



## Signaling Mechanisms for Metabolic Dysfunction Following Low-Level Arsenic Exposures: From Mouse to Man

### Background

Arsenic is a significant contaminant in drinking water worldwide that poses a global concern. The majority of this arsenic comes from natural sources, especially from artesian wells. As regions of the United States and many other nations search for ever diminishing sources of clean drinking water, the risk of exposure to arsenic increases. Additional concerns arise from mining operations and fossil fuel extractions that can mobilize arsenic out of bedrock and into groundwater and deep aquifers. Food, in particular rice and grains, can also be a relevant source of inorganic arsenic for most populations. Arsenic in large amounts has been recognized as a poison for thousands of years. However, the amounts of arsenic usually found in drinking water do not cause death immediately. Instead, they cause chronic diseases and cancers. There is growing evidence that inorganic arsenic exposure is associated with the development of Type 2 diabetes, a metabolic disease that is attributed to a combination of genetic susceptibility and environmental factors. There is also growing evidence that arsenic increases blockage of blood vessels of the heart and could cause heart attacks. This blockage often results from changes in fat and sugar metabolism leading to deposits or vessel closure.

Arsenic is odorless, colorless, and tasteless in drinking water to make it the perfect poison. A key fact to remember is that the U.S. Environmental Protection Agency (EPA) does not regulate or normally monitor the amount of arsenic in private wells. Municipal water supplies or those serving more than 25 individuals are regulated and records of compliance with keeping the level of arsenic below 10 ppb are available through the EPA. Monitoring private wells falls to the individual. Many state or local health departments have information for testing arsenic levels in wells and even programs to help individuals have their water tested.

It is well established that chronic exposure to elevated levels of arsenic in drinking water causes cancer and is associated with increased cardiovascular and developmental disease in several countries around the world. Arsenic exposures in Bangladesh alone, where well intentioned international efforts provided

water from deep wells in an effort to reduce deaths from infectious surface water, are estimated to increase the number of cancer deaths by 300,000. In many parts of the developing world, efforts to provide clean water result in exposure of populations to arsenic unless the water is tested and shown to be below the standard of 10 parts per billion (ppb). This is the maximal amount allowed in U.S. drinking water. Arsenic is a regional concern in the western and southwestern states due to moderately high levels in the bed rock and great pressure on limited water resources. Many municipalities were financially impacted between 2001 and 2006 as they had to increase their capacity to remove arsenic from drinking water when the U.S. standard dropped from 50 ppb to 10 ppb. Arsenic associates with a number of other metals in the Earth's crust; including copper, uranium, and gold, as well as with high sulfur coal. As a consequence, mining, metal smelting, and coal combustion produce arsenic laden wastes that may impact human health and pose large economic burdens on industry to remove or contain arsenic before it contaminates ground water and deep aquifers. The real risks posed by arsenic in U.S. drinking water are controversial and in need of solid scientific support that indicates both the mode of action for arsenic-induced diseases and the extent of the exposure and disease promotion in the U.S. population.

### Research

Research on the potential for cancer and cardiovascular effects of arsenic in drinking water has provided scientific evidence that supports regulating the content of arsenic in U.S. drinking water. The exact level of arsenic that is safe or how to determine whether arsenic is causing negative health effects remain controversial. Current research is focused on providing answers to those questions, including clarifying the amounts of arsenic that pose a health threat, the amount of exposures that are occurring in the U.S. population, and ultimately the real risk of disease from arsenic exposures. This research will better inform policies that regulate arsenic exposures in an effort to protect human health. Recent research into the adverse effects of arsenic is raising concerns about the current EPA standard of 10 ppb. However, an additional issue of

concern is whether water utility companies can realistically decrease arsenic levels below 10 ppb without driving the costs of water treatment to financially unsustainable levels.

The major controversy regarding arsenic regulation is whether exposure in the U.S. is significant and causes disease. It is clear that exposures in other countries increase cancer rates and cardiovascular disease. However, exposed U.S. populations are more difficult to study and there is the perceived notion that the drinking water in the U.S. contains, on average, less arsenic than other countries. There are numerous reports that isolated U.S. wells have levels of arsenic that are 10 to 100 times the allowable EPA limit. The wells are often in rural areas with low densities of diverse population. This makes epidemiological studies difficult and creates a major gap in understanding the full extent of arsenic-promoted disease in the U.S. A further complication of performing accurate assessment of arsenic-related disease relates to the different forms of inorganic and organic arsenic that are found in drinking water and exposed humans. Some organic forms, such as those that come from eating seafood are inert and pose no health threat.

These varying forms of arsenic can confuse determination of the real risk of the arsenic exposure. Knowledge of the levels of inorganic arsenic and the organic forms produced in humans provide much better assessment of the true risks of exposure to drinking water arsenic. Finally, there is controversy over whether mice are like men in their response to arsenic. Humans appear to accumulate or retain arsenic much better than mice. The relative resistance of adult mice to the cancer promoting effects of arsenic has led many scientists to believe that mice only get arsenic-induced cancers when the level of arsenic in their tissues reaches that found in human tissue. Scientists examining effects of arsenic on the blood vessels, metabolism of fats and sugars, and inflammatory cells in the body find that mice and men are equally sensitive. This symposium presents studies in humans and mice that indicate that mice can be used to predict the responses of humans to low level arsenic exposures. More importantly, studies in exposed human populations in the western states are presented that indicate that exposures are significant in the U.S. and may pose a risk of metabolic diseases.

### **Gaps in Research**

Ongoing and future studies of arsenic effects on metabolism may provide support for alternative means, such as diets fortified with specific vitamins and antioxidants to protect the health of populations at risk from low level arsenic exposures.