1

HISTORY OF ARSENIC AS A POISON AND A MEDICINAL AGENT

MICHAEL F. HUGHES

Office of Research and Development, National Health and Environmental Effects Research Laboratory, US Environmental Protection Agency, Research Triangle Park, NC, USA

Disclaimer: This article has been reviewed in accordance with the policy of the National Health and Environmental Effects Research Laboratory, US Environmental Protection Agency, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

1.1 INTRODUCTION

Arsenic is one of the most enigmatic elements known to humankind. For many centuries, arsenic has been used as an intentional human poison, for which it has generated much fear and interest. However, over this same time frame, arsenic has been used to benefit society, at least with good intentions, as a medicinal agent. The best example of this paradox is arsenic trioxide, which is also known as the white arsenic. This potent and lethal inorganic arsenical has not only been commonly used to commit homicide but also been used more recently as an effective cancer chemotherapeutic agent.

Arsenic is an insidious poison. Over the ages, arsenic came to be known as the "King of Poisons" because of its use to poison royalty [62]. Arsenic was the choice as a poison because it has no taste and could be discreetly mixed with food or drink.

Arsenic: Exposure Sources, Health Risks, and Mechanisms of Toxicity, First Edition.
Edited by J. Christopher States.

The symptoms of arsenic poisoning were similar to those of common diseases (e.g., cholera) in the world at a time when hygienic practices were poor and safe drinking water was not readily available. Also, there was no chemical test to indicate that someone had been exposed to arsenic until the 1700s.

Although the poisonous nature of arsenic was well known, in 2010, in the United States alone, there were over 5000 cases of arsenic pesticide poisoning and 1000 cases of arsenic nonpesticidal poisoning [8]. Three deaths were noted in the arsenic nonpesticidal cases.

Arsenic is found in inorganic and organic forms as well as different valence or oxidation states (Fig. 1.1). The oxidation states of arsenic include –III, 0, III, and V. Examples of arsenicals in these states are arsine, elemental arsenic, arsenite, and arsenate, respectively. Arsine is a colorless, odorless gas and highly toxic [54]. Exposure to arsine is primarily occupational, so it will not be discussed in this chapter. The form and valence state of the arsenical is important in its potential toxic effects. In general terms (i) inorganic arsenicals are more potent than organic arsenicals; (ii) trivalent (III) arsenicals such as arsenite are more potent than pentavalent (V) arsenicals such as arsenate; and (iii) trivalent organic arsenicals are equally or more potent than trivalent inorganic arsenicals [30].

The clinical signs of acute oral arsenic toxicity are progressive and depend on the form, valence, and dose of the arsenical. In a human adult, the lethal range of inorganic arsenic is estimated at 1–3 mg As/kg [18]. The symptoms of acute arsenic poisoning are listed in Table 1.1 [25, 56]. Diarrhea is due to increased permeability of the blood vessels. Depending on the type and amount of arsenic consumed, death may occur within 24 h to 4 days. Death is usually due to massive fluid loss leading to dehydration, decreased blood volume, and circulatory collapse. Survivors of acute arsenic poisoning may develop peripheral neuropathy, which is displayed as severe ascending weakness. This effect may last for several years. Encephalopathy may also develop, potentially from the hemorrhage that can occur from the arsenic exposure.

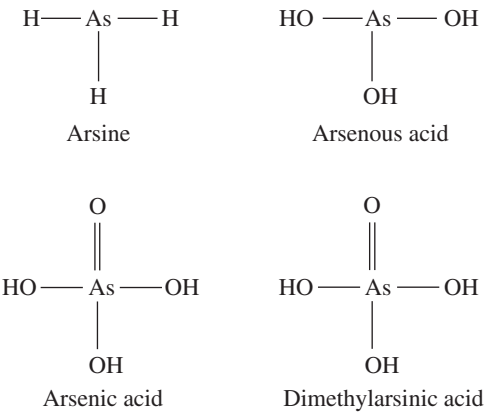


FIGURE 1.1 Structure of common arsenicals. The ionized forms of arsenous acid and arsenic acid are arsenite and arsenate, respectively. Dimethylarsinic acid is also named cacodylic acid.

TABLE 1.1 Acute and Chronic Clinical Effects of Inorganic Arsenic Exposure

Organ System	Acute Effects	Chronic Effects
Cardiac	Cardiomyopathy, hemorrhage, electrocardiographic changes	Hypertension, peripheral vascular disease, cardiomyopathy
Hematologic	Hemoglobinuria, bone marrow depression	Anemia, bone marrow hypoplasia
Gastrointestinal	Nausea, vomiting, diarrhea	Vomiting, diarrhea, weight loss
Hepatic	Fatty infiltration	Hepatomegaly, jaundice, cirrhosis, fibrosis, cancer
Neurologic	Peripheral neuropathy, ascending weakness, tremor encephalopathy, coma	Peripheral neuropathy, paresthesia, cognitive impairment
Pulmonary	Edema, respiratory failure	Cancer
Renal	Tubular and glomerular damage, oliguria, uremia	Nephritis, cancer
Skin	Alopecia	Hyperkeratosis, hypo- or hyperpigmentation, Mees' lines, cancer

Treatment for acute arsenic poisoning includes gastric lavage, administration of fluids and a chelator such as dimercaptopropanol, and hemodialysis.

In chronic arsenic poisoning, as in acute poisoning, essentially all the organs are affected [25, 56] (Table 1.1). The hallmark of chronic arsenic poisoning is the development of skin lesions. This includes hyper- or hypopigmentation and hyperkeratosis, particularly on the palms of the hands and soles of the feet. There is no known treatment for chronic arsenic poisoning that is of benefit to the individual. The best option is to minimize exposure to the source of arsenic and provide supportive care to the patient.

Arsenic is also a known human carcinogen, being classified as such by the International Agency for Research on Cancer [33] and the US Environmental Protection Agency (USEPA) [39]. Confirmed organs for cancerous development from chronic arsenic exposure include bladder, skin, and lung [51]. Potential target organs for cancer from arsenic exposure are liver, kidney, and prostate [33, 51].

1.2 INTENTIONAL POISONING BY ARSENIC

The poisonous nature of arsenic has been known for centuries, and thus, it has been used to commit homicide. It is so well known that poisoning by arsenic has been incorporated into the plots of literary works of Chaucer, Agatha Christie, and other writers, and even in the title of a 1940s Broadway play, "Arsenic and Old Lace" [6]. However, it is inconceivable that the victims would die so quickly from arsenic ingestion in that play. Their deaths would most likely be from the ingestion of cyanide and strychnine, which were also part of the poisonous concoction mixed with

elderberry wine. But would the play have gained as much attention if it had been called "Cyanide, Strychnine and Old Lace"? No one knows for sure.

There have been many suspicious poisonings, potentially by arsenic, of powerful people in centuries long ago. It has been suggested that Alexander the Great and Britanicus were poisoned by arsenic [6, 12, 25]. The Greek physician Dioscorides, in the first century A.D., included arsenic as a poison in his five-volume publication *De Materia Medica* ("Regarding Medical Materials") [48]. During the Middle Ages and Renaissance periods, murder by poisoning reached its zenith [6, 12]. Noted individuals who poisoned others with arsenic for personal gain or profit during this time include the Italians Cesare Borgia, Giulia Toffana, and Hieronyma Spara, and the French woman Marie de Brinvillers [6, 12]. Some of the poisonings were politically motivated, particularly in the Catholic Church, as several senior clergymen were poisoned with arsenic over a 500-year period [12, 48].

An interesting and curious case of arsenic poisoning involved several elderly women of the village of Nagyrev in south-central Hungary [27]. In 1929, four women were brought to trial accused of murdering family members. Their basic plan was to call a doctor to the home of the intended victim. Many of the victims were chronically ill with tuberculosis or another debilitating disease. After the doctor departed, the victims were poisoned with arsenic. When the victims passed away, questions were not asked, because it was perceived that they died from complications of the noted illness. During this time, arsenic was easily available as arsenic acid as this agent was used as a rodenticide. Also, flypaper containing arsenic was commonly used. The arsenic was easily extracted from the flypaper and could be mixed with a drink, as one of the accused allegedly did with her husband's apricot brandy. There were other suspicious deaths at this time in this village, so 50 bodies from the town's cemetery were exhumed. Forty-six of the deceased had arsenic levels high enough to be lethal. Other women were brought to trial later and charged with the murders of husbands, fathers, sons, and mothers- and fathers-in-law. Several of the women were found guilty of murder and punished, while others were acquitted of the charges. It was alleged that the period of the murders in this village lasted over two decades and perhaps was even longer. It should be noted that even today, arsenic-containing flypaper is commercially available. The British newspaper, *The Guardian,* published an article in 2007 on poisons that could be purchased over the Internet [55]. The reporter was able to purchase from a company in Iowa flypaper with a packaging label indicating that it contained 2–4% metallic arsenic.

Intentional human poisoning with arsenic is not limited to Europe alone. In the state of North Carolina in the United States, from 1972 to 1982, there were 28 deaths attributed to arsenic exposure [47]. Of these deaths, 14 were declared homicides and 7 suicides. Four of the confirmed arsenic homicides were attributed to one woman, with the crimes occurring over a 4-year period. This woman may have been involved with additional arsenic poisonings.

Napoleon Bonaparte, the French military and political leader who died in 1821, may have been poisoned by arsenic [12]. Napoleon was exiled by the British to the south Atlantic island, St. Helena, in 1815. He appeared to be in good health upon arrival. Over time, he gained weight and had frequent illness. Several doctors on the

island examined Napoleon and diagnosed hepatitis. Before his death Napoleon apparently lost weight. The official autopsy report indicated that Napoleon had a chronic stomach ulcer and died of stomach cancer. For political reasons, both the English and French accepted that stomach cancer was the cause of his death. However, Napoleon's personal physician, who actually performed the autopsy, maintained that Napoleon died from complications of hepatitis.

After 140 years, a Swedish dentist, Sten Forshufvud, became convinced that Napoleon's demise came from arsenic poisoning [23, 63]. Hair that was reportedly removed from the head of Napoleon after his death was analyzed for arsenic by neutron activation. The response was positive for arsenic [23]. As discussed in Chapter 13, trivalent arsenic readily binds to sulfhydryl groups. Keratin, the primary structural protein of hair, contains sulfhydryl groups, and thus arsenic will bind to it. Smith et al. [23, 63] analyzed another supposed portion of Napoleon's hair that was held by someone else, and it also tested positive for arsenic. These claims of high levels of arsenic in the hair of Napoleon brought about the theory that he had been intentionally poisoned. However, Lewin et al. [40] analyzed a different sample of Napoleon's hair and detected only background levels of arsenic. To complicate matters further, it has been suggested that Napoleon was treating himself with arsenic so that he could become tolerant to a lethal dose [6]. Although it is an interesting story, it is still not clear whether arsenic poisoning was the cause of Napoleon's death.

1.2.1 Chemical Warfare

Arsenic has a somewhat veiled but nonetheless wretched history of being a chemical warfare agent. There are writings of arsenic being utilized to provide smoke to cover advancing troops during battles in ancient Greece [12]. The use of arsenic in warfare became prominent in World War I by both the Germans and Allies (British, French, and United States). Arsenic was first employed in this war as an inactive agent by the French in 1916 [12]. Arsenic trichloride was mixed with phosgene in artillery shells. The arsenic minimized dissipation of the phosgene, a deadly gaseous agent, and also provided smoke so that observers could adjust the artillery to more accurately place the next round.

The Germans were the first to utilize arsenic as an active warfare agent in 1917 [12]. This particular agent, chlorodiphenylarsine, is a respiratory irritant, causing sneezing and mucous buildup in those exposed to it. The irritation develops into coughing, headache, and other detrimental effects for the soldiers. In some artillery shells, chlorodiphenylarsine was mixed with phosgene and diphosgene, both of which are deadly gases. Other arsenicals used as active agents in World War I by the Germans and Allies were dichloromethylarsine, dichlorophenylarsine, dibromophenylarsine, cyanodiphenylarsine, and others [12] (Fig. 1.2).

A very potent arsenical, β-chlorovinyldichloroarsine, which is a deadly blistering agent or vesicant, was developed late in World War I (Fig. 1.3). However, this chemical was never used in this war. This arsenical was synthesized by a US research team led by Captain Winford Lee Lewis. This agent became known as Lewisite [12]. There is some speculation that Lewisite was first synthesized by a priest in 1903 at

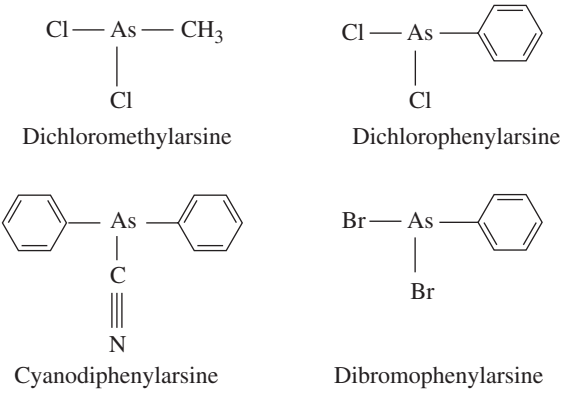
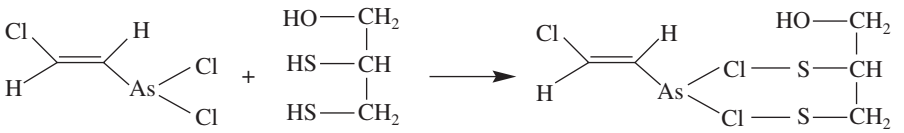


FIGURE 1.2 Structure of some arsenical war gases used in World War I.



Lewisite British Anti-Lewisite Chelated Lewisite

FIGURE 1.3 Reaction of Lewisite with 2,3-dimercaptopropanol (BAL) to form chelated Lewisite.

the Catholic University of America, in Washington, D.C. [12]. For his dissertation studies, Father John Niewland was attempting to synthesize rubber using arsenic trichloride, acetylene, and aluminum chloride. During this synthetic work, Father Niewland became ill from a noxious odor that arose from the reaction of these chemicals. There were no further studies to determine the source of the noxious odor. Years later, Captain Lewis' research team, also based at the Catholic University of America, was alerted to the potential of the noxious compound from Father Niewland's experiments because they had access to his dissertation. Whether or not Father Niewland actually synthesized Lewisite is not clear, but it was eventually prepared by Captain Lewis' research team.

One significant outcome of the threat of the use of Lewisite (and other chemicals) in warfare was the research and development of chemicals that could prevent the effects of this toxic arsenical. This research on Lewisite also led to an understanding of a mode of action for arsenic. With the threat of war looming in Europe in the late 1930s, the British formed a research team to prepare antagonists for chemical warfare agents that the Germans might employ [52]. This team was led by biochemist Rudolph Peters. Through a series of *in vitro* experiments, it was determined that Lewisite bonded with two sulfhydryl groups that are in close proximity to one another, within an essential component of the pyruvate oxidase system. Several dithiols were synthesized and tested for their ability to antagonize the effects

of Lewisite. Encouraging results were obtained with dithiols that could form a stable five- or six-membered ring with Lewisite. The most promising dithiols were those that bound more stably with Lewisite than the arsenical with the unknown biological receptor. It was determined that 2,3-dimercaptopropanol, which was eventually named British anti-Lewisite (BAL), was the best antagonist for Lewisite (Fig. 1.3). BAL penetrates cells and has low toxicity. BAL is effective both pre- and post-exposure of Lewisite.

While a major focus of chemical warfare is to directly incapacitate or kill the enemy, some effort may be directed to defoliate the surrounding landscape so the enemy is unable to conceal themselves in it as well as destroy their food supply. During the Vietnam War, the United States had a program, Operation Trail Dust, with a mission to defoliate the Vietnamese landscape with herbicides [12, 26]. Of the chemicals used in this program, the most famous was Agent Orange, which is a 1:1 mixture of the herbicides 2,4-D and 3,4,5-T. What is most known about Agent Orange is that 2,4,5-T was contaminated with dioxin. Another mission of Operation Trail Dust was to destroy the main food crop of the Viet Cong—rice. For this operation, a solution of dimethylarsinic acid, also known as cacodylic acid (Fig. 1.1), and its sodium salt was sprayed on the rice crops. The code name of this arsenical solution was Agent Blue (the names of the agents used were based on the color painted on the 55 gallon drums used to store the agent). This arsenical is a desiccant, drying out the crop it is intended to destroy. Cacodylic acid has been used in the United States as a cotton desiccant and a general weed killer but has recently been phased out of use [73]. The use of Agent Blue in the Vietnam War was approximately 10% of that of Agent Orange [12].

1.3 UNINTENTIONAL POISONING BY ARSENIC

Arsenic is an element found naturally in soil, air, and water. Because arsenic is pervasive, unintentional exposure to it has occurred in many unsuspecting populations. These exposures have led to adverse health effects, such as neuropathy, keratosis, peripheral vascular disease, malignancy, and death.

The unintentional poisoning of humans by arsenic most likely began during the first attempts to separate metals from other matter in the earth [75]. This is because arsenic is an impurity of the ores of copper, the first industrial metal, and iron. When humans discovered that metals could be cast by melting ores with fire, the exposure to arsenic and other metal contaminants most likely increased. Analysis of hair from the Tyrolean Neolithic mummy, the so-called "Ötzi-the-Iceman," who was discovered frozen in a glacier in the Alps along the Italian–Austrian border in 1991, contained copper and arsenic [7]. It is estimated that "Ötzi" died around 3300 B.C. It has been proposed that environmental arsenic pollution of cities from metallurgy caused the decline of the Etruscan civilization in Italy during the sixth century B.C. [29]. Even in more recent times, the exposure to arsenic from smelting of contaminated copper ores has continued to be problematic. Occupational exposure to arsenic by inhalation at copper smelters has led to increased deaths from lung cancer [20, 34].

1.3.1 Pigments and Dyes

Scheele's green is an arsenic- and copper-based pigment that was first prepared by Carl Schele in 1775. By its name it is green in color and was very popular in England in the 1800s. In fact, it was so fashionable during this time that Schele green was a common constituent in residential wallpaper, clothing, soap, paint, and other consumer products [5, 61]. Concerns were raised in England [5] and later in the United States [59] over the use of arsenic in wall paper and other products, in that people were being poisoned from arsenic exposure. There were reports of individuals becoming ill (e.g., fatigue and nausea) in their homes, which was attributed to arsenic in the wallpaper [5, 59]. There was even a suggestion that the wallpaper in the home of Napoleon, which contained arsenic, was the means of his alleged exposure to arsenic and his eventual death [35]. However, many of these illnesses were not well characterized, and the reports on morbidity and mortality from this type of exposure to arsenic were anecdotal.

Bartholomew Gosio, an Italian physician, found in 1892 that the mold *Scopulariopsis brevicaulis* was able to convert inorganic and organic arsenic into a gaseous arsenical [12, 13]. This arsenical has an odor of garlic and is known as "Gosio gas," and it has been suggested it was the toxic agent making people ill in their homes [35, 59]. Challenger et al. [10] determined the gas was trimethylarsine. However, trimethylarsine is about 1000-fold less toxic than arsine [13]. So it is unlikely that trimethylarsine had any significant role in the illnesses attributed to the arsenic-containing wallpaper. Sanger [59] also suggested the poisoning could have been due to absorption of inorganic arsenic dust from the wallpaper.

Efforts to ban arsenic-laden wallpaper began to arise in England [5]. Because studies on the actual reported illnesses were limited or nonexistent, it is too difficult to determine whether the arsenic in the wallpaper was actually the causative agent. By the late 1880s, the use of Schele green in wallpaper in England dramatically decreased, as different colors without arsenic became more popular [5].

In 1956, the US ambassador to Italy, Clare Boothe Luce, resigned from her post because of a chronic illness [12, 61]. This illness of unknown origin started in 1954 after she began her ambassadorship. Her symptoms included brittle fingernails, hair loss, anemia, and paresthesia in her lower right leg. It was finally determined that she had been poisoned by lead arsenate that was found in the painted bedroom ceiling of her residence in Rome. Over time, the ceiling plaster began to crumble into dust particles. Ambassador Luce was exposed to the lead arsenate tainted dust particles by inhalation and ingestion. She had noticed that the coffee she drank in her bedroom had a slight metallic taste. She returned to the United States and recovered from this chronic illness.

1.3.2 English Beer Drinkers

Cases of skin eruptions, erythema, keratosis, pigmentation, and "alcoholic paralysis" were reported in the summer of 1900 near and around Manchester, England [57]. The "alcoholic paralysis" was characterized as peripheral neuritis and paresthesia and numbness in the hands and feet. Ernest Reynolds, a local physician, saw a

connection between the skin afflictions and neuritis in patients he was treating. The neuritis occurred mainly in drinkers of beer and not hard liquor. Reynolds obtained a sample of the beer that many of the sufferers had been consuming. With the beer he conducted the Reinsch test, and the results suggested the presence of arsenic. Further investigation by a brewery-sponsored commission established that the source of the arsenic was brewery sugar [24]. It was determined that a chemical company had prepared sulfuric acid from Spanish pyrite containing arsenic. The arsenic-contaminated sulfuric acid was sold to a company that prepared the brewery sugar. The arsenic-contaminated sugar was sold to 100 or more breweries in England and was subsequently used in the beer brewing process. Over 6000 people were affected at one point by the contaminated beer [17]. Dr. Reynolds treated about 500 people alone over a 2-month period during this epidemic. He noted that 13 people died from the contaminated beer during this time.

A Royal Commission was convened to investigate this arsenic-contaminated beer incident [12, 17]. One of their recommendations was that limits for the amount of arsenic in liquids such as beer (0.14 ppm) and foods (1.43 ppm) be established. These limits were later set into law in England in 1928.

1.3.3 Japanese Infant Milk

Outbreaks of skin rash, gastrointestinal distress, and in a few cases, death, were reported in infants in 1955 in western Japan. Overall, there were almost 12,000 affected infants, including 113 deaths. An inquiry into this illness determined that the infants were bottle-fed arsenic-contaminated powdered milk [71]. The source of the arsenic was sodium phosphate, which was added to the milk as a stabilizer. The sodium phosphate was a by-product of a process from which aluminum was extracted from bauxite. The company that manufactured the milk failed to adequately clean the sodium phosphate before adding it to the powdered milk. The sale of the milk was banned within a day following discovery of the arsenic contamination. The acute symptoms disappeared in many of the affected babies following this ban. However, follow-up studies of those poisoned showed that about 325 suffered from developmental retardation and 250 had other ailments (e.g., epilepsy) [14]. It was difficult to determine the dose of arsenic the infants received because different lots of milk were prepared, and the infants were exposed for various lengths of time. More recent analysis of cancer mortality data of an exposed birth cohort that was most severely affected by the arsenic milk contamination showed that mortality from skin, pancreatic, and liver cancer was increased [79].

1.3.4 Coal in China

Coal in the area of Guizhou, China, contains a high concentration of arsenic (>100 ppm) [41]. As wood used to heat homes and to cook became depleted in the 1960s in this rural region of China, coal began being used in its place. In many homes of this region, unvented coal-burning indoor stoves are used for residential heating and to dry food resulting in indoor arsenic air concentration that may reach 250 $\mu g/m^3$

or greater. These levels are 80–90 times higher than the China Air Quality Permission Standard of 3 μg/m^3 [43]. Arsenic in the air from burning the coal can coat and permeate the smoke-dried food. Approximately 17% of the residents of this area showed the dermal lesions of chronic arsenic intoxication. Malignancies were the most serious outcome of arsenic intoxication, accounting for 50% of deaths in the arsenicosis patients. The source of arsenic exposure to people with the coal-burning stoves is primarily food (50–80%) and air (10–20%) [43]. Other elements such as fluorine and antimony are also released into the air from burning this coal, and along with the poor nutrition of the population, may be additional factors in the overall toxic response [2, 41, 43].

1.3.5 Drinking Water

In the mid- to late 1950s, it became evident that the incidence of a unique malady, Blackfoot Disease, was increasing in Taiwan [67–69]. The hands, feet, or both of people with this disease become discolored; hence, the term "Blackfoot Disease." This disease occurred in an economically poor region of southwest Taiwan, affecting mainly farmers and fishermen. Gangrene of the digits also has been reported in West Bengal [49] and Bangladesh [1], another region of high endemic exposure. This disease is rarely, if at all, observed in other regions of the world.

Blackfoot Disease is a vaso-occlusive disease in the extremities of the body. Early symptoms include numbness or cold sensation in the extremities, particularly the feet. Other symptoms include burning sensations and intermittent claudication. This disease progresses to "shooting" pain, development of ulcers, and finally gangrene in the hands and feet. Of 1300 Blackfoot Disease cases examined by Tseng [69], 68% had spontaneous or surgical amputation of gangrenous hands or feet.

Investigations into the cause of this disease pointed to arsenic exposure [67–69]. In this region of Taiwan, with a population of approximately 100,000, the main source of drinking water was deep artesian wells, some over 200 m deep. These wells began to be used as a source of drinking water in the early 1900s because many of the shallow wells in the area had become tainted with saline. It was determined that these deep artesian wells were naturally contaminated with arsenic, with concentrations ranging from 0.01 to 1.2 ppm [68]. The severity of the disease was correlated with the concentration of arsenic in the artesian well water and the length of exposure. Individuals who lived in this region, but were able to drink water from the shallow wells, did not develop Blackfoot Disease. The arsenic concentration in the shallow wells ranged from 0.001 to 0.017 ppm. A low arsenic source of water became available to this region in the 1960s. After this time, no new cases of Blackfoot Disease developed in individuals who lived in the endemic area, used this low arsenic source of drinking water, and were less than 20 years old when they began to use the low arsenic water [68]. There were some suggestions that humic substances and chemicals other than arsenic present in the artesian well water also contributed to Blackfoot Disease [67]. But, this has never been positively determined.

In this same arsenic-exposed Taiwanese population, the risk of skin cancer and other dermal effects were also increased. Tseng et al. [70] reported that the overall

prevalence rates for skin cancer, hyperpigmentation, and keratosis were 10.6/1000, 183.5/1000, and 71/1000, respectively. The prevalence rate for these afflictions increased with arsenic content of the artesian well water and with age (i.e., duration of exposure). These data have been used to determine the USEPA's oral reference dose (3×10^{-4} mg/kg/day) for arsenic and to support the classification of this metalloid as a human carcinogen [72].

A more recent calamity of unintentional arsenic exposure to a population has occurred in eastern India (West Bengal) [15, 16] and Bangladesh [38]. Like the Taiwanese, the exposure is from arsenic-contaminated drinking water. As India and Bangladesh are developing nations, surface water used as a source of drinking water in these countries is often contaminated with viruses, microorganisms, and pollutants. This has led to the occurrence of disease and mortality in people consuming this water, particularly infants. To alleviate this problem, several nongovernmental organizations (e.g., UNICEF and World Bank) in conjunction with the Bangladeshi government in the 1970s started to install tube-wells into the ground. These tube-wells were dug to provide ground water, which in theory would be less contaminated than surface water, and thus be a safer source of drinking water. Reports of dermal lesions in individuals that consumed this ground water began to emerge in the 1980s [9]. However, installation of the tube-wells in the region continued and millions are still in use. What has been determined is that the well water is naturally contaminated with arsenic due to the geological formations in the region. The water from many of these wells exceeds the World Health Organization (WHO) and USEPA arsenic drinking water standard of 10 μg/L. Tens of millions of people in this region of the world drink this contaminated water [62]. They are at risk of developing skin lesions, cardiovascular disease, diabetes, and cancer of skin, bladder, and other organs [62]. There has been a movement to test the water of each tube-well. Those wells with elevated levels are painted red to warn the user not to drink water from the well. However, this warning is not always heeded. Also, there are millions of wells, and to test all of them will take time.

Countries that have high arsenic levels in groundwater that is used as a source of drinking water include Argentina, Chile, Mexico, Thailand, Vietnam, and others [46]. Individuals in these countries who consume this contaminated water are also at risk for the development of several chronic diseases and cancer. In addition, mitigation of the high arsenic levels in the drinking water may not necessarily decrease the risk of cancer. Steinmaus et al. [64] have reported a high cancer risk in people in northern Chile 40 years after exposure cessation to high levels of arsenic in drinking water.

1.4 MEDICINAL USES OF ARSENIC

Although arsenic has been used with malicious intent over the ages, it has also been used benevolently to improve, or at least with good intentions, the health of man. There are writings of the use of arsenic sulfides in the form of orpiment (As_2S_3) and realgar (As_4S_4) by Hippocrates and Aristotle in the fourth century B.C. in pastes to treat

ailments of the skin [6, 28, 45]. Dioscorides reported on the usefulness of orpiment in the first century A.D. as a depilatory [28]. Arsenic sulfide was used in the Middle East in the 1200s for the treatment of skin diseases, hemorrhoids, and syphilis [38].

Arsenic became more widely used in Europe in the late Middle Ages to the 1800s to treat an assortment of ailments [6, 28, 45]. The English physician William Withering advocated in the late eighteenth century the use of arsenic for medical purposes [66]. One of the most recognized arsenic treatments from this era was Fowler's solution [6, 12, 28, 37]. In the 1770s, a patented solution called "Tasteless Ague and Fever Drops" was used in English hospitals as an antiperiodic medicinal. Thomas Fowler, an English physician, asked the apothecarist Mr. Hughes, to determine the constituents of the patented solution. He found that it contained arsenic and prepared a new solution, by dissolving arsenic trioxide in alkali. Lavender was added to make the solution appear as a medicinal agent. This solution became to be known as Fowler's solution. It was used to treat many ailments including fever, asthma, syphilis, rheumatism, skin disorders, and leukemia [12, 45]. Fowler's solution and other arsenical solutions were listed as medicinal agents in the *Materia Medica* published in 1903 (Table 1.2). Fowler's solution was used up until the mid-1900s when other medicinal agents were found to be more efficacious with lower toxicity.

The medicinal use of arsenicals such as Fowler's solution is not without adverse effect. Sir Jonathan Hutchinson, an English surgeon, reported at the Pathological Society of London in 1887 that the long-term internal administration of arsenic at high doses could result in epithelial cancer [31]. Hutchinson presented a case of an American physician who had taken arsenic for psoriasis. Although the psoriasis on this patient had been cured, he had developed nodules on his palms and soles, which is a characteristic of chronic arsenic poisoning. The patient later died and was found to have epithelial cancer. This and other cases presented by Hutchinson were the first reports of the potential for inorganic arsenic to be a human carcinogen.

TABLE 1.2 Arsenical Preparations Used as Medicinal Agents in the Early 1900s[a]

Preparation	Arsenical	Formulation	Therapeutic Use
Acidum arsenosum	Arsenous acid	Pill; 1% solution with potassium carbonate (Fowler's solution)	Caustic to remove skin growth, anemia, malaria psoriasis, eczema
Arseni iodidum	Iodide of arsenic	1% solution	Tuberculosis, scrofula, bronchitis
Sodium cacodylas	Sodium cacodylate	Solution	Tuberculosis
Arsenii bromidi	Bromide of arsenic	1% solution (Clemen's solution)	Diabetes
Cupri arsenis	Arsenite of copper	Solution	Intestinal antiseptic for childhood diarrhea

[a] From Ref. [65].

In the latter part of the nineteenth century and early twentieth century, synthetic chemistry techniques had advanced to the point where chemicals were readily being synthesized to combat infectious diseases. Paul Ehrlich, a German physician, is generally credited to be the father of this new era, termed chemotherapy [44, 58, 78]. Ehrlich's goal was to synthesize the "Magic Bullet," a drug that would kill the infectious agent, but not harm the patient. Ehrlich and his coworker, Alfred Bertheim, were able to determine the structure of the arsenical atoxyl. Atoxyl was the first synthetic aromatic arsenical. It was prepared by Antoine Berchampe in 1863, when he heated aniline and arsenic together [44, 58]. Berchampe believed the structure to be an anilide. Forty years later, atoxyl began to be used in Europe to treat skin diseases and cancer. It had been found to be less acutely toxic than inorganic arsenic that was used for similar purposes. Ehrlich and Bertheim determined that atoxyl was actually an amino arsenic acid. This knowledge allowed them to synthesize over 900 derivatives of atoxyl. The most famous derivative, Compound 606 or arsphenamine, was found to be effective against syphilis. It was marketed as Salvarsan to treat syphilis in 1910 and was more successful than the standard mercury salt treatments used at that time. Salvarsan remained the most useful drug for syphilis until the emergence of penicillin in the 1940s.

The use of arsenicals in medicine has decreased over the years, primarily because of the potential for toxic effects of these compounds and because more effective medicinal agents are available. However, arsenic is being used for specific diseases (See Section 1.4.4). The trivalent organic arsenical melarsoprol is used to treat human African trypanosomiasis [50]. Melarsoprol is the drug of choice for the second stage of this disease because it can cross the blood–brain barrier and kill the parasites that reside in the cerebrospinal fluid. However, there are adverse effects with using this drug. About 20% of the patients treated with melarsoprol are affected by reactive encephalopathy. In addition, some strains of this parasite are becoming resistant to the therapeutic effects of melarsoprol.

1.4.1 Arsenic Eaters of Styria

A curious aspect of arsenic exposure is the "arsenic eaters of Styria" [28, 45, 53]. People living in the region near Graz, Austria, were reported to have begun eating small amounts of arsenic in the twelfth century. Both white and yellow arsenic (orpiment) were consumed. Consumption of arsenic in this region was for an assumed beneficial effect. Reasons given for eating arsenic were to enhance a woman's complexion, improve breathing during hiking at high altitudes, aid in digestion, increase courage and sexual potency, and as a preventative measure against infectious diseases. The use of arsenic in Styria in this manner is controversial because there is limited evidence that it occurred. If it happened, it was most likely in secret, and predominantly by poor people. But considering that other Europeans were using arsenic as a tonic during 1700 and 1800s, and there is use of the traditional Chinese and Indian Medicines (see below), the eating of arsenic in Styria could have been a frequent occurrence.

1.4.2 Traditional Medicines

Traditional medicines used in countries such as China and India contain metals such as arsenic, mercury, and lead [11, 36, 42, 60]. The WHO defines traditional medicine as health practices and approaches that use plant, animal, and mineral medicines as well as spiritual and physical techniques alone or in combination to diagnose and treat illness as well maintain an individual's health (WHO [80]). These practices were developed many hundreds if not thousands of years ago and are still in place. In many developing countries, the WHO estimates that up to 80% of the population relies on traditional medicine.

Chinese traditional medicines include the arsenical minerals orpiment, realgar, and arsenolite (essentially arsenic trioxide) [42]. Indian Ayurvedic metallic herbal preparations called Bhasmas can contain arsenic, mercury, silver, and other metals [36]. The metals are purposely added to the traditional medicines for therapeutic effect. For example, realgar is a constituent of *Hongling San* (15% realgar in seven components) and used to treat heatstroke, dizziness, headache, and nausea [42]. Most, if not all, of these traditional medicines are not regulated as pharmaceutical agents in the western world. However, these traditional medicines are available via the Internet and in specialized stores in developed countries [11, 60]. Poisonings have been noted from their use [21, 22]. As people emigrate from developing to developed countries, these traditional medicines may become more prevalent and care should be taken with their use.

1.4.3 Uses in Dentistry

Arsenic has had use in dentistry, primarily to relieve dental pain and for root canal therapy [32]. There are writings of the use of arsenic in China in 2700 B.C. for painful teeth to "kill a tooth worm." Two thousand years later, arsenic was used in the Middle East and Europe for tooth pulp devitalization, to treat dental fistula and tooth pain, and for root canal therapy. For the latter treatment, the roots of teeth were coated with yellow arsenic (orpiment) before extraction. To alleviate tooth pain, in some cases, a mixture of opium and arsenic was used.

John Roach Spooner of Canada is generally recognized as the first practitioner in North America to devitalize the dental pulp with arsenic. This occurred in the early 1800s. While arsenic was used by dentists in North America during the early to late 1800s, this was not without controversy. Several practitioners cautioned the use of arsenic because of its potent and acute toxic properties. In fact, there were several deaths of dental patients that had been treated with arsenic, although it was not completely determined whether the arsenic treatment was the cause of death. The use of arsenic in dentistry started to fade at the end of the 1800s. However, even today, homeopathic dentistry recommends the use of arsenicum album (diluted arsenic trioxide) for the treatment of tooth ache [74].

1.4.4 Treatment for Leukemia

One of the more interesting uses of arsenic is for the treatment of relapsed acute promyelocytic leukemia [19]. Treatment for this rare form of leukemia with arsenic trioxide reemerged in China in the early 1970s [3]. Arsenic had been used in China to

treat leukemia up to the 1950s but became disfavored because of newly found radiation treatments and implementation of alkylating agents. However, because of political and cultural turmoil in China in the 1950s and 1960s, western-type anti-leukemia therapy became unavailable to the Chinese people. In 1971, researchers from Harbin Medical University learned that traditional Chinese medicine was being used in the village of Lindian in northeast China to treat cancer effectively. Analysis of the medicine showed it contained arsenic trioxide, mercuric oxide, and toad extract. TD Zhang of Harbin Medical University determined that arsenic trioxide was the active ingredient. In 1973, arsenic trioxide was successfully used in humans to treat chronic myelogenous and acute promyelocytic leukemia [3]. Word of its use as an anti-leukemia agent became known in the United States in the late 1990s. The Food and Drug Administration approved of the use of arsenic trioxide for treatment of refractive acute promyelocytic leukemia in 2001. Although arsenic trioxide is an effective cancer therapeutic agent, it has to be used cautiously, with careful monitoring of the patients because of the potential acute lethal toxicity of this arsenical [76].

Research is underway for candidates to supplement or replace arsenic trioxide as a treatment for leukemia. One of the candidates is realgar, which is a mineral found in ores removed from the ground. Realgar is a common constituent of traditional Chinese and Indian medicines. The acute toxicity of realgar is about 100-fold less than arsenic trioxide [42, 77]. Positive results using realgar in treating leukemia have been reported [77], but it currently is not approved for cancer treatment in the United States. Realgar is poorly soluble in water, which makes it less bioavailable than other arsenicals [4, 77]. Nanoparticles and quantum dots have been developed containing realgar in an attempt to increase its bioavailability, and animal studies suggest this occurs [4, 77]. Bioleaching of arsenic from realgar is another potential means for the dissolution of this arsenical for its medicinal use [81].

1.5 SUMMARY

Arsenic has a long history of being an intentional and unintentional human poison. For intentional exposure, there have been many unfortunate instances where arsenic was used for homicidal intent. However, with current analytical chemistry capabilities, the probability of determining the cause of the poisoning and perhaps the conviction of the accused is great. There is a great effort to reduce unintentional exposure, primarily in drinking water, by many world-wide governmental agencies and nongovernmental organizations. Adverse outcomes from this particular type of exposure, primarily in developing countries, may reach calamitous heights in the next few years. Arsenic has specific medicinal uses such as the treatment for acute promyelocytic leukemia and trypanosomiasis. However, its use needs to be carefully monitored because of the high probability of side effects. Research is underway to find less toxic forms of arsenic that will hopefully have a beneficial effect. Arsenic has had a long history of being a poison and a medicine. Human exposure to this metalloid will continue primarily because of its pervasiveness in the environment and less so from its use as a medicinal agent.

REFERENCES

[1] S. Ahamed, M.K. Sengupta, S.C. Mukherjee, S. Pati, A. Mukherjeel, M.M. Rahman, M.A. Hossain, B. Das, B. Nayakl, A. Pal, A. Zafar, S. Kabir, S.A. Banu, S. Morshed, T. Islam, M.M. Rahman, Q. Quamruzzaman, D. Chakraborti, An eight-year study report on arsenic contamination in groundwater and health effects in Eruani village, Bangladesh and an approach for its mitigation. The Journal of Health, Population and Nutrition 24 (2006) 129–141.

[2] D. An, Y.G. He, Q.X. Hu, Poisoning by coal smoke containing arsenic and fluoride. Fluoride 30 (1997) 29–32.

[3] W.Y. Au, A biography of arsenic and medicine in Hong Kong and China. Hong Kong Medical Journal 17 (2011) 507–512.

[4] P. Balaz, J. Sedlak, Arsenic in cancer treatment: Challenges for application of realgar nanoparticles (A mini review). Toxins 2 (2010) 1568–1581.

[5] P.W.J. Bartrip, How green was my valance? Environmental arsenic poisoning and the Victorian domestic ideal. English Historical Review 109 (1994) 891–913.

[6] R. Bentley, T.G. Chasteen, Arsenic curiosa and humanity. The Chemical Educator 7 (2002) 51–60.

[7] H.M. Bolt, Arsenic: An ancient toxicant of continuous public health impact, from iceman Otzi until now. Archives of Toxicology 86 (2012) 825–830.

[8] A.C. Bronstein, D.A. Spyker, L.R. Cantilene, J.L. Green, B.H. Rumack, R.C. Dart, 2010 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th Annual Report. Clinical Toxicology 49 (2011) 910–941.

[9] A.K. Chakraborty, K.C. Saha, Arsenical dermatosis from tubewell water in West Bengal. The Indian Journal of Medical Research 85 (1987) 326–334.

[10] F. Challenger, C. Higginbottom, L. Ellis, The formation of organo-metalloidal compounds by microorganisms. Part I. Trimethylarsine and dimethylarsine. Journal of the Chemical Society 95 (1933) 101.

[11] K. Cooper, B. Noller, D. Connell, J. Yu, R. Sadler, H. Olszowy, G. Golding, U. Tinggi, M.R. Moore, S. Myers, Public health risks from heavy metals and metalloids present in traditional Chinese medicines. Journal of Toxicology and Environmental Health, Part A 70 (2007) 1694–1699.

[12] W.R. Cullen Is Arsenic an Aphrodisiac? The Sociochemistry of an Element, The Royal Society of Chemistry, Cambridge, MA, 2008.

[13] W.R. Cullen, R. Bentley, The toxicity of trimethylarsine: An urban myth. Journal of Environmental Monitoring 7 (2005) 11–15.

[14] M. Dakeishi, K. Murata, P. Grandjean, Long-term consequences of arsenic poisoning during infancy due to contaminated milk powder. Environmental Health: A Global Access Science Source 5 (2006) 1–7.

[15] D. Das, A. Chatterjee, B.K. Mandal, G. Samanta, D. Chakraborti, B. Chanda, Arsenic in ground water in six districts of West Bengal, India: The biggest arsenic calamity in the world. Part 2. Arsenic concentration in drinking water, hair, nails, urine, skin-scale and liver tissue (biopsy) of the affected people. The Analyst 120 (1995) 917–924.

[16] D. Das, A. Chatterjee, G. Samanta, B. Mandal, T.R. Chowdhury, G. Samanta, P.P. Chowdhury, C. Chanda, G. Basu, D. Lodh, Arsenic contamination in groundwater in six

districts of West Bengal, India: The biggest arsenic calamity in the world. The Analyst 119 (1994) 168N–170N.

[17] P. Dyer, The 1900 arsenic poisoning epidemic. Brewery History 130 (2009) 65–85.

[18] M.J. Ellenhorn Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning, Williams & Wilkins, Baltimore, 1997.

[19] A. Emadi, S.D. Gore, Arsenic trioxide: An old drug rediscovered. Blood Reviews 24 (2010) 191–199.

[20] P.E. Enterline, R. Day, G.M. Marsh, Cancers related to exposure to arsenic at a copper smelter. Occupational and Environmental Medicine 52 (1995) 28–32.

[21] E. Ernst, Heavy metals in traditional Indian remedies. European Journal of Clinical Pharmacology 57 (2002) 891–869.

[22] E. Ernst, Toxic heavy metals and undeclared drugs in Asian herbal medicines. Trends in Pharmacological Sciences 23 (2002) 136–139.

[23] S. Forshufvud, H. Smith, A. Wassen, Arsenic content of Napoleon I's hair probably taken immediately after his death. Nature 192 (1961) 103–105.

[24] G. Gall, What's your poison. Brewery History 128 (2008) 49–53.

[25] M.S. Gorby, Arsenic poisoning. Western Journal of Medicine 149 (1988) 308–315.

[26] G. Greenfield, Agent Blue and the business of killing rice. *Ecologist* (2004). http://www.countercurrents.org/us-greenfield180604.htm. Accessed June 13, 2015.

[27] F. Gyorgyey, Arsenic and no lace. Caduceus 3 (1987) 40–65.

[28] J.S. Haller, Therapeutic mule: The use of arsenic in the nineteenth century materia medica. Pharmacy in History 17 (1975) 87–100.

[29] A.P. Harrison, I. Cattani, J.M. Turfa, Metallurgy, environmental pollution and the decline of Etruscan civilization. Environmental Science and Pollution Research International 17 (2010) 165–180.

[30] M.F. Hughes, Arsenic toxicity and potential mechanisms of action. Toxicology Letters 133 (2002) 1–16.

[31] J. Hutchinson, Arsenic cancer. British Medical Journal 2 (1887) 1281–1282.

[32] J.M. Hyson, A history of arsenic in dentistry. Journal of the California Dental Association 35 (2007) 135–139.

[33] IARC A Review of Human Carcinogens. C. Metals, Arsenic, Fibres and Dusts, International Agency for Research on Cancer, Lyon, France, 2012.

[34] L. Jarup, G. Pershagen, S. Wall, Cumulative arsenic exposure and lung cancer in smelter workers: A dose response study. American Journal of Industrial Medicine 15 (1989) 31–41.

[35] D.E.H. Jones, D.W.D. Ledingham, Arsenic in Napoleon's wallpaper. Nature 299 (1982) 626–627.

[36] A. Kumar, A.G. Nair, A.V. Reddy, A.N. Garg, Bhasmas: Unique Ayurvedic metallic-herbal preparations, chemical characterization. Biological Trace Element Research 109 (2006) 231–254.

[37] H.A. Langenhan, History of the arsenical solutions. Journal of the American Pharmaceutical Association 8 (1919) 189.

[38] E. Lev, Medicinal exploitation of inorganic substances in the Levant in the Medieval and Early Ottoman Periods. Adler Museum Bulletin 28 (2002) 11–16.

[39] T. Levine, A. Rispin, C. Chen, H. Gibb. Special Report on Ingested Inorganic Arsenic. Skin Cancer, Nutritional Essentiality, USEPA, Washington, DC, 1988. http://www.epa.gov/raf/publications/pdfs/EPA_625_3-87_013.PDF. Accessed April 09, 2015.

[40] P.K. Lewin, R.G.V. Hancock, P. Voynovich, Napoleon Bonaparte: No evidence of chronic arsenic poisoning. Nature 299 (1982) 622–628.

[41] D. Li, D. An, Y. Zhou, J. Liu, M.P. Waalkes, Current status and prevention strategy for coal-arsenic poisoning in Guizhou, China. Journal of Health, Population, and Nutrition 24 (2006) 273–276.

[42] J. Liu, Y. Lu, Q. Wu, R.A. Goyer, M.P. Waalkes, Mineral arsenicals in traditional medicines: Orpiment, realgar, and arsenolite. The Journal of Pharmacology and Experimental Therapeutics 326 (2008) 363–368.

[43] J. Liu, B. Zheng, H.V. Aposhian, Y. Zhou, M.L. Chen, A. Zhang, M.P. Waalkes, Chronic arsenic poisoning from burning high-arsenic-containing coal in Guizhou, China. Environmental Health Perspectives 110 (2002) 119–122.

[44] N.C. Lloyd, H.W. Morgan, B.L. Nichlson, R.S. Ronimus, R. Riethmiller, Salvarsan: The first chemotherapeutic compound. Chemistry in New Zealand 69 (2005) 24–27.

[45] A. Lykknes, L. Kvittingen, Arsenic: Not so evil after all? Journal of Chemical Education 80 (2003) 497–500.

[46] B.K. Mandal, K.T. Suzuki, Arsenic round the world: A review. Talanta 58 (2002) 201–235.

[47] E.W. Massey, D. Wold, A. Heyman, Arsenic: Homicidal intoxication. Southern Medical Journal 77 (1984) 848–851.

[48] W.J. Meek, The gentle art of poisoning. Journal of the American Medical Association 158 (1955) 335–339.

[49] S.C. Mukherjee, K.C. Saha, S. Pati, R.N. Dutta, M.M. Rahman, M.K. Sengupta, S. Ahamed, D. Lodh, B. Das, M.A. Hossain, B. Nayak, A. Mukherjee, D. Chakraborti, S.K. Dulta, S.K. Palit, I. Kaies, A.K. Barua, K.A. Asad, Murshidabad: One of the nine groundwater arsenic-affected districts of West Bengal, India. Part II: Dermatological, neurological, and obstetric findings. Clinical Toxicology 43 (2005) 835–848.

[50] A.J. Nok, Arsenicals (melarsoprol), pentamidine and suramin in the treatment of human African trypanosomiasis. Parasitology Research 90 (2003) 71–79.

[51] NRC Arsenic in Drinking Water, National Academy Press, Washington, DC, 1999.

[52] M.G. Ord, L.A. Stocken, A contribution to chemical defence in World War II. Trends in Biochemical Sciences 25 (2000) 253–256.

[53] G. Przygoda, J. Feldmann, W.R. Cullen, The arsenic eaters of Styria: A different picture of people who were chronically exposed to arsenic. Applied Organometallic Chemistry 15 (2001) 457–462.

[54] S. Pullen-James, S.E. Woods, Occupational arsine gas exposure. Journal of the National Medical Association 98 (2006) 1998–2001.

[55] J. Randerson, Lethal poisons for sale in the web marketplace. *The Guardian*. March 28, 2007. http://www.theguardian.com/technology/2007/mar/29/news.uknews. Accessed April 9, 2015.

[56] R.N. Ratnaike, Acute and chronic arsenic toxicity. Postgraduate Medical Journal 79 (2003) 391–396.

[57] E.S. Reynolds, An account of the epidemic outbreak of arsenical poisoning occurring in beer drinkers in the north of England and the Midland counties in 1900. Medico-Chirurgical Transactions 4 (1901) 409–452.

[58] S. Riethmiller, From Atoxyl to Salvarsan: Search for the Magic Bullet. Chemotherapy 51 (2005) 235–242.

[59] C.R. Sanger, On chronic arsenical poisoning from wall papers and fabrics. Proceedings of the American Academy of Arts and Sciences 29 (1893) 148–177.

[60] R.B. Saper, R.S. Phillips, A. Sehgal, N. Khouri, R.B. Davis, J. Paquin, V. Thuppil, S.N. Kales, Lead, mercury, and arsenic in US- and Indian-manufactured Ayurvedic medicines sold via the Internet. JAMA: The Journal of the American Medical Association 300 (2008) 915–923.

[61] S. Scheindlin, The duplicitous nature of inorganic arsenic. Molecular Interventions 5 (2005) 60–64.

[62] A.H. Smith, E.O. Lingas, M. Rahman, Contamination of drinking-water by arsenic in Bangladesh: A public health emergency. Bulletin of the World Health Organization 78 (2000) 1093–1103.

[63] H. Smith, S. Forshufvud, A. Wassen, Distribution of arsenic in Napoleon's hair. Nature 194 (1962) 725–726.

[64] C.M. Steinmaus, C. Ferreccio, J.A. Romo, Y. Yuan, S. Cortes, G. Marshall, L.E. Moore, J.R. Balmes, J. Liaw, T. Golden, A.H. Smith, Drinking water arsenic in northern Chile: High cancer risks 40 years after exposure cessation. Cancer Epidemiology, Biomarkers and Prevention 22 (2013) 623–630.

[65] A.A. Stevens Modern Materia Medica and Therapeutics, W.B. Saunders & Co., Philadelphia, PA, 1903.

[66] X. Thomas, J. Troncy, Arsenic: A beneficial therapeutic poison—a historical overview. Adler Museum Bulletin 35 (2009) 3–13.

[67] C.H. Tseng, Blackfoot disease and arsenic: A never-ending story. Journal of Environmental Science and Health. Part C, Environmental Carcinogenesis & Ecotoxicology Reviews 23 (2005) 55–74.

[68] W.P. Tseng, Effects and dose: Response relationships of skin cancer and blackfoot disease with arsenic. Environmental Health Perspectives 19 (1977) 109–119.

[69] W.P. Tseng, Blackfoot disease in Taiwan: A 30-year follow-up study. Angiology 40 (1989) 547–558.

[70] W.P. Tseng, H.M. Chu, S.W. How, J.M. Fong, C.S. Lin, S. Yeh, Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. Journal of the National Cancer Institute 40 (1968) 453–463.

[71] K. Tsuchiya, Various effects of arsenic in Japan depending on type of exposure. Environmental Health Perspectives 19 (1977) 35–42.

[72] US Environmental Protection Agency. Arsenic, inorganic (CASRN 7440-38-2). System, Integrated Risk Information. 2003. http://www.epa.gov/iris/subst/0278.htm. Accessed April 9, 2015.

[73] US Environmental Protection Agency. Organic Arsenicals. 2013. http://www.epa.gov/oppsrrd1/reregistration/organic_arsenicals_fs.html. Accessed April 9, 2015.

[74] P. Wander, Top 5 reasons we visit … the dentist. Health & Homeopathy (2010) 17–20.

[75] T.A. Wertime, Man's First Encounters With Metallurgy: Man's discovery of ores and metals helped to shape his sense of science, technology, and history. Science 146 (1964) 1257–1267.

[76] P. Westervelt, R.A. Brown, D.R. Adkins, H. Khoury, P. Curtin, D. Hurd, S.M. Luger, M.K. Ma, T.J. Ley, J.F. DiPersio, Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide. Blood 98 (2001) 266–271.

[77] J. Wu, Y. Shao, J. Liu, G. Chen, P.C. Ho, The medicinal use of realgar (As4S4) and its recent development as an anticancer agent. Journal of Ethnopharmacology 135 (2011) 595–602.

[78] A. Yarnell, Salvarsan. Chemical and Engineering News 83 (2005) 116.

[79] T. Yorifuji, T. Tsuda, P. Grandjean, Unusual cancer excess after neonatal arsenic exposure from contaminated milk powder. Journal of the National Cancer Institute 102 (2010) 360–361.

[80] WHO Fact Sheet Number 134 (2008).

[81] J. Zhang, X. Zhang, Y. Ni, H. Li, Bioleaching of arsenic from medicinal realgar by pure and mixed cultures. Process Biochemistry 42 (2007) 1265–1271.