Welcome to the CLU-IN Internet Seminar

Arsenic - Health and Remediation Applications, Session 2 - Emerging Issues in Arsenic Exposure and Disease

Sponsored by: NIEHS Superfund Research Program

Delivered: November 2, 2012, 2:00 PM - 4:00 PM, EDT (19:00-21:00 GMT)

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Joshua W. Hamilton, Ph.D., Dartmouth College SRP Center (jhamilton@mbl.edu)
Moderator:

Visit the Clean Up Information Network online at www.cluin.org

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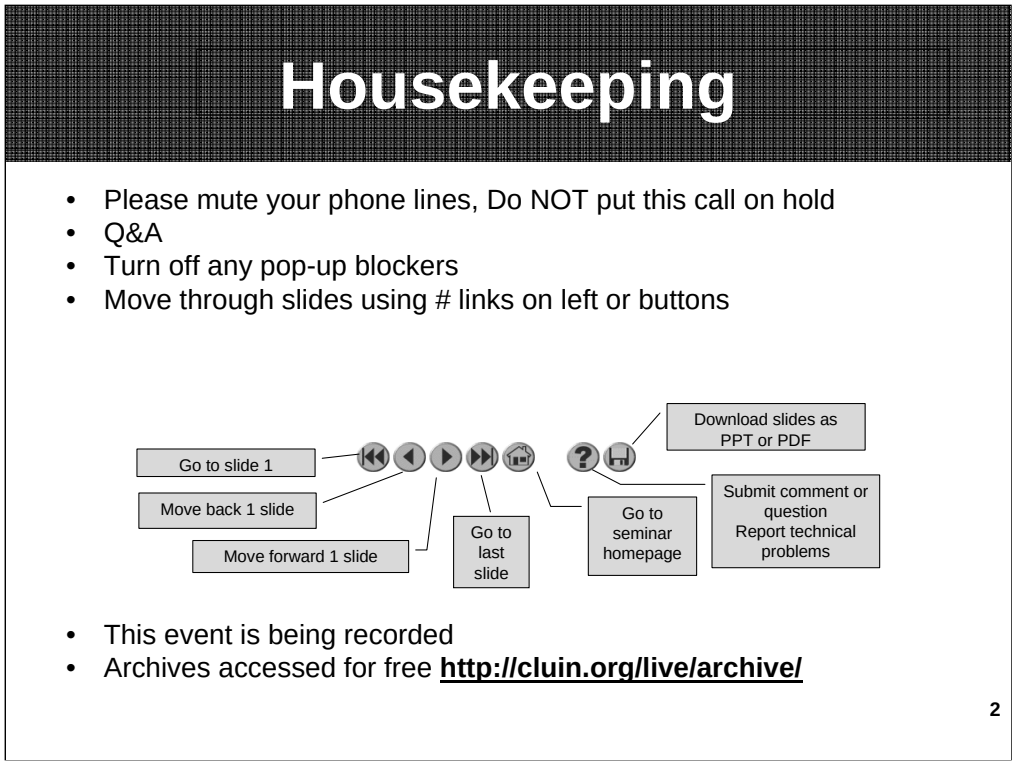


Although I'm sure that some of you have these rules memorized from previous CLU-IN events, let's run through them quickly for our new participants.

Please mute your phone lines during the seminar to minimize disruption and background noise. If you do not have a mute button, press *6 to mute #6 to unmute your lines at anytime. Also, please do NOT put this call on hold as this may bring delightful, but unwanted background music over the lines and interupt the seminar.

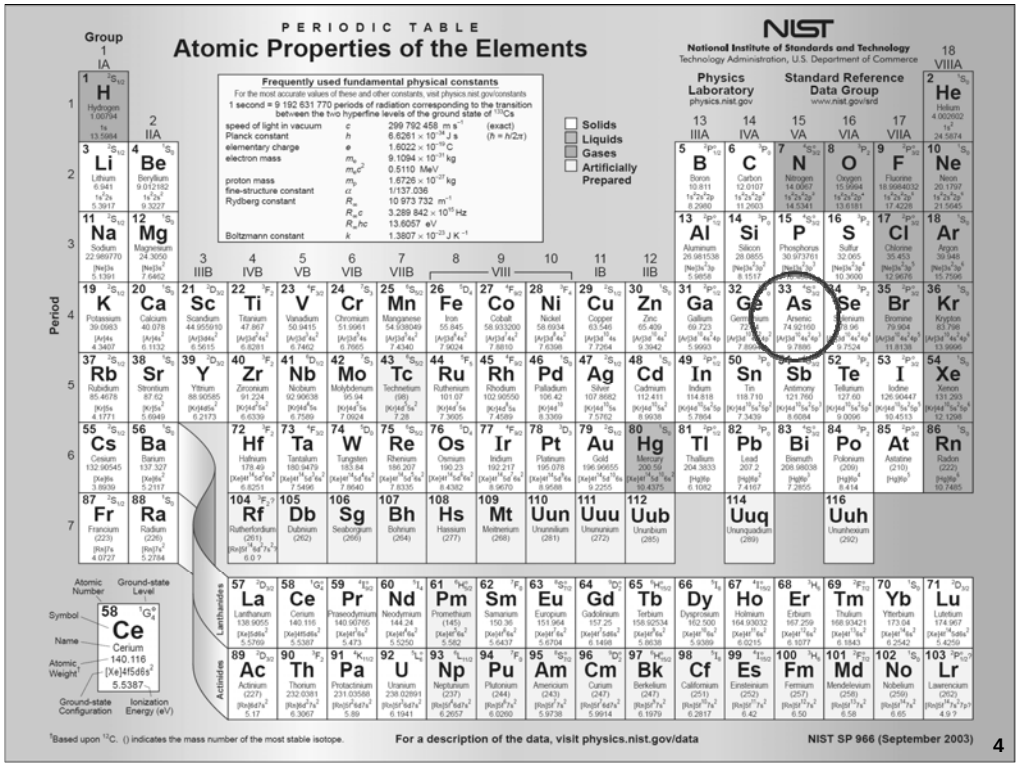
You should note that throughout the seminar, we will ask for your feedback. You do not need to wait for Q&A breaks to ask questions or provide comments. To submit comments/questions and report technical problems, please use the ? Icon at the top of your screen. You can move forward/backward in the slides by using the single arrow buttons (left moves back 1 slide, right moves advances 1 slide). The double arrowed buttons will take you to 1st and last slides respectively. You may also advance to any slide using the numbered links that appear on the left side of your screen. The button with a house icon will take you back to main seminar page which displays our agenda, speaker information, links to the slides and additional resources. Lastly, the button with a computer disc can be used to download and save today's presentation materials.

With that, please move to slide 3.

The Astonishing Long-Term Effects of *In Utero* & Early Childhood Exposure to Arsenic

Allan H. Smith MD, PhD
Professor of Epidemiology
University of California, Berkeley

Recent findings from the Arsenic Health Effects Research Program
With support from NIH including the NIEHS Superfund Program


PERIODIC TABLE
Atomic Properties of the Elements
NIST
National Institute of Standards and Technology
Technology Administration, U.S. Department of Commerce
Physics Laboratory
physics.nist.gov
Standard Reference Data Group
www.nist.gov/srd
Frequently used fundamental physical constants
For the most accurate values of these and other constants, visit physics.nist.gov/constants
1 second = 9 192 631 770 periods of radiation corresponding to the transition between the two hyperfine levels of the ground state of 133Cs
speed of light in vacuum c 299 792 458 m s−1 (exact)
Planck constant h 6.6261 × 10−34 J s (h = h/2π)
elementary charge e 1.6022 × 10−19 C
electron mass me 9.1094 × 10−31 kg
mec2 0.5110 MeV
proton mass mp 1.6726 × 10−27 kg
fine-structure constant α 1/137.036
Rydberg constant R∞ 10 973 732 m−1
R∞c 3.289 842 × 1015 Hz
R∞hc 13.6057 eV
Boltzmann constant k 1.3807 × 10−23 J K−1
Solids
Liquids
Gases
Artificially Prepared
Group
Period
Lanthanides
Actinides
Atomic Number
Ground-state Level
Symbol
Name
Atomic Weight†
Ground-state Configuration
Ionization Energy (eV)
†Based upon 12C. () indicates the mass number of the most stable isotope.
For a description of the data, visit physics.nist.gov/data
NIST SP 966 (September 2003)
4

The Berkeley Arsenic Health Effects Research Group (ASRG)

Arsenic Research Group

Not

Allan Smith's Research Group

Associate Director: Craig Steinmaus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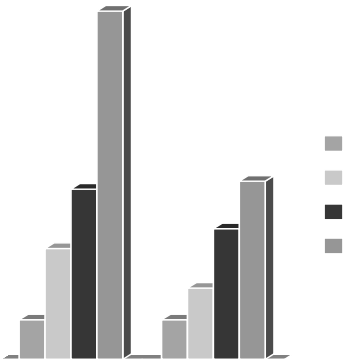
When I first started research on arsenic in water over 20 years ago, we only knew it caused skin lesions and skin cancer.

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)

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
- bischlormethyl ether
- nickel
- arsenic

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

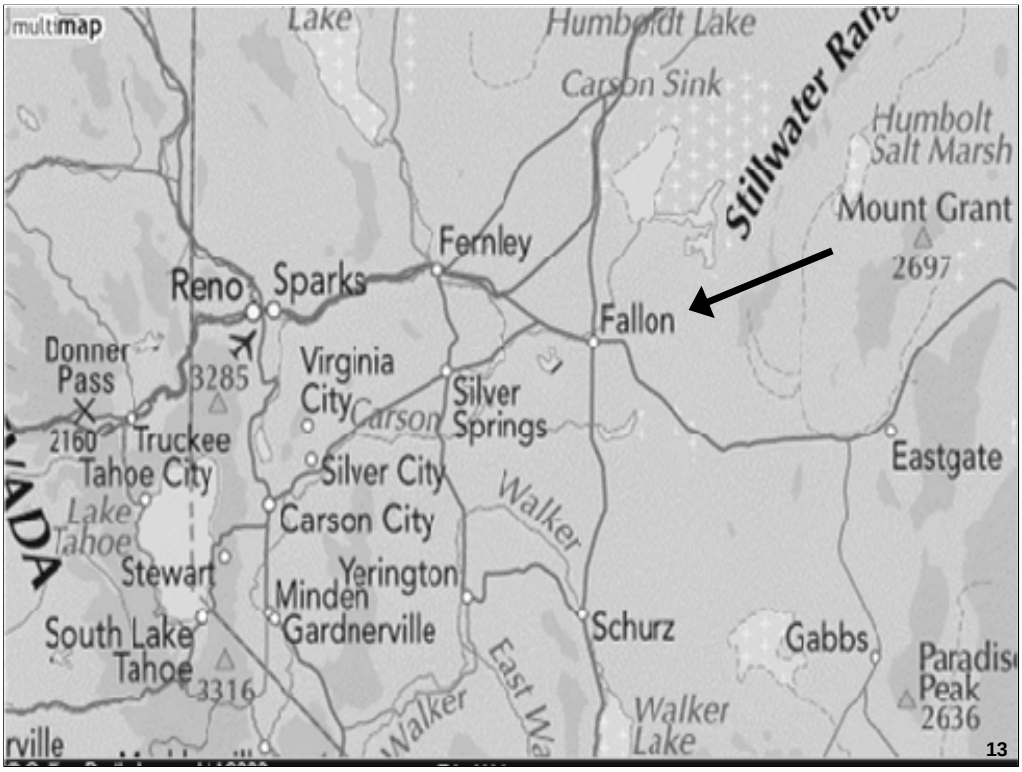
The lost and forgotten arsenic-exposed population

"the number of people consuming water from private wells with arsenic concentrations above 10 µg/L **could be over 2 million people"**

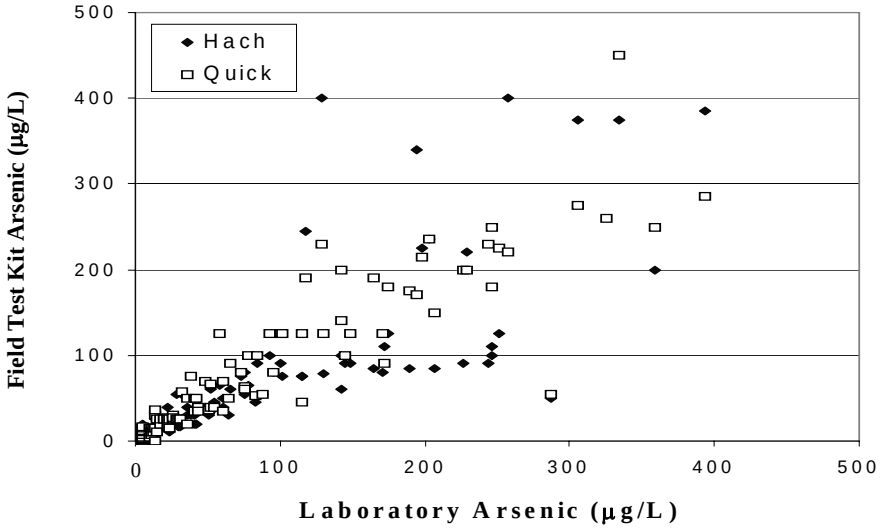
Where is this population?

Right here in the USA

Steinmaus et al. In Press.

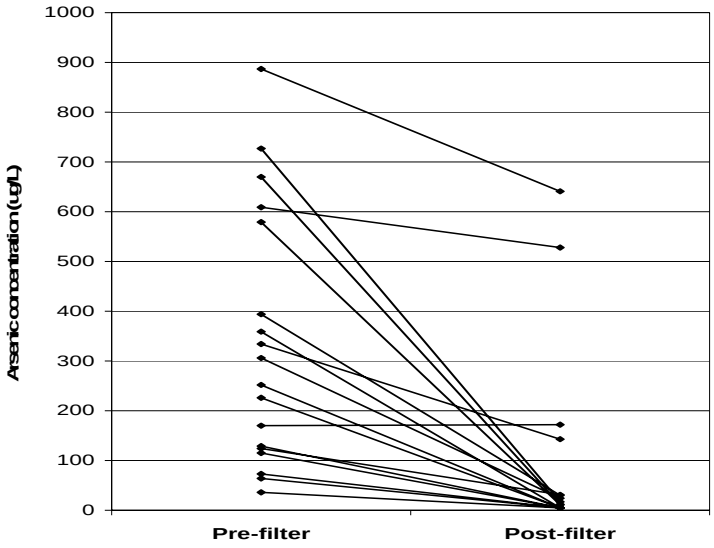

multimap
Lake
Humboldt Lake
Carson Sink
Stillwater Range
Humbolt
Salt Marsh
Mount Grant
2697
Fernley
Reno
Sparks
Fallon
Donner
Pass
2160
3285
Truckee
Tahoe City
Virginia
City
Carson
Silver
Springs
Silver City
Carson City
Eastgate
Walker
Lake
Tahoe
Stewart
Yerington
Minden
Gardnerville
Schurz
Gabbs
South Lake
Tahoe
3316
East Walker
Walker
Lake
Paradise
Peak
2636
13

There are high concentrations of arsenic in private wells in the U.S. too



Steinmaus CM, George CM, Kalman DA, Smith AH.
Environ Sci Technology, 40:3362-3366, 2006

People with private wells are on their own



Gearoge CM …… Steinmaus C. Arch Environ Occup Health 61:171-175, 2006.

CHILE

Region **II**

Region **V**

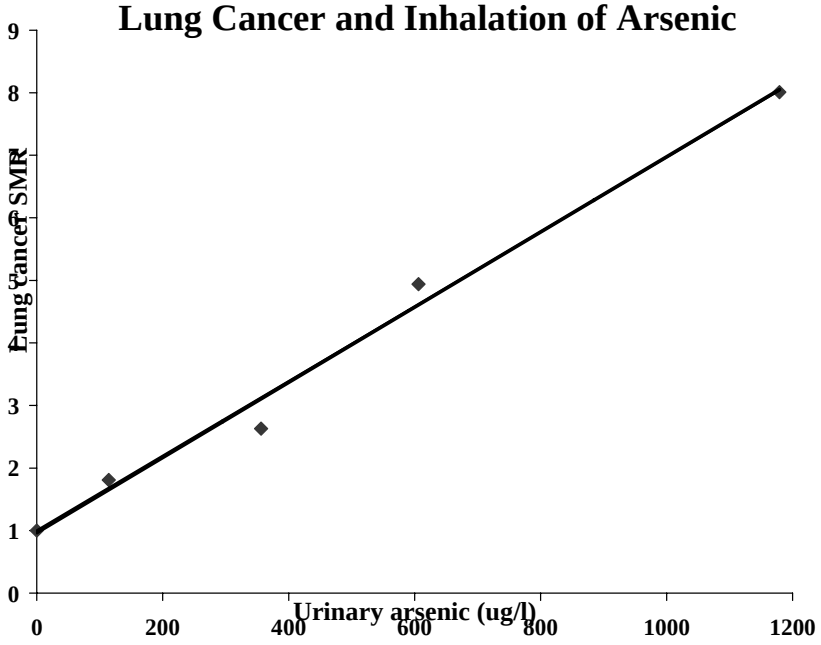
Lung Cancer Mortality Region II Chile, 1989-1993

Age Group	30-39	40-49	50-59	60-69	70-79	SMR	p value
Women							
Observed	5	23	21	41	47		
Expected	1.2	3.0	8.0	16.0	13.3		
O/E	4.2	7.7	2.6	2.6	3.5	3.1	p<0.001
Men							
Observed	14	48	142	177	129		
Expected	1.2	8.1	28.5	61.8	32.1		
O/E	11.7	5.9	4.9	2.9	4.0	3.8	p<0.001

Smith A. H. et al. American Journal of Epidemiology, 1998.

Mario Goycolea

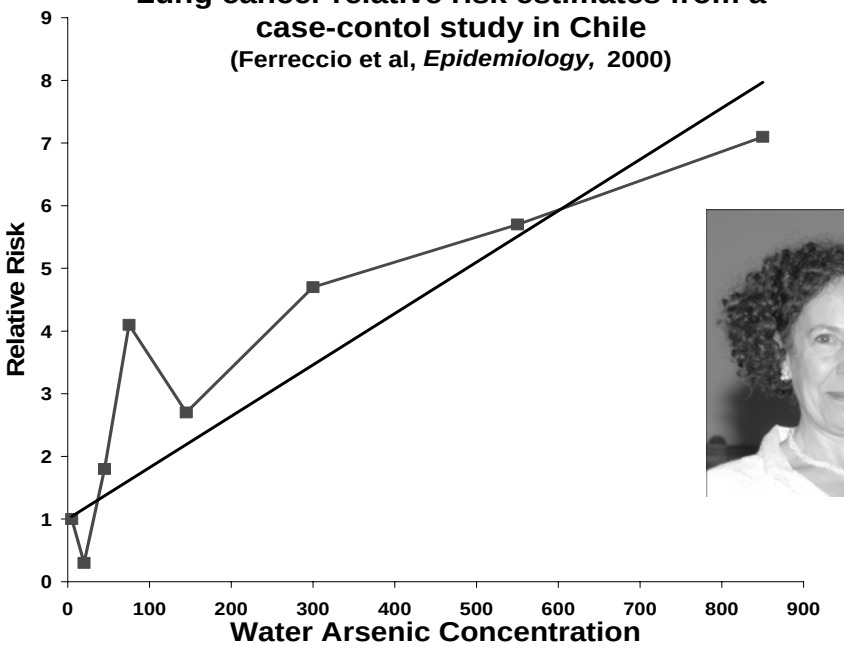
Lung Cancer and Inhalation of Arsenic



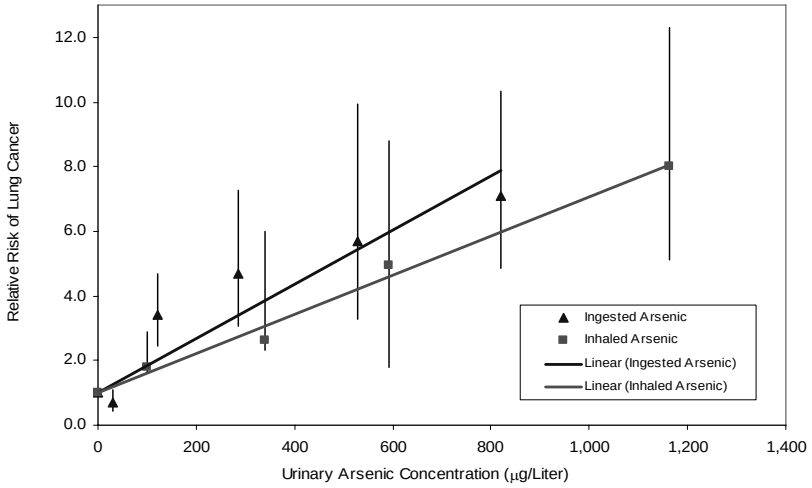
Enterline PE et al, Am J Epidemiol 1987;125:929-38

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.



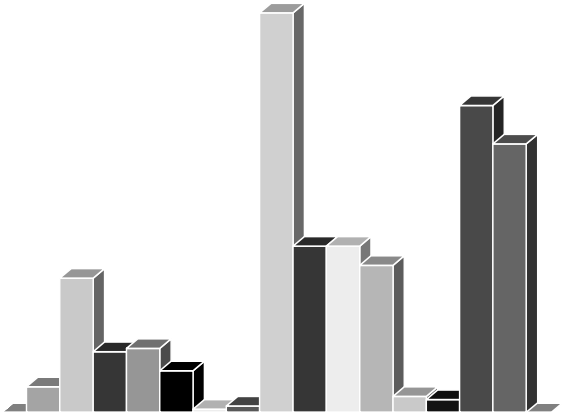
Smith AH, Ercumen A, Yuan Y, Steinmaus CM.. J Exposure Science and Environmental Epidemiology 19:343-8, 2009

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

Smith AH, Lopipero PA, Bates MN, Steinmaus CM.
Arsenic epidemiology and drinking water standards.
Science 296: 2145-6, 2002

Cancer risk from contaminants in drinking water other than arsenic

Per 100,000

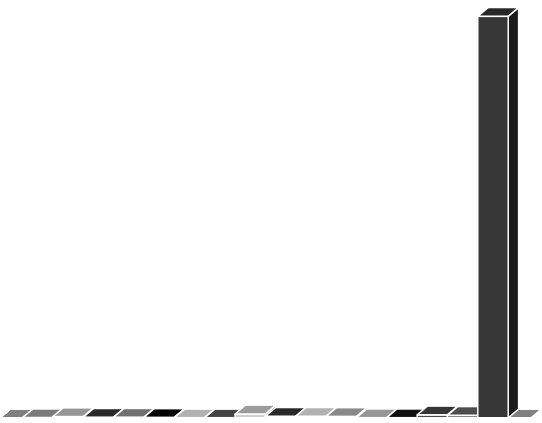


Top of the list:

Ethylene dibromide

Cancer risk from contaminants in drinking water including arsenic

Per 100,000



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

Marshall G, Ferreccio C, et al.

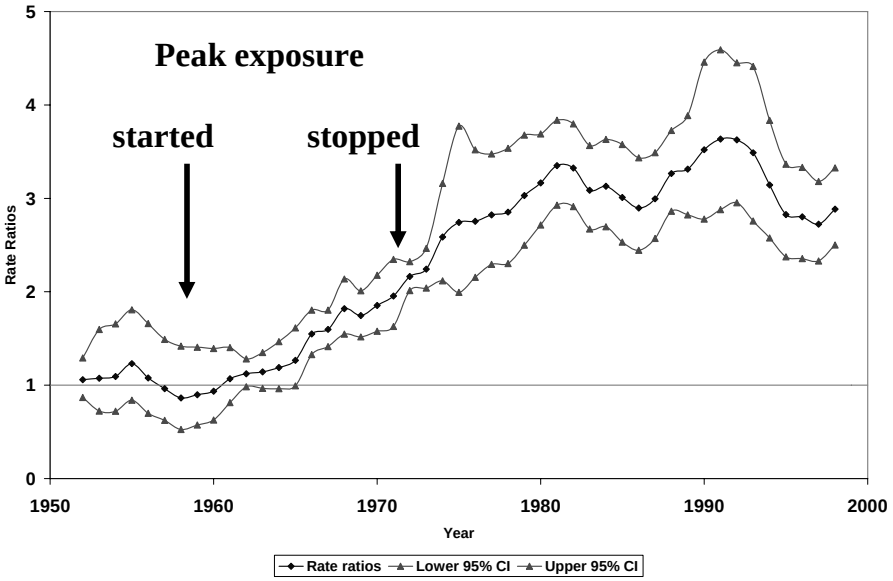
Fifty-year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water.

J Natl Cancer Inst 99:920-928, 2007

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 Marshall et al, J. Natl Cancer Inst, 2007



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

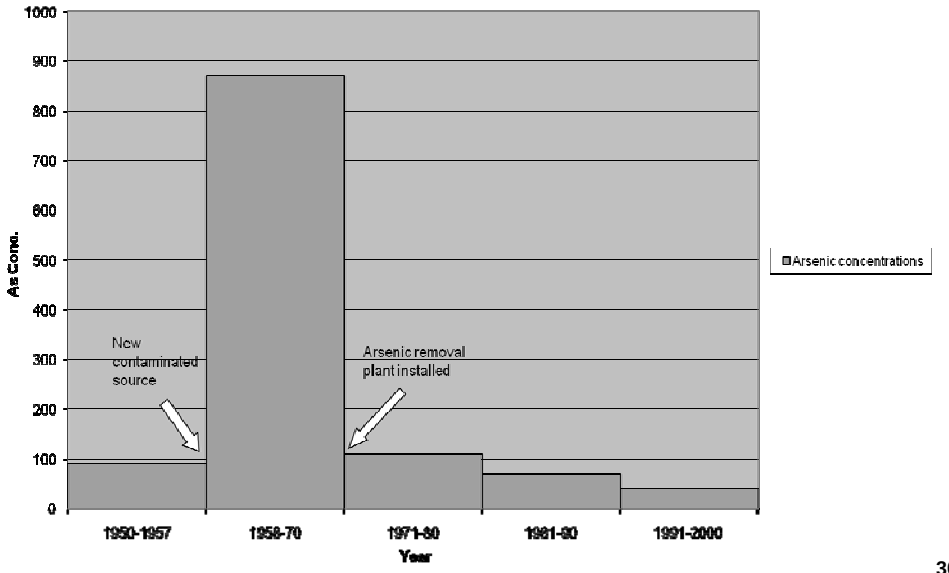
Effect of early life exposure

In *utero*

and in the first few years of childhood

Source: Project Well, West Bengal, India, 2003

Arsenic concentrations in drinking water in the city of Antofagasta (popn 200,000) in Chile



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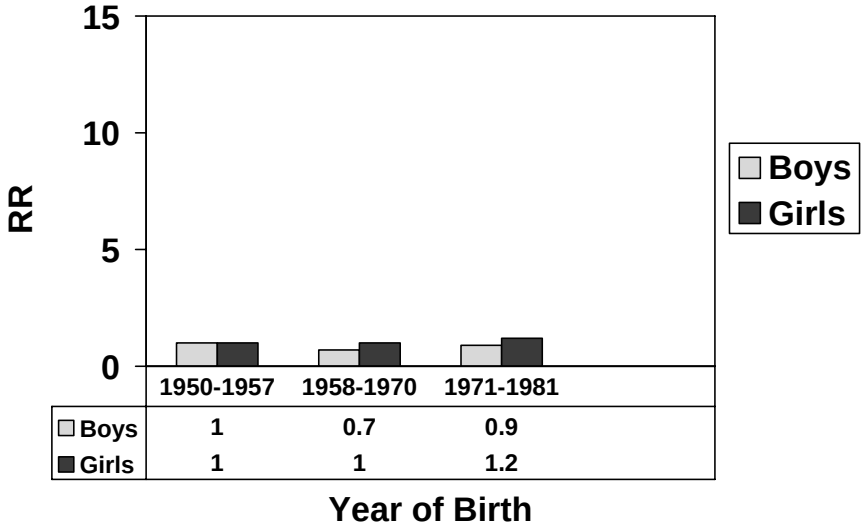
All childhood cancers

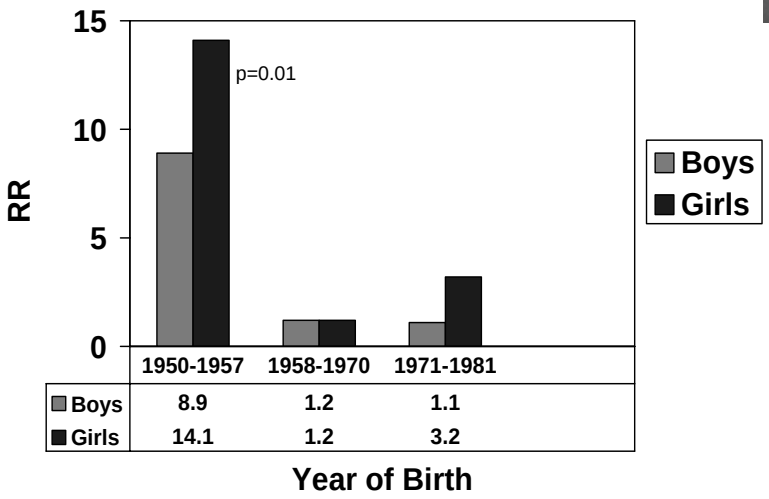


	1950-1957	1958-1970	1971-1981
Boys	1	0.7	0.9
Girls	1	1	1.2

Year of Birth

Liaw J, et al *Increased childhood liver cancer mortality and arsenic in drinking water in northern Chile.* **Cancer Epidemiol Biomarkers Prev. 2008.**

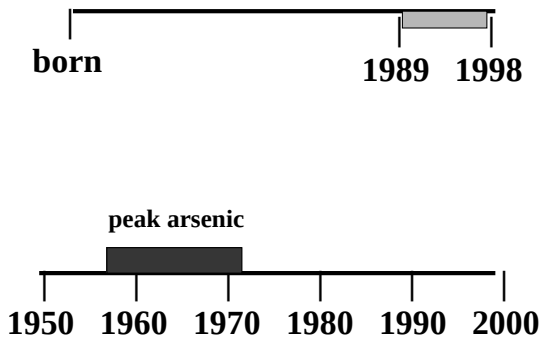
Liver cancer



	1950-1957	1958-1970	1971-1981
Boys	8.9	1.2	1.1
Girls	14.1	1.2	3.2

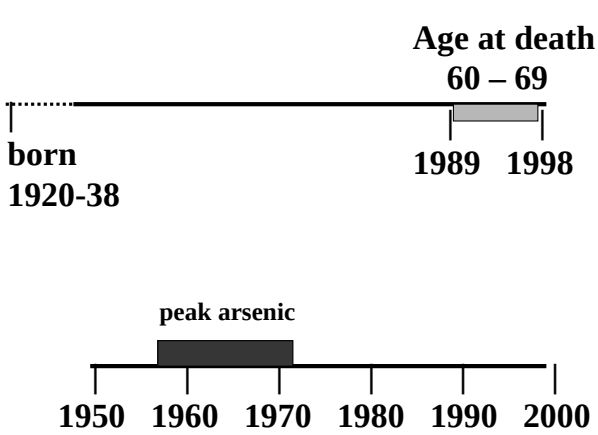
Year of Birth

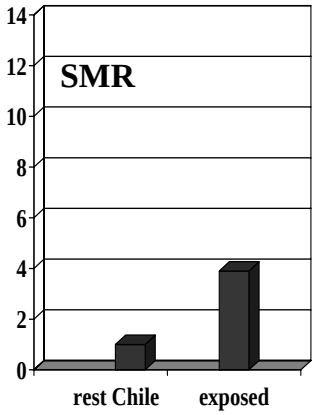
Lung cancer mortality in men according to exposure in childhood



Lung cancer mortality in older men

(SMR = standardized mortality ratio = observed/expected deaths)

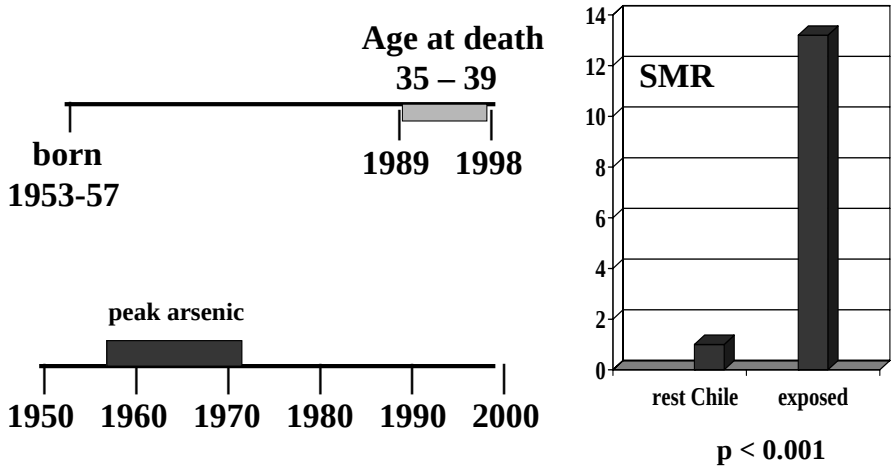




p < 0.001

Lung cancer mortality in men according to exposure in childhood

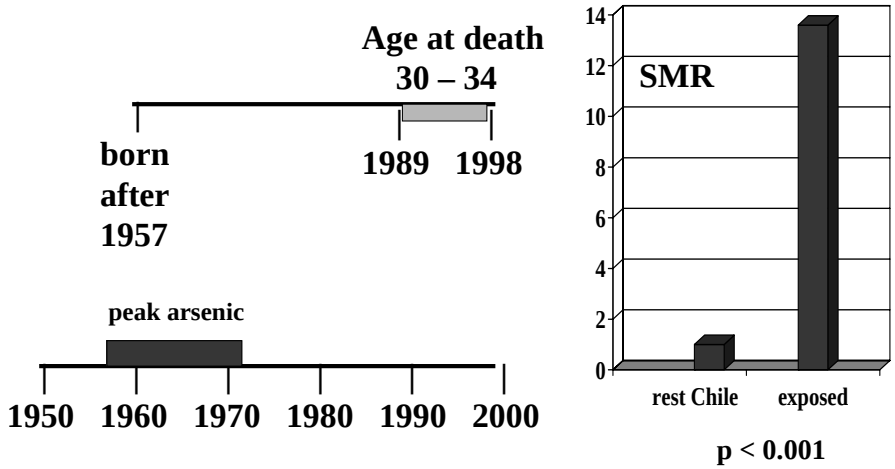
(SMR = standardized mortality ratio = observed/expected deaths)



p < 0.001

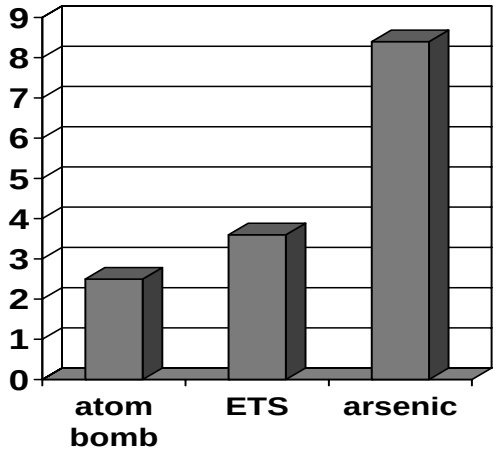
Lung cancer mortality in men according to exposure in childhood

(SMR = standardized mortality ratio = observed/expected deaths)



p < 0.001

Childhood exposures and young adult lung cancer relative risks

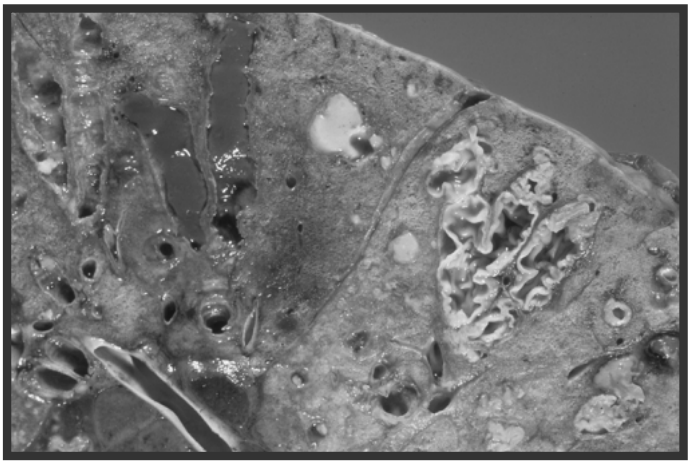


- Atomic bomb survivors Hiroshima and Nagasaki aged 10-20 in 1945. No cases in those exposed *in utero* or under age 10.
- A study giving lung cancer relative risks in the age range 30-39 following many hours of daily passive smoking as children (only four cases).
- Lung cancer relative risks in age range 30-39 in Region II of Chile following early life exposure to arsenic in water. There were 32 lung cancer deaths with 3.8 expected (RR=8.4, $p<0.001$).

Smith AH et al. Environmental Health Perspectives 2006

End Stage Lung Disease

Obstruction, Infection, Hemoptysis, Bronchiectasis



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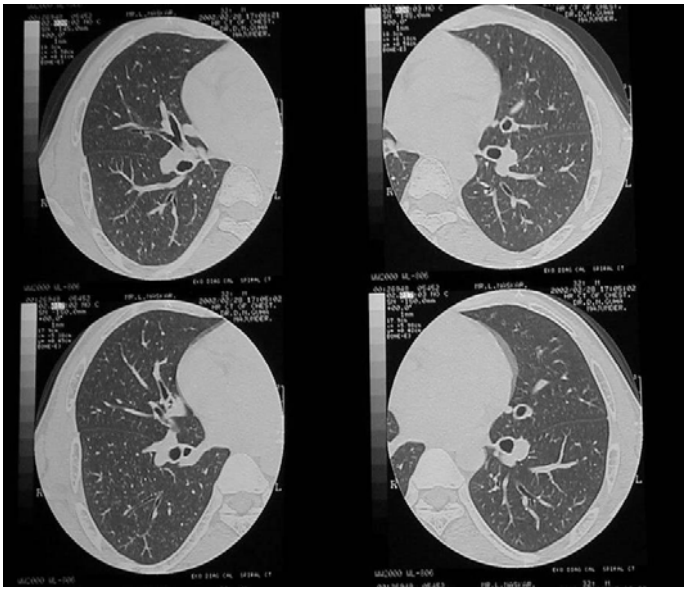
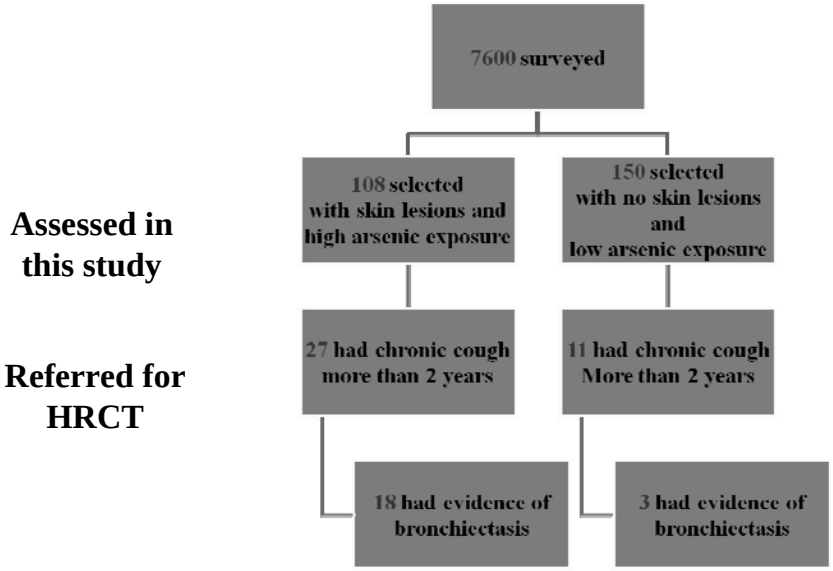
High resolution computed tomography (HRCT) with readings in India and the United States without knowing who had arsenic skin lesions.



Dr. D. N. Guha Mazumder

Craig Steinmaus

Study design, x-ray (HRCT) study in West Bengal, India



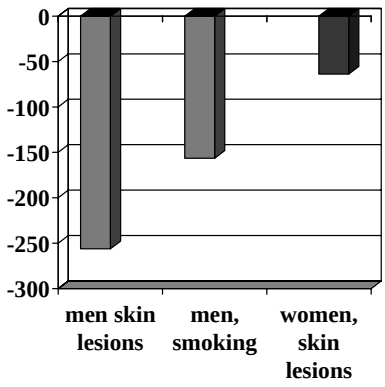
Assessed in this study

Referred for HRCT

10-fold increased prevalence of bronchiectasis OR=10.1, p<0.01

Epidemiology 2005

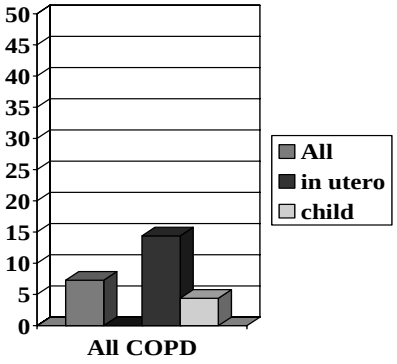
Lung function findings of reduced FEV1 adjusted for age and height

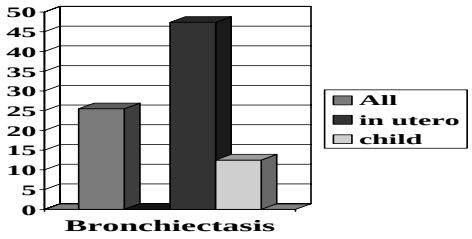


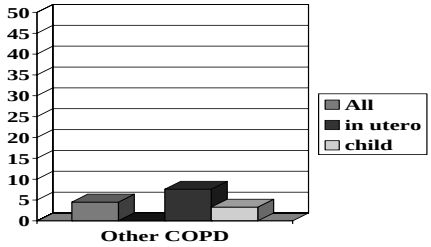
- For all men combined
  P=0.007
- **Among men in this population, arsenic- caused skin lesions were associated with a greater FEV1 reduction (-256ml) than from smoking (-156ml)**

Von Ehrenstein OS et al. Am J Epidemiol 162: 533-41, 2005

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)





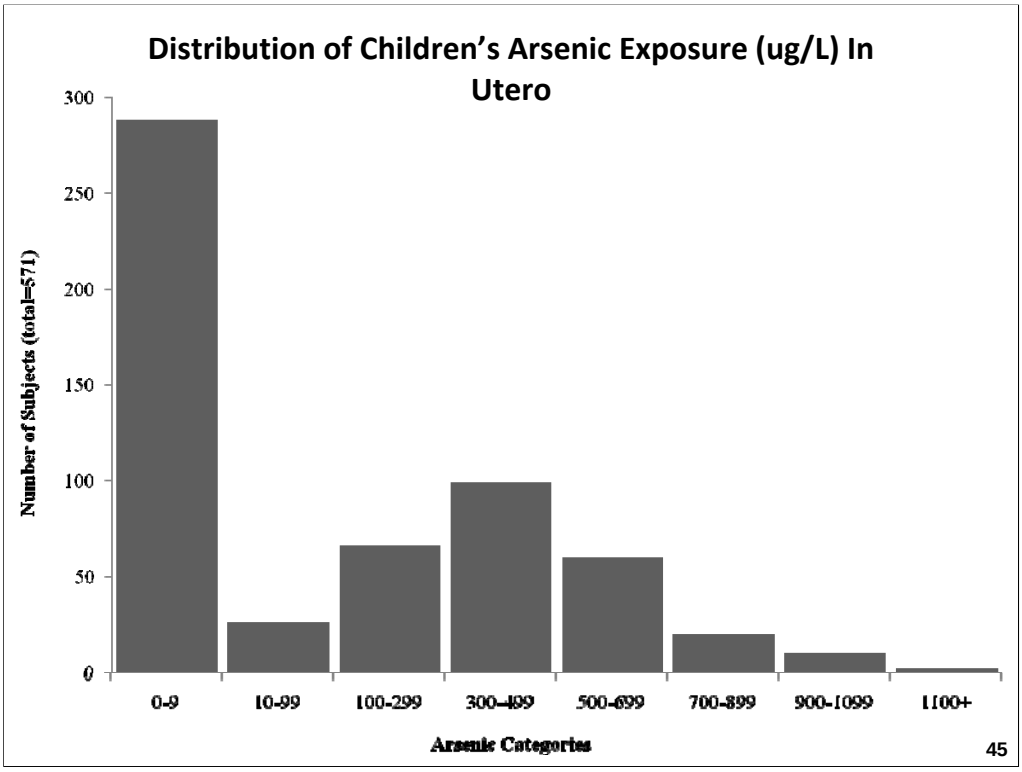


p<0.001 except other COPD p=0.004

A dugwell with modified design to reduce bacterial contamination

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


Distribution of Children's Arsenic Exposure (ug/L) In Utero
Number of Subjects (total=571)
300
250
200
150
100
50
0
0-9
10-99
100-299
300-499
500-699
700-899
900-1099
1100+
Arsenic Categories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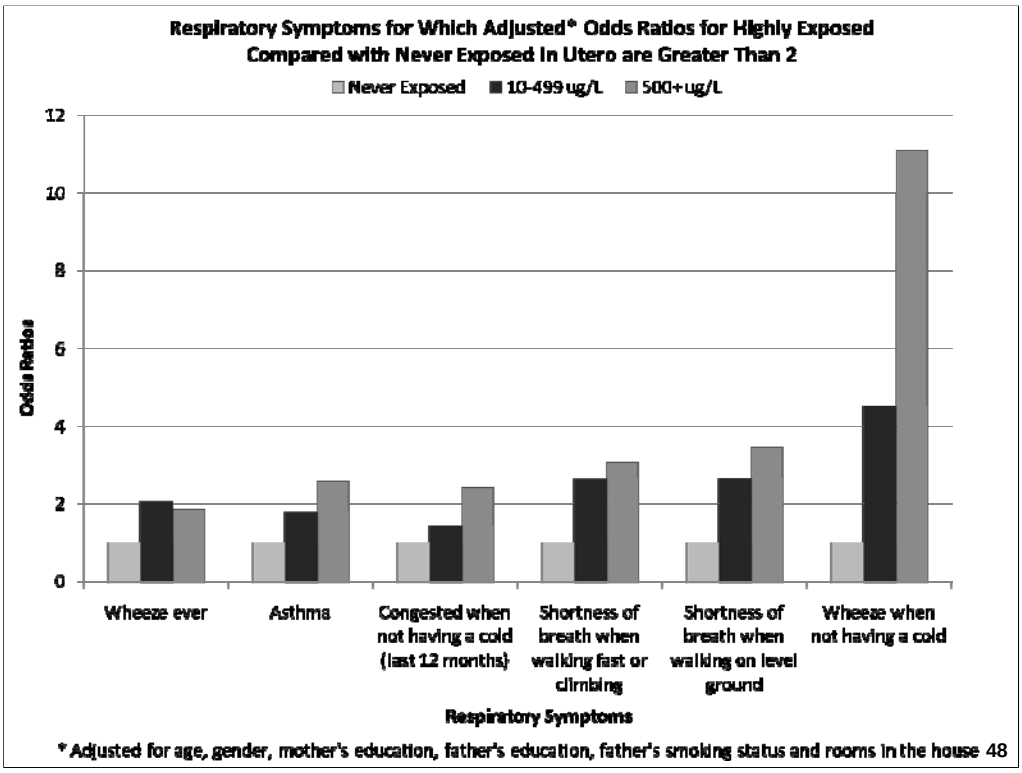
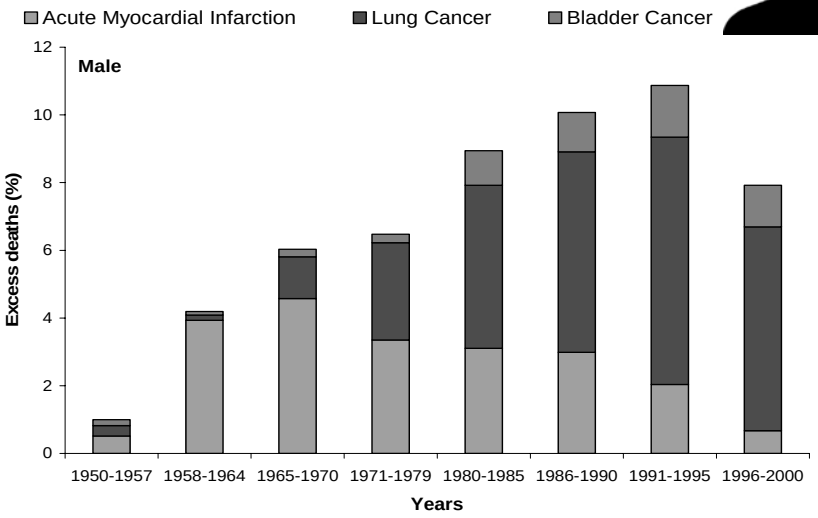

Respiratory Symptoms for Which Adjusted* Odds Ratios for Highly Exposed Compared with Never Exposed In Utero are Greater Than 2
Never Exposed
10-499 ug/L
500+ug/L
Odds Ratios
12
10
8
6
4
2
0
Wheeze ever
Asthma
Congested when not having a cold (last 12 months)
Shortness of breath when walking fast or climbing
Shortness of breath when walking on level ground
Wheeze when not having a cold
Respiratory Symptoms
* Adjusted for age, gender, mother's education, father's education, father's smoking status and rooms in the house

Excess deaths among men in Region II of Chile from acute MI, lung cancer and bladder cancer.

Yuan Y et al. Am J Epidemiol 166:1381-1391, 2007



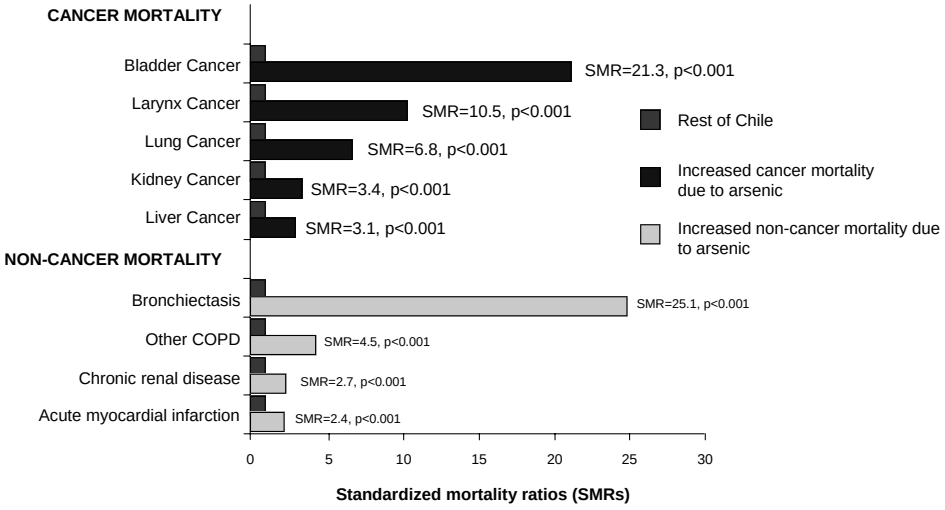
At the peak more than 1 in 10 of *all* deaths were due to arsenic

Early life exposure and myocardial infarction mortality in young adults

The highest rate ratios were for young adult men aged 30–49 years who were born during the high-exposure period with probable exposure in utero and in early childhood (rate ratio = 3.23, 95% CI: 2.79, 3.75; $p < 0.001$)

Yuan Y et al. Am J Epidemiol 2007

Ecologic study of mortality of young adults aged 30-49 following exposure to high concentrations of arsenic in drinking water in early life (not yet published)



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Scientific plausibility

Studies in mice by NIEHS have shown increased tumors in offspring of mice dosed with 85,000 ug/L, including bladder and lung tumors.

(e.g. Tokar EJ, Diwan BA, Waalkes MP. Toxicology Letters 209:179– 185, 2012)

The very high doses were given to achieve internal organ concentrations similar to highly exposed humans.

Extrapolating risk to lower exposure

- The exposures involved in Chile were to 850ug/L.
- Some risks might be detectable by very large epidemiology studies with exposure around 100 ug/L
- Even if there are risks at less than 50 ug/L, it is unlikely that epidemiological studies would ever find them
- We need to think in terms of extrapolation of risks downwards and margins of safety

Early life exposure to high concentrations of arsenic in water has major impact on young adult mortality beyond that from any other environmental exposure

The END

Note: Funding for these studies was provided by NIEHS research grants including the Superfund Research Program

MOUSE MODELS OF HUMAN IN UTERO AND ADULT EXPOSURES TO LOW-DOSE ARSENIC

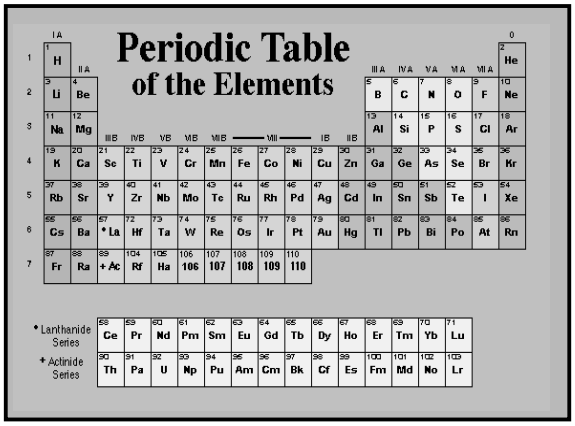
Joshua W. Hamilton Ph.D.
Senior Scientist, Bay Paul Center,
Marine Biological Laboratory (MBL), Woods Hole MA
Professor, Pathology & Laboratory Medicine,
Brown University, Providence RI
Project Leader, Dartmouth's Superfund Research Program
on Toxic Metals, Hanover NH

Arsenic and Old Concerns

"It is an uncanny thought that this lurking poison (arsenic) is everywhere around us, ready to gain unsuspected entrance to our bodies in the food we eat, the water we drink and the air we breathe."

Karl Vogel, 1928

METALS:
Toxic Metals, Heavy Metals, Essential Metals



- three-fourths of all elements are metals or metalloids
- a "heavy metal" refers to its atomic weight, not its toxicity
- many metals are essential or play a normal role in biology
- many toxic metals that are not essential can mimic essential metals
- like all chemicals, all metals are toxic at high enough doses
- like all chemicals, all metals are non-toxic at very low doses

Toxic metals in the environment

- Toxic metals are a major concern at both Superfund / toxic waste sites and in the environment in general
- Eight of the top fifty substances on the CDC's ATSDR priority list are metals, including the top three chemicals of concern in the environment: arsenic, lead and mercury
- Eight of the twenty-two substances on the EPA's OSWER list of chemicals of highest concern at Superfund sites are metals: arsenic, lead, mercury, cadmium, chromium, nickel, zinc and copper

Arsenic: "poison of kings and king of poisons"

- Ancient Rome - Women's club used arsenic to poison husbands
- Renaissance - The Borgias used arsenic to poison rivals and increase their wealth
- Were Napolean and Mozart poisoned by arsenic?

Cesare Borgia

"The death of Napolean"

a lock of Napolean's hair

Arsenic as an environmental contaminant

- Previous US and WHO drinking water standard (Maximum Contaminant Level, MCL) for arsenic was 50 parts per billion (ppb) from 1950's through 2001
- US recently lowered MCL to 10 ppb (Jan. 2006), but 7-14 year implementation
- current WHO and EU arsenic standard is 10 ppb
- WHO program of digging tube wells in India, Bangledesh to alleviate cholera problem led to massive population exposure to excess arsenic in drinking water
- highly contaminated areas (India, South America) can contain as much as 1800 ppb (180 times the WHO standard)
- Estimated 250 million to 1 billion people affected worldwide by excess arsenic

Arsenic as a causative agent in human disease

- Chronic human exposure to inorganic arsenic at sub-acute doses has been linked to increased risk of:
  - Cancers- esp. lung, skin and bladder but also liver, kidney, and other malignancies
  - Diabetes (type 2, non-insulin-dependent, "adult-onset")
  - Vascular and cardiovascular disease
  - Reproductive and developmental problems
  - Neurological problems
- U.S. & South America - range is typically 1-100 ppb
- Asia - range is typically 10-1000 ppb

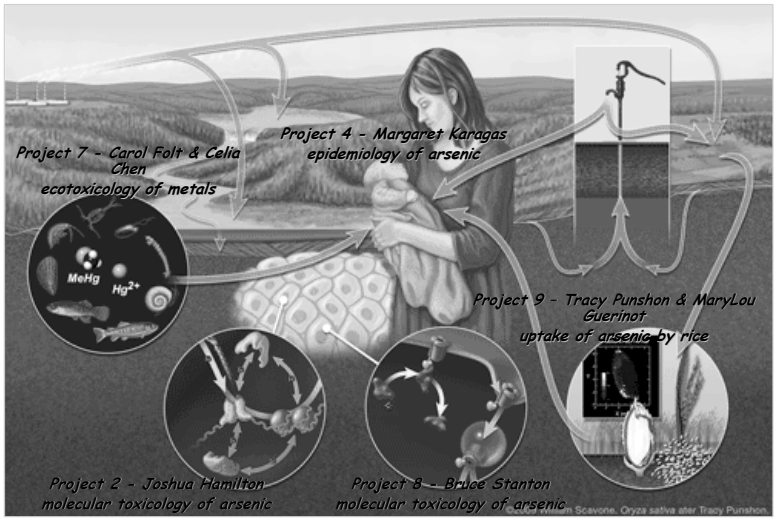
Arsenic as an environmental contaminant in New England

- In New Hampshire, ~40% of the population gets its drinking water from private, unregulated wells
- Of these wells, greater than one in five has excess arsenic, representing about 10% of the state's population (~120,000 people)
- Similar ratios are found in Maine (~150,000 people)
- In the U.S. as a whole, as many as 25 million people may be drinking excess arsenic in their drinking water
- NH and ME also have elevated levels of arsenic in soil both naturally and from lead arsenate pesticide use (avg. 20 ppm vs. 1-5 ppm in most of U.S.)

MBL Biological Discovery in Woods Hole

Center for Environmental Health Sciences at Dartmouth

Dartmouth TOXIC METALS *Research Program*



"Toxic Metals in the Northeast"

NIH-NIEHS Sponsored Dartmouth Superfund Basic Research Program Project on Toxic Metals

An interdisciplinary research program on toxic metals in the environment and their impact on ecosystems and human health

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Arsenic as an endocrine disruptor

What is an endocrine disruptor?

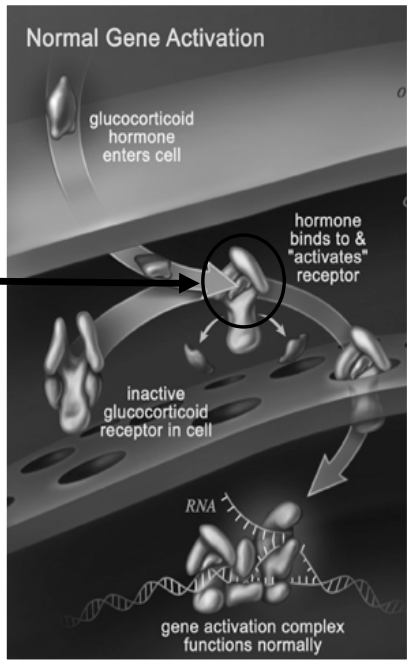
"Collectively, chemicals with the potential to interfere with the function of endocrine systems are called endocrine disrupting chemicals (EDCs). EDCs have been defined as exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes."

Strategic Research Plan for Endocrine Disruptors, 1998

Office of Research and Development
U.S. EPA

Hormone receptor biology and endocrine disruption

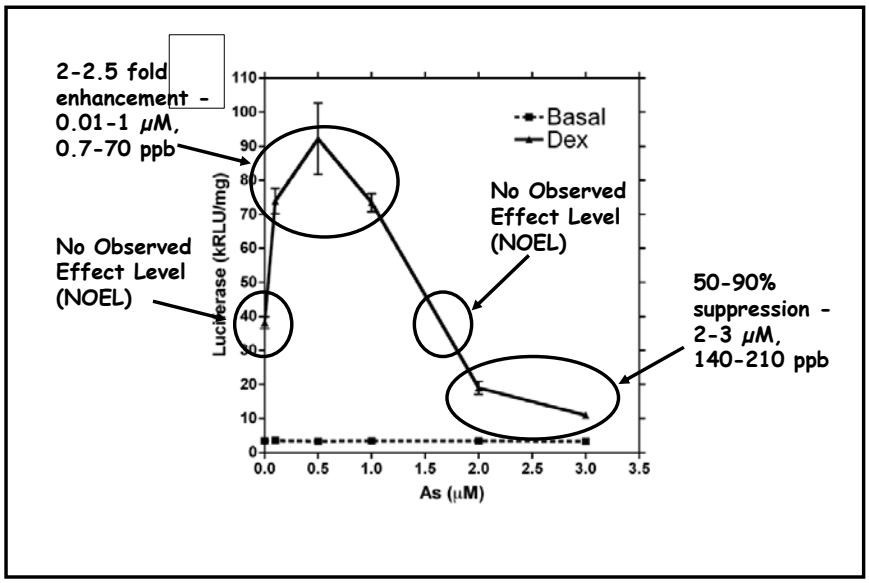
organic Endocrine Disrupting Chemicals - EDCs (pesticides, etc.)



competitive agonists - mimic hormone, bind to receptor, activate receptor

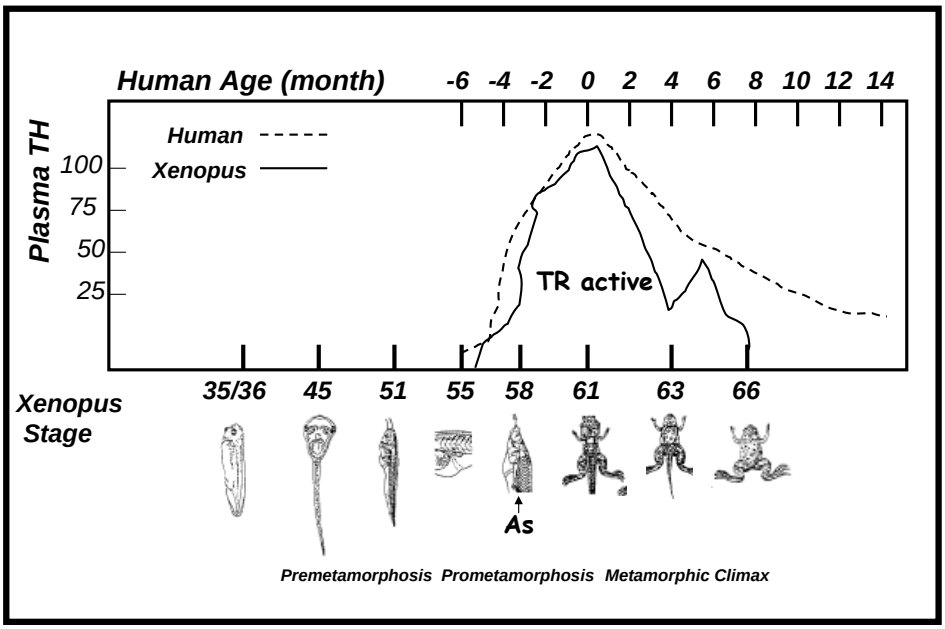
competitive antagonists - mimic hormone, bind to receptor, block normal hormone binding and activation

function
at lower (0.01-1.0 μM) and higher (2-3 μM) doses



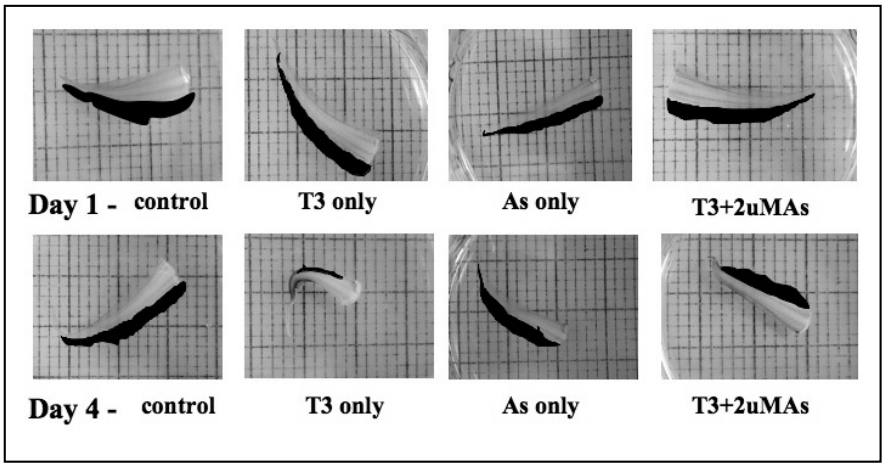
JE Bodwell et al. Chem Res Toxicol 17:1064-1076, 2004

Xenopus



YB Shi. et al.(2002) *Pharmacol Ther* 94:235-251

Effects of arsenic on thyroid hormone-mediated ex vivo tail shrinkage in Xenopus



JC Davey et al. *Environ Hlth Perspect* 116:165-172, 2008

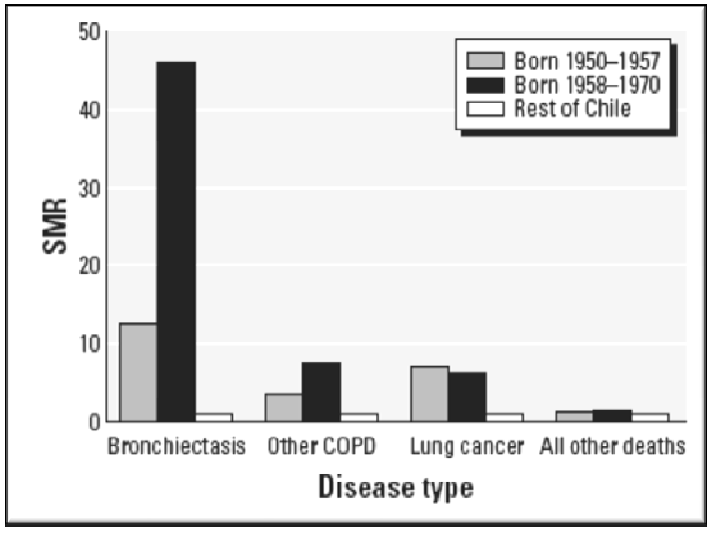
Summary of arsenic as an endocrine disruptor

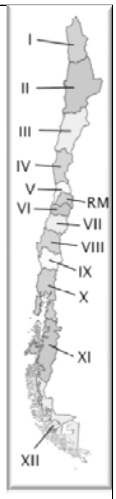
- Arsenic affects all five steroid hormone receptors:
  - Estrogen Receptor
  - Progesterone Receptor
  - Androgen (Testosterone) Receptor
  - Glucocorticoid (Cortisol) Receptor
  - Mineralocorticoid (Aldosterone) Receptor
- Arsenic affects other nuclear hormone receptors:
  - Retinoic Acid Receptor
  - Thyroid Hormone Receptor
  - PPAR Receptors
- Arsenic enhances hormone signaling at very low doses
- Arsenic suppresses hormone signaling at higher doses

Arsenic and lung disease

- Arsenic exposure is associated with increased risk of:
  - Lung Cancer
  - Bronchiectasis
  - COPD
  - Emphysema
  - Chronic Lung Infections
- Arsenic is unique in increasing lung disease risk via ingestion rather than (or in addition to) inhalation
- Arsenic synergistically increases risk of lung disease from other lung toxicants including tobacco smoke, environmental air contaminants, bacterial and viral infections

Arsenic and long-term risk of bronchiectasis in Region II of Chile





Marshall, *J Natl Canc Inst* 2000 -- Ferreccio, *Epidemiology* 2000 -- Smith, *Environ Hlth Perspect* 2006

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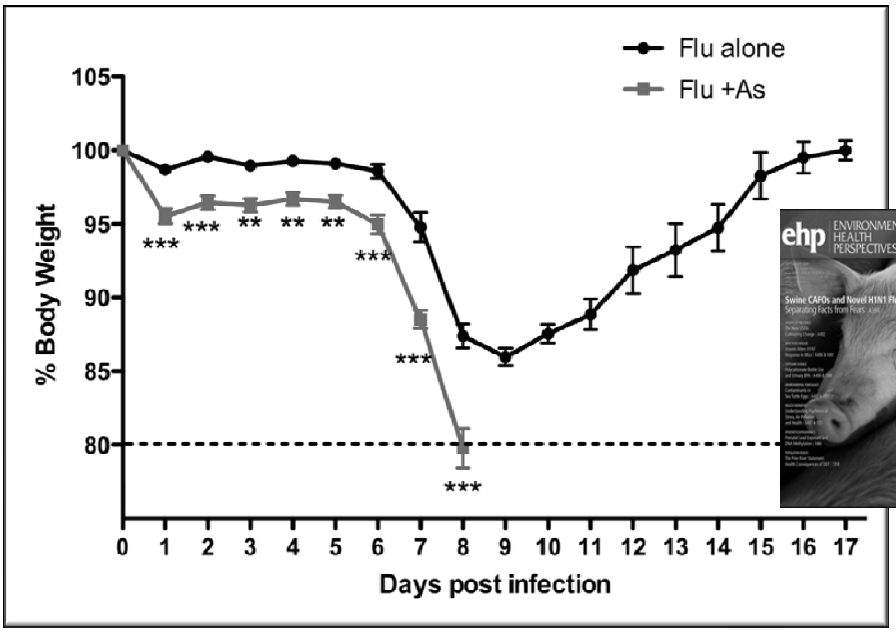
Arsenic in drinking water (100 ppb) increases H1N1 flu-induced morbidity in mice



CD Kozul et al., *Environ Hlth Perspect* 117: 1441-1447, 2009

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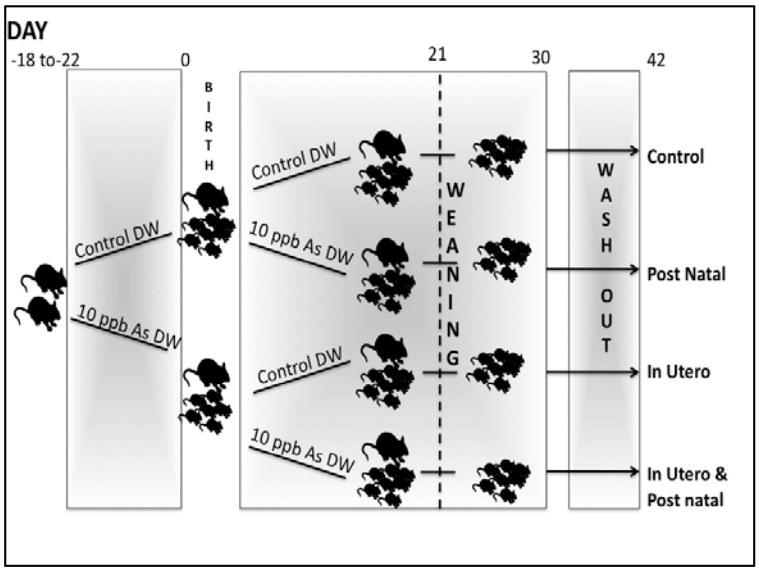
Arsenic and metabolic diseases

- Arsenic exposure has been associated with:
  - Changes in serum cholesterol and triglycerides
  - Development of type 2 diabetes and other metabolic disorders
  - Lower than normal birth weights
  - Decreases in body weight and growth during early childhood
  - Vascular and cardiovascular disease

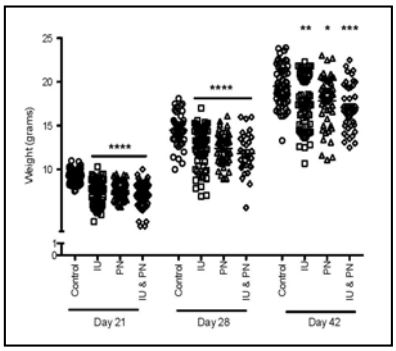
Effects of arsenic on mouse fetal and maternal health

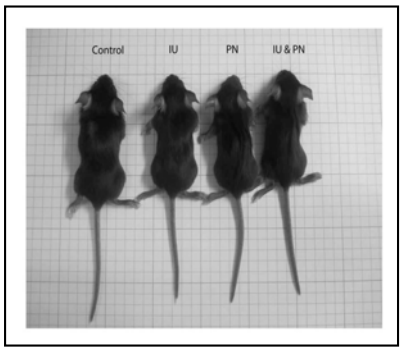


CD Kozul Horvath et al., *PLoS One* 2012

Arsenic at 10 ppb in drinking water affects mouse fetal growth and development

Pregnant C57BL/6J mice were given 10 ppb arsenic in drinking water during the in utero or post-natal weaning only, or in utero and post-natal periods

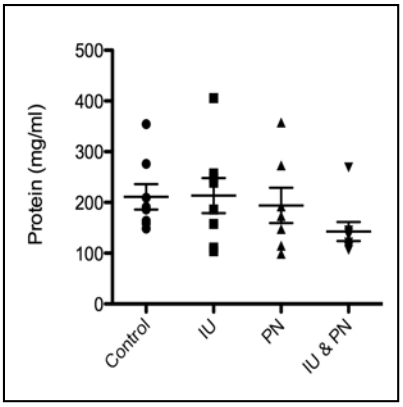


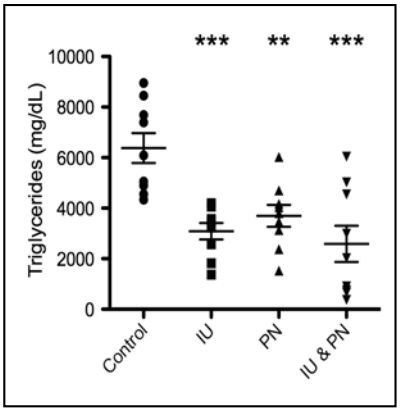


CD Kozul Horvath et al., *PLoS One* 2012

Arsenic at 10 ppb in drinking water affects mouse maternal breast milk nutrients

Pregnant C57BL/6J mice were given 10 ppb arsenic in drinking water during the in utero or post-natal weaning only, or in utero and post-natal periods

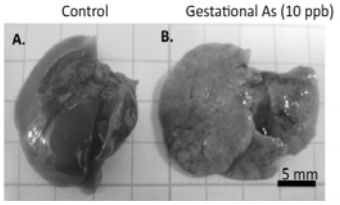


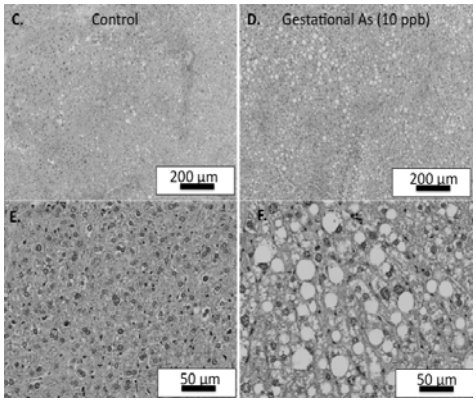


CD Kozul Horvath et al., *PLoS One* 2012

Arsenic at 10 ppb in drinking water causes fatty liver in pregnant mice

Pregnant C57BL/6J mice were given 10 ppb arsenic in drinking water during the in utero only, post-natal weaning only, or in utero and post-natal periods





CD Kozul Horvath et al., *PLoS One* 2012

Acknowledgements

- Hamilton lab (past & present):
  - Ron Kaltreider
  - Mike Ihnat
  - Jennifer Davey
  - Tom Hampton
  - Athena Nomikos
  - Julie Gosse
  - Courtney Kozul-Horvath
  - FJ Zandbergen
  - Vansa Chatikavanij
  - Maggie Vantangoli
  - Adeola Adebayo
- Collaborators:
  - Dean Wilcox (Dartmouth)
  - Jack Bodwell (Dartmouth)
  - Lynn Sheldon (Dartmouth)
  - Bruce Stanton (Dartmouth)
  - Mike Ihnat (Oklahoma)
  - Richard Enelow (Dartmouth)
  - Monique Depaepe (Brown)

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