Introduction

The element arsenic (As, atomic number 33, atomic weight 74.91) is ubiquitous in the environment. It ranks 20th in abundance in the earth's crust, 14th in seawater and 12th in the human body. It is present in nature in three different oxidation states, and a multitude of different chemical compounds. In the purified state, As is most often seen as a gray solid with a metallic appearance, but yellow, brown, and black forms are also known. An intermediate element between the metals and the non-metals, As classically is considered a “heavy metal” for toxicological purposes, since it is one of the major metallic threats to human health. It has been known of since ancient times and continues to be used medicinally to this day [1].

Arsenic in the environment

As is emitted into the environment from volcanoes (estimated at 8,000 tons of As annually), but in far greater amounts from human activity - through metal smelting, combustion of fossil fuels and pesticide use [1]. Arsenical pesticides are still widely used in agriculture (in spite of their progressive withdrawal in certain countries) and the effects of arsenicals in the food chain are often seen from the measured levels of As in the human samples analysed at Biolab.

Inorganic arsenic (arsenite, arsenate) is a naturally occurring toxicant and carcinogen [2] which contaminates groundwater supply systems in countries around the world [3]. The results of the current exposure of tens of millions of people to high arsenic concentration in drinking water in West Bengal and Bangladesh are widely considered to represent the worst public health disaster in recent history [4]. In many other countries wells drawing from watersheds near mines, for example, may be dangerously contaminated with As [5].

In the sea, the phytoplankton take up inorganic As and de-toxify it by conversion to organic As compounds [6]. Fish that consume phytoplankton store the As in their muscle tissue as arsenobetaine, arsenosugars and arsenolipids. Fish consumption can therefore be a significant source of As exposure in humans, but these forms of As are considered to be of relatively low toxicity. However, the extent of metabolic interconversion between organic and inorganic As (i.e. the re-conversion of non-toxic compounds to toxic forms of As) is poorly defined and may depend on nutritional status, the gut microbiota and genetic polymorphisms affecting metabolism (see below).

Chronic toxicity from ingestion or inhalation of As may be occupational or environmental [7,8,9]. Documented cases of arsenic poisoning have also been associated with ingestion of traditional Chinese remedies and Korean herbal preparations used to treat haemorrhoids. Accidental ingestion, ingestion with suicidal intent, and intentional poisoning with non-food sources of As are most commonly associated with acute toxicity. It is possible that Napoleon died from arsenic poisoning, although this is disputed – along with the suggestion that the poison was administered by his British captors [10,11].

Detoxification of arsenic

The type and severity of the toxicity experienced after As ingestion depends on the species of As ingested [12]. Arsenate (AsV) is a structural analogue of phosphate, and inhibits phosphorylation processes in
metabolism. For example, ADP-arsenate will spontaneously hydrolyze, resulting in uncoupling of oxidative phosphorylation, while arsenite (As³⁺) has a very high affinity for thiol groups, and thus binds to and inhibits enzymes that have thiol groups in their active sites. In addition, inorganic arsenic is a potent carcinogen [2].

Arsenate enters cells via the phosphate transport system. Both prokaryote and eukaryote cells reduce intracellular arsenate to arsenite. However, while prokaryotes (bacteria) can pump arsenite out of the cell using a dedicated pump mechanism, eukaryocytes require other means for its removal. Certain mammals, including humans, continue the process by methylating arsenite to forms that are excreted in the urine (methylarsonic acid – MMA – and dimethylarsinic acid –DMA). Unfortunately this pathway starts with the reduction of arsenate to arsenite within the cell (even though arsenite is more toxic than arsenate), since only arsenite can be methylated. The ability to eliminate As by this route is influenced by nutrition and gender, as well as by a number of genetic polymorphisms. Malnourished individuals exposed to high levels of As are relatively less able to methylate As and hence are at greater risk of toxicity when exposed to high levels of As [13].

**Toxic effects of arsenic**

Inorganic forms of As are more toxic than organic forms. The trivalent forms are the most toxic and react with thiol groups, while the pentavalent forms are less toxic but uncouple oxidative phosphorylation. Very few organ systems escape the toxic effects of arsenic [1].

Trivalent inorganic As inhibits pyruvate dehydrogenase by binding to the sulfhydryl groups of dihydrolipoamide. Consequently, conversion of pyruvate to acetyl coenzyme A (CoA) is decreased, citric acid cycle activity is decreased, and production of cellular ATP is decreased. Trivalent As inhibits numerous other cellular enzymes through sulfhydryl group binding. Trivalent As inhibits cellular glucose uptake, gluconeogenesis, fatty acid oxidation, and further production of acetyl CoA; it also blocks the production of glutathione, the principal intracellular free radical scavenging- and preventative antioxidant.

The effects of pentavalent inorganic As occur partly because of its transformation to trivalent As; toxicity proceeds as outlined above. More importantly, pentavalent As resembles inorganic phosphate and substitutes for phosphate in glycolytic and cellular respiration pathways. High-energy phosphate bonds are not made, and uncoupling of oxidative phosphorylation occurs. For example, in the presence of pentavalent As, adenosine diphosphate (ADP) forms ADP-arsenate instead of ATP; the high-energy phosphate bonds of ATP are lost.

As is listed as a presumed carcinogen, based on the increased prevalence of lung and skin cancer observed in human populations with multiple exposures [2]. It is not clear whether its carcinogenic properties are due to inhibition of DNA repair mechanisms or alterations in the status of DNA methylation.

**Food sources of arsenic**

Nutritional sources of As are not unusual; as well as in fish (arsenobetaine) [14] it is found in wines, meat and milk. Flour and rice contain inorganic arsenic, particularly if grown or cooked in areas with arsenic contamination of the soil and water [15,16].

The extent of contamination of chicken meat with As remains a cause for concern and comes from the intentional use of arsenic as a growth promoter, a practice that has been widespread for years (Roxarsone, originally patented in 1923) [17]. This compound has been withdrawn by the manufacturers in the USA and has been banned by the EEC – but of course much of the low-cost chicken we consume comes from other sources.
**Arsenic in clinical samples**

Biolab offers total As determination in urine, blood and hair, along with As in drinking water. In cases of suspected severe As poisoning, speciation of As should be carried out (this is available at Health and Safety laboratories and requires a separate referral). The Biolab reference intervals for total arsenic are as follows:

- Urine As (the preferred sample for monitoring exposure) $< 94 \mu\text{mol/mol of creatinine}$
- Whole blood As $< 60 \text{nmol/L}$
- Hair As $< 1.0 \mu\text{g/gm of hair}$
- Drinking water As $< 10 \mu\text{g/L}$

**Patient preparation:**

Seafood ingestion should be avoided for two days before taking samples for As analysis, but otherwise no special preparation is required and the patient can continue to take nutritional supplements and medication before the collection of the sample.

**Specimen requirements**

For blood As measurement, the sample should be collected into an 8 ml trace element-free potassium EDTA tube. Collection tubes and needles can be supplied by Biolab. If a number of blood tubes are being taken at the same collection, the trace element-free tube should be filled first to avoid cross-contamination. Postal samples (overnight delivery) are acceptable.

A 24 hour urine collection is preferred for urine arsenic determination, but a 6 hour urine collection is acceptable. The total volume of urine collected should be recorded and, after mixing, 15 mL of urine should be sent to Biolab in a plastic, screw cap container. A postal sample kit can be supplied.

For hair analysis, hair should be cut from the nape of the neck, as close to the scalp as possible. At least 0.5gm of hair is required, which is about one heaped tablespoon full. Only hair up to $1\frac{1}{2}$" (4cm) from scalp can be used. Please allow for this when the hair is long by sending in a larger total sample, for example 2 tablespoons-full of hair.

For water analysis, 20 mL of water should be sent in a plastic, screw cap container (available from Biolab). If the domestic water supply is being tested, water should be taken from the initial run of the tap first thing in the morning (i.e. after the water has been in contact with the fixtures and fittings for more than 6 hours).

**Turn around time:** 5 working days.

**References:**


