

Review:

CURRENT DEVELOPMENTS IN TOXICOLOGICAL RESEARCH ON ARSENIC

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ABSTRACT

There is a plethora of recent publications on all aspects relevant to the toxicology of arsenic (As). Over centuries exposures to arsenic continue to be a major public health problem in many countries. In particular, the occurrence of high As concentrations in groundwater of Southeast Asia receives now much attention. Therefore, arsenic is a high-priority matter for toxicological research. Key exposure to As are (traditional) medicines, combustion of As-rich coal, presence of As in groundwater, and pollution due to mining activities. As-induced cardiovascular disorders and carcinogenesis present themselves as a major research focus. The high priority of this issue is now recognized politically in a number of countries, research funds have been made available. Also experimental research on toxicokinetics and toxicodynamics and on modes of toxic action is moving very rapidly. The matter is of high regulatory concern, and effective preventive measures are required in a number of countries.

Keywords: arsenic, research focus, history, toxicology

INTRODUCTION

Toxicological research on arsenic is of increased importance in recent years, world-wide, and recent publications cover all aspects of toxicology. Trends are visible in these publications, which are analysed in this review against the historical background. This review describes recent trends, as opposed to classical knowledge. It is an updated extension of an editorial published in Archives of Toxicology (Bolt, 2012).

Inorganic arsenic is acutely toxic, and ingestion of large doses leads to gastrointestinal symptoms, disturbances of cardiovascular and nervous system functions, and eventually death. Bone marrow depression, haemolysis, hepatomegaly, melanosis, polyneuropathy and encephalopathy may be observed. Chronic human exposure has been linked to a variety of dermal symptoms (exfoliative dermatitis, keratosis, viti-

ligo, skin cancer), peripheral neuropathy, encephalopathy, bronchitis, pulmonary fibrosis, hepato-splenomegaly, portal hypertension, peripheral vascular disease/ “black-foot disease”, atherosclerosis, cancer and diabetes mellitus (Pimparker and Bhawe, 2010). According to WHO, 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 to skin changes such as hyperkeratosis and pigmentation changes. The current WHO drinking water guideline value is 10 µg As/L. Exposure-response relationships have been observed for a variety of end-points, and increased risks of lung and bladder cancer and of arsenic-associated skin lesions are reported to be associated with drinking water concentrations ≥ 50 µg As/L.

HISTORICAL REMARKS

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 a poison. According to Lewin (1920) 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, 1920). For instance, Napoleon's health began rapidly to fail in February 1821. He suffered from chronic As intoxication when he died on May 5, 1821, as evidenced by analysis of his hair (Kintz et al., 2007; see Table 1). Biomonitoring of As in human hair is regarded as a useful tool in field research 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). A number of very recent environmental studies are making use of this parameter (Geier et al., 2012; Evrenoglou et al., 2012; Marchiset-Ferlay et al., 2012; Savabieasfahani et al., 2012; Miklavčič et al., 2013).

By contrast to its intentional use, arsenic as a chronic human environmental toxicant has an even much longer history by a couple of thousand years. At present, the oldest example of environmental exposure to arsenic is testified by hair analysis of the Tyrolean Neolithic mummy called "Ötzi", who died of homicide 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 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).

The textbook-relevant case of arsenic-related peripheral vascular disease was found in the early 20th century, as an endemic along the Southwestern coast of Taiwan. This disease involved the lower extremities, characterised 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 20th 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 (Golka et al., 2010). In particular, the occurrence of high As concentrations in groundwaters of Southeast Asia has received much attention in the past decade (Kim et al., 2011). Therefore, arsenic is a high-priority matter for toxicological research in a number of countries (Bolt and Hengstler, 2011).

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	Reference
(Pre-)Historical		
Neolithic Tyrolean "Ötzi"	44*	Brothwell and Grime (2002)
Saint Helena, Napoleon	37.4, 42.1	Kintz et al., 2007
Coal combustion		
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
Mining		
Xikuangshan Sb mining area, China, environmental exposure	3.99	Wu et al., 2011
Shantou, China, W mining area, environmental exposure	4.21	Liu et al., 2009
	2.92	Liu et al., 2010
Food and drinking water		
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
Monya/Ardebok, West Bengal, India, As in tube-well water	up to 8.2	Maity et al., 2012
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 (mean values between 0.56 and 6.49, dependent on location)	up to 23.8	de Fátima Pinheiro Pereira et al., 2010
Controls		
Guizhou/China, (no arseniosis)	0.56, 0.60	Baoshan et al. (2005)
Altamira/Amazon, Brazil	0.43	de Fátima Pinheiro Pereira et al., 2010
Rio de Janeiro, Brazil	0.70	de Fátima Pinheiro Pereira et al., 2010
Egypt	0.54	de Fátima Pinheiro Pereira et al., 2010
Canada and USA	0.70	de Fátima Pinheiro Pereira et al., 2010
Italy	0.09	de Fátima Pinheiro Pereira et al., 2010
Malaysia	0.28	de Fátima Pinheiro Pereira et al., 2010
Puerto Rico	0.08	Moreno-Santini et al., 2012
UK, different ethnic groups	0.116-0.141	Brima et al., 2006
* calculation of Bolt (2012)		

CONTEMPORARY ARSENIC EXPOSURES

An analysis of the literature reveals the following key exposures to arsenic:

- 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, i.e. in the treatment of 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 distinct 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 arseniosis had been detected by 1998 (Baoshan et al., 2005). Genetic polymorphisms at XPD/ERCC2 appear to modulate the risk for arsenic-related skin lesions in such patients (Lin et al., 2010).
- High As concentrations in groundwater, especially in Southeast Asia, have received much attention. This refers to 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 these groundwaters is connected with the release of As from river sediments, and it is estimated that more than 10 million residents in Southeast Asia are presently 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 2000 µg/L (McClintock et al., 2012). Such situations are being further investigated (de Fátima Pinheiro Pereira et al., 2010). As mentioned initially, the World Health Organization has recommended a provisional guideline value of 10 µg/L for arsenic in drinking water (WHO, 1996).

- High groundwater levels of As and increased exposure of the general population occur also in conjunction with mining activities. In 2012, examples are being reported from Portugal (Coelho et al., 2012), India (Chakraborti et al., 2012) and China (Li et al., 2012).
- Co-exposure and possible interaction of As with other environmental toxicants is also a field of public concern. Most important appears to be co-exposure to fluoride, both by ground water pollution (Chouhan and Flora, 2010) and by indoor combustion of coal (Lin et al., 2012). Also, interactions with iron (Kumasaka et al., 2012) and with nutritional deficiencies (Deb et al., 2012) are a matter of present research.

CURRENT RESEARCH FOCUS

The environmental situation of exposures to As has triggered the 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 further develop.

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; Bolt and Stewart, 2010; Chang et al., 2012; Watanabe and Hirano, 2012). 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 by Hayakawa et al. (2005) has demonstrated that arsenic-glutathione complexes are substrates for the human CYT19. In general, *toxicokinetics* of As species remain an important experimental research focus (Kobayashi et al., 2008; Naraharisetti et al., 2008; Juárez-Reyes et al., 2009).

As mentioned above, there may be relevant environmental co-exposures of As with other inorganic compounds that lead to *combined action*, with questions of the mechanisms involved. For instance, Yajima et al. (2012) address apoptotic mechanisms induced by co-exposure with barium, which can additionally be present in As-containing drinking-water wells. Other publications address co-exposures of arsenic and fluoride. Thus, 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.

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., 2012a; Wang 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; Sinha et al., 2012)

Mechanisms of As-induced *carcinogenesis* are an important area of research (Pastoret et al., 2012; Anwar-Mohamed et al., 2012). Oxidative stress plays a pivotal role (Shi et al., 2004). The public health impact of malignancies caused by arsenic is obvious (Bolt, 1991). Authors from leading governmental U.S. institutions (NTP, NIEHS, NCI) raised serious concern of transplacental 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 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., 2012b). A study by Escobar-García et al. (2012) suggests a specific role of the glutathione S-transferase GST01-1 in As-mediated inflammatory response and apoptotic processes, and the idea is being put forward that A140D and E208K polymorphisms increase the risk for inflammatory and apoptosis-related diseases in As-exposed populations. The role of GST01 polymorphisms as a modifying factor of As toxicity has been confirmed in another study (Chen et al., 2012a). Gene-environmental interactions focussing on human As exposures and As-induced effects are a very attractive and rapidly developing research area.

CONCLUSION

In essence, there is a very rapid recent development of research into human environmental exposures to arsenic and related As-induced diseases, which are highly relevant to public health in a number of countries. It appears that the high priority of this issue is being recognized politically in a number of countries, and that research funds have been made available. In this context, experimental research on As toxicokinetics and toxicodynamics and on modes of toxic action is moving very rapidly. The matter is of high regulatory concern, and preventive measures are urgently required in a number of countries.

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