Arsenic Curiosa and Humanity

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Abstract: Despite its undoubted toxicity, arsenic is a much-used element, finding applications in agriculture, industry, and medicine. Arsenic as a poison has a prominent role in plays and novels as well as in real life. In medicine, arsenic was so widely used in the 19th century as a cure-all that it has been termed a “therapeutic mule.” Some arsenic compounds are still used in the treatment of parasitic disease. Moreover, in a striking development for a material regarded as a carcinogen, arsenous trioxide (brand name, Trisenox) was recently approved for treatment of leukemia. Arsenic has had a profound overall impact on human lives.

Introduction

Arsenic and arsenic compounds have had a long and Janus-type interaction with humanity; on the one hand they have been extensively utilized, but on the other hand their poisonous properties have caused misery and many deaths. While minerals containing arsenic were known from the earliest times, elemental arsenic was not conclusively identified until 1649. The mineral, realgar, As4S4, was probably described as early as the 4th century BC by Aristotle. The name derives from an Arabic word meaning “powder of the cave.” Similarly, the mineral orpiment, AsSb, has a long history, the name being an adaptation of the Latin, auripigmentum, meaning “gold pigment.” The etymology of arsenic itself is complex but traces to the Greek word, arsenikon (arshenikon) or arrhenikon used for “yellow orpiment,” a word tracing back even further to words from Syriac, Middle Persian, and Old Iranian. In addition, the similar Greek word, arshenkos (arschenikos) or arrenikos meaning “masculine, male” also contributed to its naming.

The highly poisonous nature of arsenic compounds has been known for centuries. The colorless and tasteless compound, arsenious oxide (arsenic(III) oxide, also termed arsenous oxide and often simply white arsenic or arsenic), was at one time employed as a rat poison; because it was easily available; it was also commonly used for criminal purposes, both in real life and in fiction (see later in this article).

Chemistry is so vast a discipline that most students are exposed to little more than the basic chemical facts about arsenic and its compounds; however, arsenic has had a very pervasive influence on humanity in many ways, perhaps more so than most other metals and metalloids. The name, arsenic, is essentially a household word, being synonymous with poison. Arsenic figures prominently in literature as well as in industry, the sciences, in medical practice, and in everyday life. We recount here some of the many curious influences of arsenic on human lives, influences not usually found in chemical textbooks.

Nonmedical Uses for Arsenic and Its Compounds

Over the years, arsenic compounds have found application in the manufacture of cosmetics, foods, glass, insecticides, medications, pigments, pyrotechnics, rodenticides, and wood preservatives, as well as in embalming, metallurgy, tanning, and taxidermy. There have, in consequence, been many cases of poisoning due to industrial uses of arsenic. Although such incidents are declining, the Toxic Exposure Surveillance System reported for the USA in 1998 that there were 956 nonpesticide related arsenic exposures and 339 arsenic-containing pesticide exposures. In the nonpesticide category, there were 4 fatalities [1].

Since about 1991, almost all of the arsenic metal and compounds used in the United States have been imported, mainly from China. In 1997, for the United States, the imported amounts were 1,200 metric tons of arsenic metal, 30,000 tons of arsenic trioxide, and 1 ton of arsenic acid. Of these quantities, 88% of the metal was from China, the remainder being from Japan, Hong Kong, and other countries. For arsenic trioxide, 48% came from China, 20% from Chile, 12% from Mexico, and 20% from elsewhere. Prices for arsenic trioxide in 1997 averaged 26 cents per pound, and for metal from China, 44 cents per pound.

Some old technologies requiring arsenic are clearly declining. For instance, although arsenic was alloyed with lead in the making of shot to harden the metal and to ensure roundness, concerns over environmental toxicity of lead have caused a rapid decline in the use of lead shot and in many places (e.g. the USA) a ban on its use in hunting water fowl. Nevertheless, arsenic is still a component of the lead alloys used in batteries. Embalming with the aid of arsenic (see later) has been discontinued and arsenical pigments are no longer freely available. Moreover, inorganic arsenic trioxide has been replaced as a weed killer by other materials, including some organic compounds of arsenic. The present day use of arsenic and its compounds varies from country to country. In the United States, the major amount is in wood preservation, particularly as chromated copper arsenate (about 16,000 metric tons). Smaller amounts are involved in glass manufacture (900 tons) and for the production of nonferrous alloys (700 tons). This latter category includes one of the new applications for arsenic, in the semiconductor industries where growing crystals (e.g., of germanium, silicon) are “doped” with minute traces of arsenic introduced from the very toxic gas, arsenic, AsH3. Gallium arsenide (GaAs) and indium arsenide (InAs) are
also components of diodes, lasers, and transistors. At this time, about 15 metric tons of high-purity arsenic are used in semiconductor manufacture each year in the United States.

A surprisingly large amount of arsenic, about 5,500 tons, is consumed in the manufacture of herbicides and animal feed additives for agricultural purposes. The materials are sodium salts of dimethyarsinic acid, \( (\text{CH}_3)_2\text{AsO(OH)} \), or monomethylarsonic acid, \( \text{CH}_3\text{AsO(OH)}_2 \). The former, also known as cacodylic acid or dimethylarsonic acid, is usually referred to as DMAA and the latter, as the disodium salt, is DSMA and as the monosodium salt, MSMA. A chemical catalog gives the price of pure DMSA as $104.35 for 100 g, but doubtless the price is lower on the DMAA used in agriculture. These derivatives find extensive application in growing cotton and as selective herbicides in facilitating the growth of desired grasses, for example, for golf course varieties of organic arsenic compounds, often related to arsanilic acid (phenylarsonic acid, C\( _6 \text{H}_5\text{AsO(OH)}_2 \)), is used in the pig and poultry industries as anthelmintics, and as antirickettsial and antihistomonad agents.

Unfortunately, Lewisite, dichloro(2-chlorovinyl)arsine, Cl-CH=CH-AsCl\(_2\), and other arsenic compounds were deployed as poison gases in World War I; they are vesicants and respiratory and systemic poisons. Similar chemical warfare agents were prepared for retaliation in the event that they were used against the allies in World War II; fortunately, this did not happen. Today, sets of vials containing small amounts of sulfur mustard and Lewisite, used by the US army in training for identification of chemical warfare agents from 1928–1969, must be destroyed. However, to do this, a minefield of complicated technical, legal, environmental, and societal issues must be traversed [2]. One part of the difficulty is that these kits are classified as chemical warfare material.

**Medical Uses for Arsenic Compounds**

Several arsenic compounds have been utilized in medicine. In early times in the East, a mixture of opium, slaked lime and water was favored as a depilatory; the action resulted from formation of a hydro sulphide of calcium. Moreover, a paste of realgar was recommended by Hippocrates (460–377 B.C.) for treatment of ulcers. There are many other medical examples of the early applications of arsenic compounds [3]. The 1899 *Materia Medica* prepared by Merck & Co. lists “acid, arsenous” for internal treatment of “malarial fever, skin disease, chorea, neuralgia, gastralgia, uterine disorders, diabetes, bronchitis” and applied externally “to remove warts, cancers, etc.” [4]. Arsenic halides are also listed with the bromide indicated for treatment of diabetes. Two arsenic preparations have eponymous names. One was Donovan’s solution (a mixture of arsenic and mercuric iodides), which found dermatological use. The most famous was Fowler’s solution (potassium arsenite), said to be a most convenient form for administering arsenic; the 1899 *Materia Medica* cautions, however, “Never give it on an empty stomach!.” Fowler’s solution was apparently a general cure-all in Victorian times. Both Donovan’s and Fowler’s solutions are still described in the 1996 Merck Index (12th edition).

Fowler’s solution has a fascinating history [5]. In the reign of King George III, a patent medicine was claimed as an “infallible remedy for agues and intermitting fevers, even in the most obstinate cases where the bark and every other medicine hath proven ineffectual” (the bark would have been Peruvian Bark, i.e., quinine). This medicine was prepared from “cobalt,” probably a pyrite ore containing arsenic. The “patent ague drops” or “tasteless ague and fever drops” were occasionally employed in hospitals. In 1783, Dr Fowler suggested to the apothecary, Mr. Hughes, to duplicate the preparation; Hughes apparently realized the role of arsenic and prepared an alkaline solution of white arsenic that did have therapeutic properties. It became known as Fowler’s solution and was first listed officially in the London pharmacopoeia of 1809, perhaps it can be claimed as a very early example of a generic drug. In addition to being a general cure-all, it found application specifically as an antineoplastic (anticancer agent) and for dermatological purposes.

In fact, in the 19th century, arsenic was a major component of the *Materia Medica*, being used both internally and externally, and it has been dubbed the “therapeutic mule” [3]. One physician wrote “If a law were passed compelling physicians to confine themselves to two remedies only in their entire practice, arsenic would be my choice for one, opium for the other. With these two I believe one could do more than any two of the pharmacopoeia” (quoted by Haller) [3]. The popularity of arsenic increased with the knowledge of the Styrian arsenic-eaters (see later).

It has been suggested that the symptoms of Charles Darwin’s mysterious malady match those of arsenic poisoning [6]. It is known that he medicated himself with arsenic early in life to treat eczema of the lips and to cure a not clearly specified hand ailment (possibly “a tremor with some degree of dermatitis”). However, there is no real evidence for his regular, long-term consumption of a material such as Fowler’s solution. Moreover, as was common in his day, he was frequently treated with another poison, calomel, Hg\( _2\)Cl\(_2\).

Early in the 20th century, “arsenious acid” (presumably a solution of arsensious trioxide) was injected into mice infected with parasitic protozoans (trypanosomiasis). Both the trypanosomes and the mice were killed; however, the mice had “died cured” suggesting that arsenic compounds had potential in chemotherapy [7]. In 1905, sodium \( \alpha \)-aminophenylarsonate \( \text{[NH}_2\text{C}_6\text{H}_4\text{AsO(OH)}(\text{ONa})\] \) was found to have a modest effect on human trypanosomiasis and the material was (optimistically!) named “atoxyl.” The current edition of the Merck Index gives no present-day use for atoxyl but includes the warning, “Poisonous!” From these beginnings, Ehrlich initiated extensive investigations of the use of organic compounds of arsenic in chemotherapy. One compound with the laboratory number of 606, was arsphenamine (salvarsan, C\( _6\text{H}_5\text{Ni}_2\text{O}_2\text{As}\cdot2\text{HCl}\cdot2\text{H}_2\text{O} \)) the famous “magic bullet” for treatment of syphilis. Ehrlich’s work with these arsenic compounds inaugurated the era of synthetic chemotherapy. Like atoxyl, arsphenamine was quite toxic and had the reputation of terminating the disease by eliminating the sufferer. The treatments were lengthy and very unpleasant, arsphenamine being injected intravenously over a one-hour period. Courses of the arsenic treatment were alternated with “mercury rubs” or intramuscular mercuric succinamide (mercuric imidosuccinate); hence the aphorism, “two minutes with Venus, 2 years with mercury” (ascribed to J. Earle Moore) [8]. Later, less toxic derivatives were developed, such as 3-amino-4-hydroxyphenylarsinoxide hydrochloride (also known as oxophenarsine hydrochloride and Mapharsen), and the treatment became somewhat more bearable.

In the 1940s, the drug melarsoprol, \( 2\cdot[4\cdot(4,6\text{-diamino}-1,3,5\text{-triazin-2-yl})\text{amino}]\text{phenyl} -1,3,2\text{-dithiarsolane-4-meth-} \)