Health Effects of Arsenic:
an old problem and emerging new concerns

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
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 Napoleon and Mozart poisoned by arsenic?
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, Bangladesh 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.)
An interdisciplinary research program on toxic metals in the environment and their impact on ecosystems and human health
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
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
Arsenic has opposite effects on steroid receptor function at lower (0.01-1.0 µM) and higher (2-3 µM) doses.

No Observed Effect Level (NOEL)
- 50-90% suppression - 2-3 µM, 140-210 ppb
- 2-2.5 fold enhancement - 0.01-1 µM, 0.7-70 ppb
Thyroid hormone mediated metamorphosis - Xenopus

Human Age (month)

Plasma TH

Human

Xenopus

TR active

Xenopus Stage

35/36 45 51 55 58 61 63 66

Premetamorphosis

Prometamorphosis

Metamorphic Climax

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

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

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

CD Kozul et al., *Environ Hlth Perspect* 117: 1441-1447, 2009
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 only, post-natal weaning only, or in utero and post-natal periods.
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 only, post-natal weaning only, or in utero and post-natal periods.
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.
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