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Review

What is the best biomarker to assess arsenic exposure *via* drinking water?

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ABSTRACT

Arsenic (As) is a ubiquitous element. The current WHO guideline for As in drinking water is 10 μg/L. Furthermore, about 130 million people have only access to drinking water containing more than 10 gAs/L. Although numerous studies have shown the related adverse effects of As, sensitive appropriate biomarkers are still required for studies of environmental epidemiology. A review of the literature has shown that various biomarkers are used for such research. Their limits and advantages are highlighted in this paper: (*i*) the detection of As or its derivatives in the blood is an indication of the dose ingested but it is not evidence of chronic intoxication. (*ii*) The detection of As in urine is an indispensible procedure because it is a good marker for internal dose. It has been demonstrated to correlate well for a number of chronic effects related to As levels in drinking water. However confounding factors must be taken into account to avoid misinterpretation and this may require As speciation. (*iii*) As in the hair and nails reflects the level of long term exposure but it is difficult to relate the level with the dose ingested. (*iv*) Some studies showed a correlation between urinary As and urinary and blood porphyrins. However, it is difficult to use only porphyrins as a biomarker in a population survey carried out without doing further studies. (*v*) Genotoxic effects are based on the characterization of these potential effects. Most studies have detected increases in DNA damage, sister chromatid exchange, micronuclei or chromosomal aberrations in populations exposed to As in drinking water. Micronuclei assay is the technique of choice to follow these populations, because it is sensitive and easy to use.

To conclude, whatever epidemiological studies are, the urinary and toenail biomarkers are useful to provide indications of internal dose. Moreover, micronuclei assay can be complementary use as biomarker of early effects.

Contents

1. Introduction

Arsenic (As) is a metalloid, which exists naturally in the environment in inorganic and organic forms and in different oxidation states (−3, 0, +3, +5). People may be exposed to As by eating food, drinking water, breathing air and/or by skin contact with soil or water. For an individual who is not occupationally exposed, the main exposure to As is through ingestion of food and/or drinking water. In countries where the concentration of arsenic exceeds 50 μg As/L in drinking water, food is a negligible source of contamination. By contrast, the lower the concentration of As in water, the greater is the role of

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dietary intake and smoking in the analysis of the effects of As on human health (Dictor et al., 2004).

In 1980 inorganic arsenic (iAs) was classified as a carcinogen by the International Agency for Research on Cancer (IARC, 2004), but its long-term toxic effects have been known since the nineteenth century (US EPA, 1982). The long-term consumption of water containing arsenic is a major health risk, and in some countries, the effects on health are well documented. About 130 million people, mainly in developing countries, are being poisoned by As in their drinking water with levels higher 10 μgAs/L, the guideline values defined by the World Health Organization) (Mandal et al., 2001; van Halem et al., 2009). The first epidemiological survey concerning the health effects of exposure to arsenic in drinking water studied cancerous skin lesions and non-cancerous skin lesions, such as hyperpigmentation and keratoses of the palms and soles, in subjects with "Black Foot Disease" in Taiwan (Chen et al., 1962). In Bangladesh, India and other countries, programs to provide safe drinking water have helped to curb infectious diseases (typhoid, cholera, hepatitis A), but they highlighted a new problem of public health related to As in drinking water (WHO, 2008). Since the mid-1980s, the number of epidemiological studies has increased worldwide. Initially, they focused on cutaneous manifestations and cancers, but more recently on cardiovascular diseases and non-insulin-dependent diabetes. These investigations were first conducted in endemic areas with a high concentration of As (*i.e.*, several hundred micrograms per liter, with a maximum value of >1000 μg/L) such as Taiwan, India and Bangladesh. For these populations, significant health risks have been highlighted and linked to the chronic ingestion of As–contaminated water, mainly for primary cancers (skin, lung, bladder, kidney) and other chronic diseases such as skin lesions arsenic-induced, peripheral and cardiovascular diseases, neurological diseases and diabetes, observed in arseniasis-endemic areas (De Vizcaya-Ruiz et al., 2009; Rahman et al., 2009; States et al., 2009). More recently, similar effects have been observed in studies performed in countries with lower As levels (between >50 μgAs/L and several hundred of micrograms), such as Chile, Argentina, USA and Europa (Mandal et al., 2001; Rahman et al., 2009; States et al., 2009).

In recent years, epidemiological studies have helped to identify the risks associated with the consumption of arsenic and its effects on health. Furthermore, many unknowns remain and the research focuses on the mechanism of action of As, and in particular its effects at low doses. The rapid progress in the field of molecular biotechnology has accelerated the development of molecular epidemiology and the use of biomarkers, which were identified and used in these studies. A biomarker can be used to evaluate (in time and in space) the impact of the environment on the health status of individuals. Moreover, various biomarkers of exposure, effect and susceptibility have been identified and used in epidemiological studies. Most of these studies included the molecular dosimetry of internal dose and biologically effective dose of exposure to environmental risk factors, and also the characterization of early biological effects and preclinical lesions (Chen et al., 2005). Biomarkers are needed to understand the mechanism of As toxicity, and to properly assess the risks associated with As in population studies (Hall et al., 2006). Relationships between external exposure and dose of iAs, environmental monitoring, biological monitoring and response (*i.e.* occurrence of disease) are summarized in Fig. 1, adapted from those of Nordberg (2010) and Aitio et al. (2007).

Several biomarkers are frequently used in population studies. At present, there are no clear indications as to which is the most effective biomarker (sensitive, specific) to use in an epidemiological studies which try to measure the effects of arsenic present in water at low concentrations on the population. In this context, a review of the literature on biomarkers associated with As exposure by drinking water has been performed.

2. Metabolism of arsenic

The fate of ingested or inhaled inorganic arsenic (iAs) in the human body is largely dependent on its valence state. The two most common valence states of iAs to which humans might be environmentally exposed are the trivalent and pentavalent forms, respectively, arsenite (iAs^{III}) and arsenate (iAs^{V}).

The soluble forms of iAs are absorbed from the gastro-intestinal tract and distributed in the tissues. iAs is cleared from the blood within a few hours after it is absorbed *via* drinking water. The inorganic arsenicals are known to be taken up by the liver, transformed to monomethylated (MMA) and dimethylated arsenicals (DMA) through consecutive reductive methylation, and then excreted into urine as pentavalent methylated As form (Naranmandura et al., 2006; Suzuki et al., 2002). One part only accumulates in biological structures rich in keratin, such as hair and

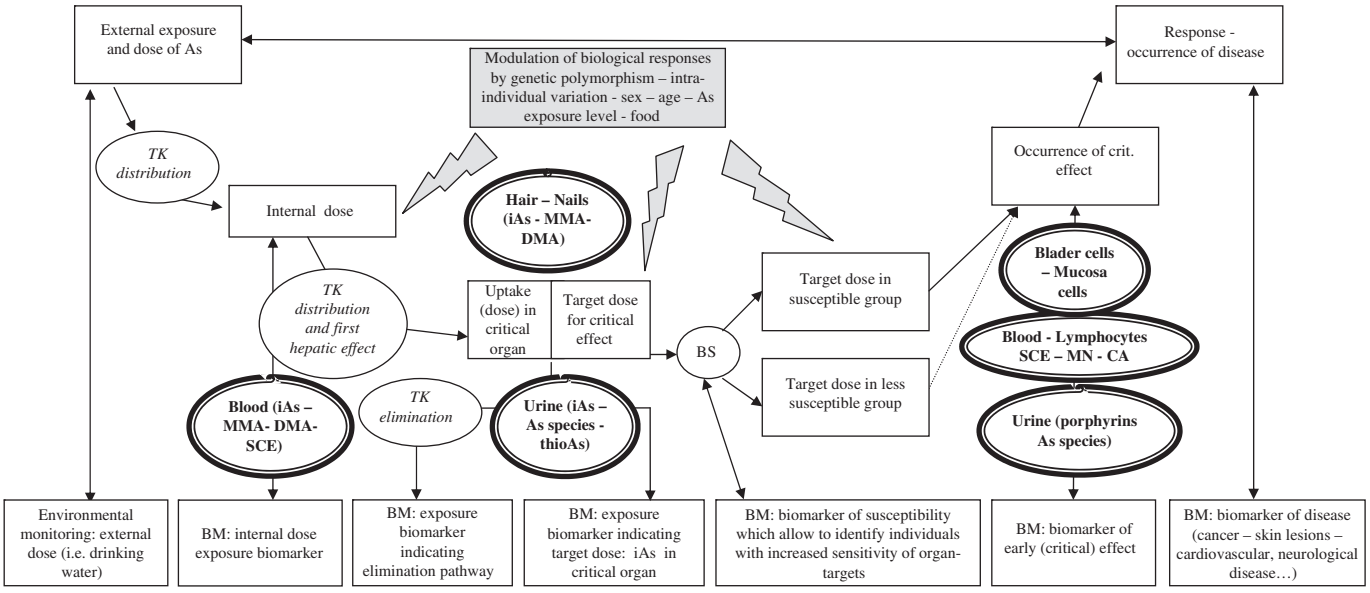

Fig. 1. Relationship between exposure and dose, environmental monitoring, biological monitoring (BM), and response (*i.e.* occurrence of disease) to As exposure via drinking water [adapted from the pathway of metal exposure published by Nordberg (2010)]. TK: toxicokinetic; BS: biomarker of susceptibility; BM: biological monitoring; iAs: inorganic arsenic – MMA: monomethylarsonous acid; DMA: dimethylarsinic acid; CA: chromosomal abnormality; MN: micronuclei; SCE: sister hromatid exchange.