Arsenic: an ancient toxicant of continuous public health impact, from Iceman Ötzi until now

Hermann M. Bolt

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Early knowledge on the toxicity of arsenicals has accumulated in Asian civilizations, where especially arsenic sulphide (*realgar*) had been traditionally used, both as a medicine and as a poison. According to Lewin (1929) such knowledge arrived at the Hellenic Mediterranean world following the conquests of Alexander the Great. Since then, there has been a continuous European history of both use of arsenic as a medicine and abuse as a homicide, until recently (Lewin 1929). For instance, Napoleon's health began rapidly to fail in February 1821. He suffered from chronic As intoxication when he died on 5 May 1821, as now evidenced by analysis of his hair (Kintz et al. 2007; see Table 1). Biomonitoring of As in human hair is now regarded to be a useful tool in field studies evaluating chronically elevated As exposures (Pandey et al. 2007; Orloff et al. 2009; Kazi et al. 2011), although being less indicative at low (non-elevated) exposures (Cleland et al. 2009).

Soluble inorganic arsenic is acutely toxic, and ingestion of large doses leads to gastrointestinal symptoms, disturbances of cardiovascular and nervous system functions, and eventually death. In survivors, bone marrow depression, haemolysis, hepatomegaly, melanosis, polyneuropathy and encephalopathy may be observed (WHO 2001). Chronic human exposure has been linked to a variety of dermal symptoms of arseni(c)osis¹ (i.e. exfoliative dermatitis, keratosis, vitiligo, skin cancer), peripheral neuropathy, encephalopathy, bronchitis, pulmonary fibrosis, hepato-splenomegaly, portal hypertension, peripheral vascular disease/"blackfoot disease", atherosclerosis, cancer

(lung, urinary bladder, other organs) and diabetes mellitus (Pimparker and Bhawe 2010).

In contrast to its intentional use, arsenic as a chronic human environmental toxicant has an even much longer history by a couple of 1,000 years. At present, the oldest environmental exposure to arsenic is scientifically testified by hair analysis of the Tyrolean Neolithic mummy called "Ötzi", who died between 3359 and 3105 BC (Oeggel 2009). In his case, copper enrichment near the hair surface and high arsenic contents in keratin cells of the interior of the hair shaft strongly argue in favour of a long-term involvement in copper working, accompanied by high arsenic exposure (Brothwell and Grime 2002). Table 1 compares these data with contemporary concentrations of arsenic in hair. Regarding historical aspects, a challenging theory is now being advanced that desertion of several important Etruscan settlements at the end of the Archaic period in Italy had been a consequence of man-made pollution and associated arsenic environmental poisoning (Harrison et al. 2010).

According to the evaluation of WHO (2001), long-term exposure to arsenic in drinking water is causally related to increased risks of cancer in the skin, lungs, bladder and kidney, as well as other skin changes such as hyperkeratosis and pigmentation changes. These effects have been demonstrated in many studies using different study designs. Exposure–response relationships have been observed for each of these end-points. The effects have been most thoroughly studied in Taiwan, but there is considerable evidence from studies on populations in other countries as well. Increased risk of lung and bladder cancer and of

H. M. Bolt (✉)
Leibniz Research Centre for Working Environment and Human Factors (IfADo), Ardeystr. 67, 44139 Dortmund, Germany
e-mail: bolt@ifado.de

¹ In the present literature the terms arseniosis, arsenicosis and arseniasis are used without clear distinctions. In the present editorial, the denominations generally follow those of the respective authors.

Table 1 Recently reported elevated As levels in human hair specimens (mean values; single data, when indicated)

Geographic area and conditions	µg As/g hair	References
<i>(Pre-)historical</i>		
Neolithic Tyrolean “Ötzi”	44 ^a	Brothwell and Grime (2002)
Saint Helena, Napoleon	37.4, 42.1	Kintz et al. (2007)
<i>Coal combustion</i>		
Guizhou/China, indoor combustion of high-As coal, villages with arseniosis cases	43.4, 48.6, 53.5	Baoshan et al. (2005)
Slovakia, As-rich coal combustion in power plant, environmental exposure	>3	Bencko et al. (2009)
<i>Mining</i>		
Xikouangshan Sb mining area, China, environmental exposure	3.99	Wu et al. (2011)
	4.21	Liu et al. (2009)
Shantou, China, W mining area, environmental exposure	2.92	Liu et al. (2010)
<i>Food and drinking water</i>		
Pakistan, consumption of As-contaminated fish	Up to 4.94	Shah et al. (2011)
Gaighata, West Bengal, India, As in groundwater	Up to 5.99	Roychowdhury (2010)
Jalangi/Domkol, West Bengal, India, As in tube-well water	Up to 4.7	Uchino et al. (2006)
Kandal Province, Cambodia, As in groundwater	Up to 7.95	Gault et al. (2008)
An Giang, Mekong River Delta, Vietnam, As in drinking water	Up to >10	Hanh et al. (2011)
San Antonio de los Cobres, Argentina, As in drinking water	Up to 1.5	Concha et al. (2006)
Illapata, Chile, As in drinking water	4.20	Yanez et al. (2005)
Santana, Brazil	Up to 23.8 ^b	De Fátima Pinheiro Pereira (2010)
<i>Controls</i>		
Guizhou/China (see above) controls, no arseniosis	0.56, 0.60	Baoshan et al. (2005)
Altamira/Amazon, Brazil	0.43	De Fátima Pinheiro Pereira (2010)
Rio de Janeiro, Brazil	0.70	dto.
Egypt	0.54	dto.
Canada and USA	0.01	dto.
Italy	0.09	dto.
Malaysia	0.28	dto.
UK reference, non-exposed, different ethnic groups	0.116–0.141	Brima et al. (2006)

^a Average As content (Brothwell and Grime 2002): 0.11 % of S content; normal S content: 40 mg S/g hair (Forslind et al. 1985)

^b Mean values between 0.56 and 6.49 µg As/g hair, dependent on residence location

arsenic-associated skin lesions has been reported to be associated with ingestion of drinking water at concentrations ≥ 50 µg arsenic/L (WHO 2001).

The textbook case of arsenic-related peripheral vascular disease was found in the early twentieth century, being endemic along the southwestern coast of Taiwan. The disease involved the lower extremities, characterized by typical clinical symptoms of progressive arterial occlusion; it was called “blackfoot disease” because of the gangrenous appearance of feet of patients. The prevalence of the disease ranged from 6.51 to 18.85 per 1,000 capita in different villages. Epidemiologic studies revealed that blackfoot disease was associated with the consumption of fossil Artesian well water containing high levels of arsenic. Co-

occurrence of blackfoot disease and arsenic-related skin lesions such as hyperpigmentation, hyperkeratosis, and skin cancer was also observed. Recent studies confirmed the association also of preclinical peripheral vascular disease with arsenic exposure. The incidence of clinical manifestation of blackfoot disease decreased dramatically after the installation of tap water in these villages over the last 2–3 decades of the twentieth century (Tseng 2002). Thus, the number of publications on this classical disease has now decreased.

In essence, it is evident that over centuries exposures to arsenic continue to be a public major health problem in many countries. Because of this reason, arsenic is a priority matter for toxicological research in a number of countries.

For *Archives of Toxicology*, this is clearly visualized by an increasing number of submitted manuscripts on arsenic toxicity. Hence, the journal dedicates a special issue to this topic, thereby providing an up-to-date insight into the diversity of the present toxicological research on arsenic.

Contemporary focus on As exposures

- Heavy metals, including arsenic, are being used in traditional medicines in Asia, which is being addressed as a major toxicological problem, for instance in China and India (Liu et al. 2008; Kamath et al. 2012). Recently, arsenic trioxide is being recommended for a very special medicinal use, that is, in the treatment for acute promyelocytic leukaemia (Emadi and Gore 2010).
- As can be seen from Table 1, the combustion of As-rich coal is a major reason for chronic intoxication, especially in some areas of China (Baoshan et al. 2005; Wang et al. 2007; Lin et al. 2010). As a worst-case reported from the Chinese Southwest Province of Guizhou, coal with an As content of up to 35,000 ppm is burned indoors in open pits for daily cooking and crop drying. In a few villages, approximately 3,000 patients with skin lesions indicative of chronic arsenicosis had been detected by 1998 (Baoshan et al. 2005). As already reported in *Archives of Toxicology*, genetic polymorphisms at XPD/ERCC2 appear to modulate the risk of arsenic-related skin lesions in such patients (Lin et al. 2010).
- High As concentrations in groundwater, especially in Southeast Asia, have received much attention in the past decade. This refers to the parts of India and Bangladesh, with groundwater levels equal or greater than 200 µg/L (Guha Mazumder and Dasgupta 2011), and especially the floodplain areas along the Mekong river (Laos, Cambodia, Vietnam). The source of elevated As concentrations in groundwater is considered to be release of As from river sediments, and it is estimated that more than 10 million residents in Southeast Asia are at risk from consuming As-contaminated groundwater (Kim et al. 2011). Data from Latin America show that this problem is not restricted to Asia. It has been estimated that some 4.5 million people in Latin America are chronically exposed to high levels of As (>50 µg/L drinking water), with extremes up to 2,000 µg/L (McClintock et al. 2011). Such situations are being further investigated (de Fátima Pinheiro Pereira et al. 2010). The World Health Organization has recommended a provisional guideline value of 10 µg/L for arsenic in drinking water (WHO 1996).

- Co-exposure and possible interaction of As with other environmental toxicants is also a field of public concern. Most important is co-exposure to fluoride, both by ground water pollution (Chouhan and Flora 2010) and by indoor combustion of coal (Lin et al. 2012).

Focal areas of present research

The environmental situation, as described above, has triggered main avenues of present research. So far, only few environmental studies include a *speciation of As* (e.g., inorganic trivalent/pentavalent forms), and the present results are not entirely uniform (Sanz et al. 2007; de Fátima Pinheiro Pereira et al. 2010). Therefore, it ought to be expected that As speciation research will develop rapidly.

Connected with this field, a focal research point of the last years has been adsorption, distribution, metabolism and excretion (ADME) of As species/compounds (Dopp et al. 2008, 2010). It was soon recognized that the toxicities of As(III) and As(V) are different (Laib and Moritz 1989) and that the toxicity of As(V) results in part from its reduction to As(III) (Huang and Lee 1996). Metabolism of inorganic As proceeds mainly by a sequence of repetitive reduction and oxidative methylation steps, the latter mediated by arsenic methyl transferase (CYT19). A highly cited key publication of this journal by Hayakawa et al. (2005) has demonstrated that arsenic-glutathione complexes are substrates for the human CYT19. In general, *toxicokinetics* of As species remains an important experimental research focus, as evidenced by recent contributions to this journal (Kobayashi et al. 2008; Naraharisetti et al. 2008; Juárez-Reyes et al. 2009). In this issue, Chang et al. (2012) assess the role of specific cysteine residues in proteins for protein binding of arsenite.

As mentioned above, there may be relevant environmental co-exposures of As with other inorganic and organic compounds that lead to *combined action*, with questions of the mechanisms involved. In the present issue of *Archives of Toxicology*, Yajima et al. (2012) address apoptotic mechanisms induced by co-exposure with barium, which can additionally be present, at concentrations >150 µg/L, in As-containing (>200 µg/L) drinking-water wells in Bangladesh. Two other publications in this issue address co-exposures of arsenic and fluoride. Lin et al. (2012) describe a population-based study in a rural area in Northwest China with a large number of cases diseased with a combination of arseniasis and fluorosis. The causal factor was again indoor combustion of coal rich in both As and F, which led to extremely high co-exposures via the inhalation route. In an experimental study on rabbit aorta as

a cardiovascular target, Ma et al. (2012) show that inflammatory responses play a critical role in the combined cardiovascular toxicity of As and F. Also, mechanisms involved in combined action of As and aryl hydrocarbon receptor ligands are being investigated (Anwar-Mohamed et al. 2012).

Indeed, with regard to the different manifestations of toxicity of arsenic (Singh et al. 2011), *cardiovascular disorders*, such as hypertension, atherosclerosis and myocardial injury, are receiving increased interest (Manna et al. 2008; Balakumar and Kaur 2009; Chen et al. 2012). A mechanism likely to be involved is *oxidative stress*, connected with activation of eNOS and enhanced the phosphorylation of MLCK (Singh et al. 2011). The entire field of As-induced *oxidative stress and related signalling pathways* is clearly of increasing scientific relevance (Flora 2011; Jomova and Valko 2011; Jomova et al. 2011; Tseng et al. 2012; Wang et al. 2012; Yen et al. 2012).

Oxidative stress plays a pivotal role in As-induced *carcinogenesis* (Shi et al. 2004). The public health impact of malignancies caused by arsenic is obvious. In this issue of Archives of Toxicology, authors from leading governmental US institutions (NTP, NIEHS, NCI) present a study that raises the serious concern of trans-placental carcinogenesis by a specific As compound, methylarsenous acid (Tokar et al. 2012). Against such a background, the priority of current research into mechanisms of As-induced malignant transformation is evident (Xu et al. 2012).

There is now a remarkable development of *genetic polymorphism studies*, in conjunction with epidemiological research in As-exposed populations. A diversity of polymorphic enzymes is presently being investigated, including XPD/ERCC2 (Lin et al. 2010), arsenic methyl transferase (Agusa et al. 2009, 2010a), glutathione S-transferases (Agusa et al. 2010b), Mn-superoxide dismutase and 8-oxoguanine DNA glycosylase (Chen et al. 2012). A study published in this issue (Escobar-García et al. 2012) suggests a specific role of the glutathione S-transferase GSTO1-1 in As-mediated inflammatory response and apoptotic processes. The idea is put forward that the A140D and E208K polymorphisms increase the risk of inflammatory and apoptosis-related diseases in As-exposed populations. Although the present single studies generally require confirmation by independent studies/data sets, it appears that gene-environmental interactions focussing on human As exposures and As-induced effects are a very attractive and rapidly developing research area.

In essence, there is presently a rapid development of research into human environmental exposures to arsenic and related diseases, which are highly relevant to public health in a number of countries. In this context, experimental research on As toxicokinetics and toxicodynamics

and on modes of toxic action is moving very rapidly. Both aspects are well evidenced by the contributions to the present special issue of *Archives of Toxicology*. As demonstrated in this issue, there is now accumulating evidence that several mechanisms are involved in the carcinogenicity of arsenic, with a particular impact of oxidative stress and related consequences. As present recommendations of human exposure limits are only pragmatic (ATSDR 2012), this new scientific development can be foreseen to enable very soon the derivation of health-based exposure limits for arsenic at the workplace and in the general environment.

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