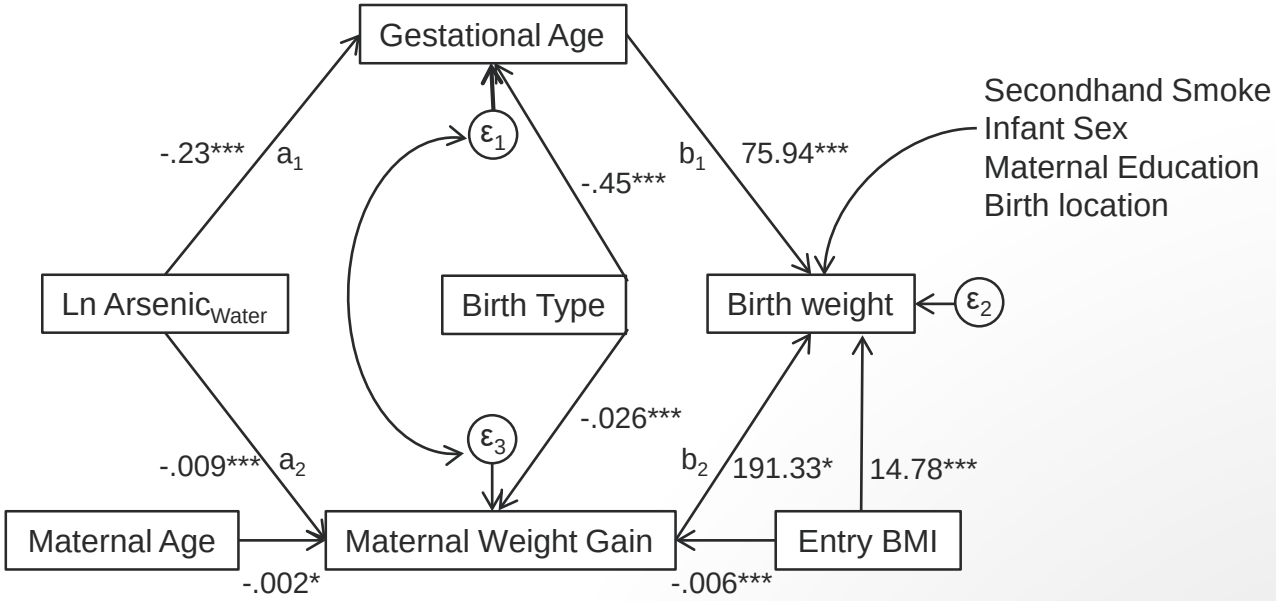
Arsenic Exposure and Morning Sickness

- 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

Arsenic exposure reduces birth weight by decreasing gestational age and reducing maternal weight gain



- Every unit increase in natural log water arsenic was indirectly associated with decreased birth weight (β=-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)

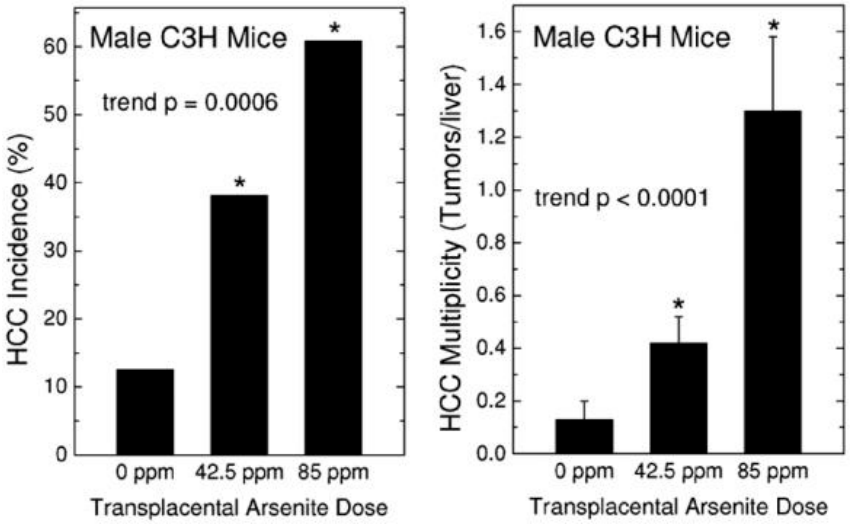
Infections	At least one infection	Lasting 2 or more days	With a physician visit	Treated with prescription medication
Respiratory tract infections (RTI)				
Any upper RTI	1.1 (0.8, 1.6)	1.2 (0.9, 1.7)	1.1 (0.8, 1.6)	**1.6 (1.0, 2.5)**
	133	*111*	*53*	*28*
Cold, runny or stuffed nose	1.0 (0.8, 1.4)	1.1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

Farzan et al (2013) Environmental Research, 126.

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

Arsenic and epigenetic modifications



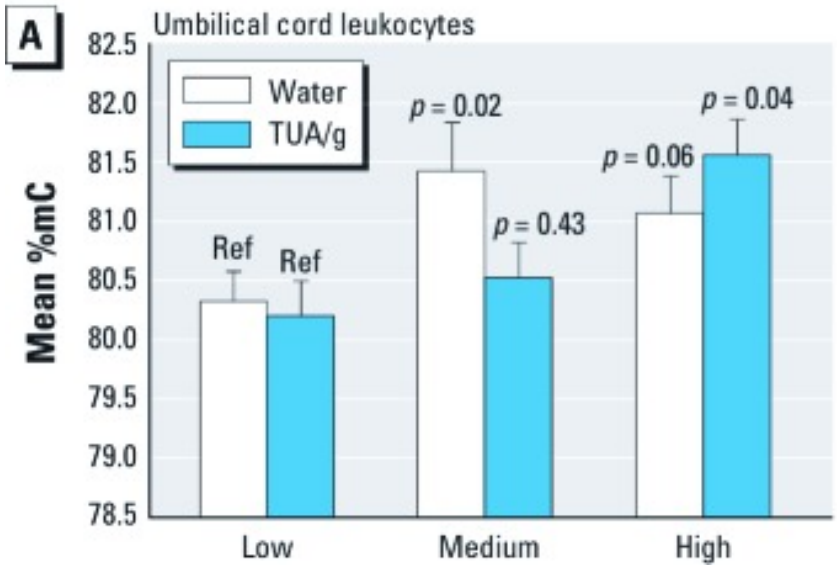
- Mice exposed to arsenic in utero had increased hepatocellular carcinoma incidence and multiplicity in adulthood (Waalkes et al., 2003)
- Arsenic decreased global and gene-specific DNA methylation in liver tissue (Waalkes et al, 2004, Xie et al, 2004)
- In vivo evidence that prenatal exposure to arsenic 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)

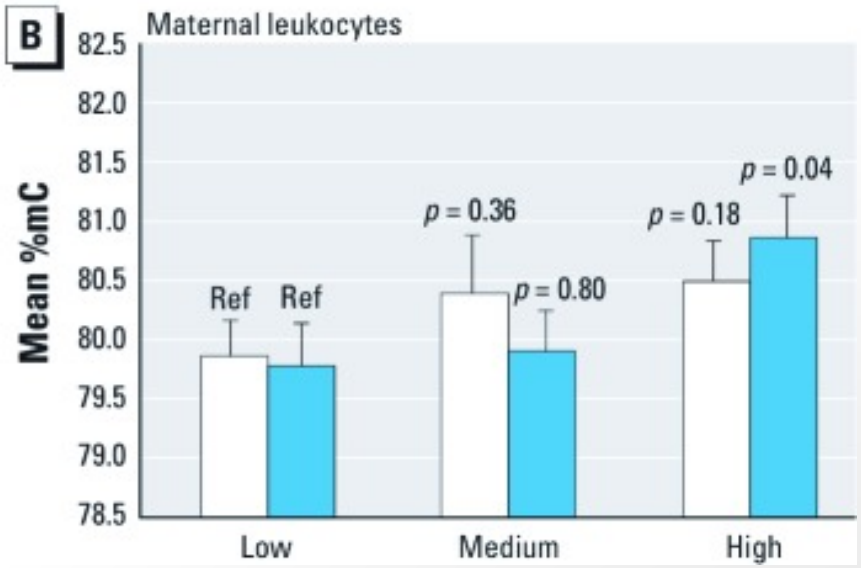
Early life exposure and chronic disease

- 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 power 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)





Water → **<1 µg/L** **1 – 2.2µg/L** **> 2.2µg/L**

TUA → 0.004-0.34 µg/g **0.35-0.64 µg/g** **> 0.64 µg/g**

<1 µg/L **1 – 2.2µg/L** **> 2.2µg/L**

0.004-0.34 µg/g **0.35-0.64 µg/g** **> 0.64 µg/g**

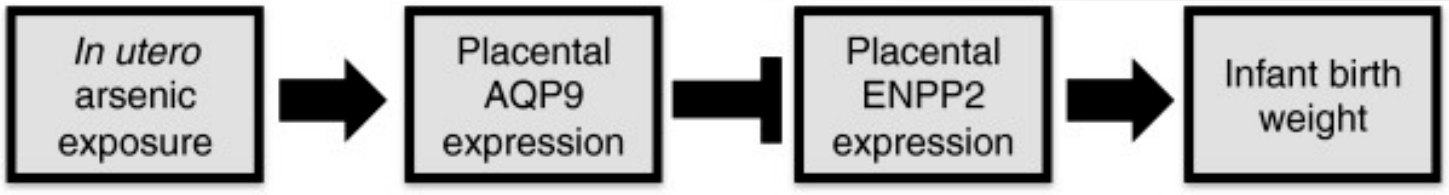
(A) umbilical cord leukocytes adjusted for average maternal BMI (21.0) and prematurity (≥ 37 weeks gestation)

(B) maternal leukocytes adjusted for average maternal BMI (21.0).

Kile et al (2012) Environmental Health Perspectives

In utero arsenic exposure, placental gene expression, and infant birthweight (n=133)

- 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



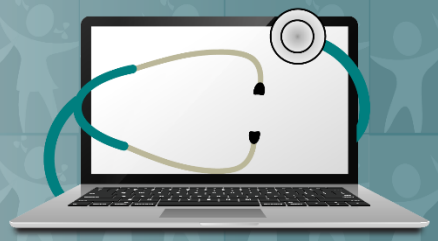
Fei et al, Environmental Health, 2013.

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

PEHSU NATIONAL CLASSROOM

Pediatric Environmental Health Specialty Units



www.pehsu.net/nationalclassroom.html

Webinars

- Series of scientific webinars that provide a forum for discourse on scientific issues.
- Live and On-Demand
- Case Conferences
  Journal Clubs
  Grand Rounds
- CE Available

Online Courses

- Evidence-based online courses on a variety of children's environmental health topics.
- Interactive and Self-Paced
- CE Available

Resource Catalog

- Fact sheets, journal publications, reports, and other resources for parents, community members, patients and healthcare professionals
- Topics included:
  Air Quality, Pesticides, Natural Disasters, BPA, Mold, Lead, Mercury