Food and Chemical Toxicology 80 (2015) 287–297

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Invited Review

Toxicological importance of human biomonitoring of metallic and metalloid elements in different biological samples

F. Gil *, A.F. Hernández

Department of Legal Medicine and Toxicology. School of Medicine, University of Granada, Spain

ARTICLE INFO

Article history:
Received 26 December 2014
Accepted 24 March 2015
Available online 30 March 2015

Keywords:
Biological monitoring
Metallic and metalloid elements
Biological matrices
Reference limits
Biomarkers of exposure

ABSTRACT

Human biomonitoring has become an important tool for the assessment of internal doses of metallic and metalloid elements. These elements are of great significance because of their toxic properties and wide distribution in environmental compartments. Although blood and urine are the most used and accepted matrices for human biomonitoring, other non-conventional samples (saliva, placenta, meconium, hair, nails, teeth, breast milk) may have practical advantages and would provide additional information on health risk. Nevertheless, the analysis of these compounds in biological matrices other than blood and urine has not yet been accepted as a useful tool for biomonitoring. The validation of analytical procedures is absolutely necessary for a proper implementation of non-conventional samples in biomonitoring programs. However, the lack of reliable and useful analytical methodologies to assess exposure to metallic elements, and the potential interference of external contamination and variation in biological features of non-conventional samples are important limitations for setting health-based reference values. The influence of potential confounding factors on metallic concentration should always be considered. More research is needed to ascertain whether or not non-conventional matrices offer definitive advantages over the traditional samples and to broaden the available database for establishing worldwide accepted reference values in non-exposed populations.

1. Introduction

Although the presence of a xenobiotic in the environment always represents a risk for living organisms, the onset of toxicity needs to consider key factors such as physicochemical properties of the compound, routes of exposure, health status, genetic susceptibility, etc. that are determinants of the reaction of the organism against harmful chemicals. Biomarkers provide useful information on the nature and the effect of an exposure, as well as on the susceptibility of individuals or populations to the toxic effects of such an exposure. However, this review will focus only on biomarkers of human exposure to metal and metalloid elements. Human biological monitoring has become an important tool in environmental and public health for the assessment of internal doses of harmful substances and to evaluate temporal changes in populations exposed to a particular environmental contaminant (Gil and Hernández, 2009; Hernández et al., 2014).

Toxic metals and metalloids are contaminants of great significance because they are widely distributed in air, water, soil and other environmental compartments as a result of anthropogenic or geological releases. The term "heavy metals" has been used inconsistently in the scientific literature and in legislation related to chemical hazards and the safe use of chemicals, thus creating confusion and misunderstanding. This term has never been defined by IUPAC, and there is a tendency to assume that the so-called "heavy metals" have highly toxic properties, so it should be abandoned and replaced by metal-ions (Nieboer and Richardson, 1980) or metallic elements. Moreover, this term has no coherent scientific basis as it refers to a metal and all its compounds, thus implying that they all have the same physicochemical, biological and toxicological properties, which is not certainly true (Duffus, 2002). On the other hand, although arsenic is not a metal, it has been often included under the term "heavy metal" which is totally inappropriate. Arsenic (As) is an element that has the physical appearance and properties of a metal, but it behaves chemically like a non-metal (Duffus, 2002). For the purpose of this review, we will use the term "metallic and metalloid elements" which is intended to cover major toxic metal and metalloid compounds.

The contamination chain of metallic and metalloid elements resulting from anthropogenic sources usually follows a cyclic order: industry, atmosphere, soil, water, foods and humans. According to biomonitoring data from the Centers for Disease Control (CDC) and other US biomonitoring studies, people are widely exposed to metallic and metalloid elements (COEH, 2011). Human exposure to these compounds may occur occupationally, environmentally, or through

* Corresponding author. Departamento de Medicina Legal y Toxicología, Facultad de Medicina. Universidad de Granada, C/Avda. Madrid 11, 18071 Granada, Spain. Tel.: +34 958 24 35 46/+34 958 24 99 30; fax: +34 958 24 61 07.
E-mail address: fgil@ugr.es (F. Gil).

http://dx.doi.org/10.1016/j.fct.2015.03.025
0278-6915/

dietary intake, with food and water being the most common sources of exposure in the general population (ATSDR (Agency for Toxic Substances and Disease Registry), 2014). Hence, this contamination has raised great environmental concern because of its potential long-term effects on human health (Armah et al., 2014).

Some metallic and metalloid elements present well known toxic properties such as neurotoxic effects (including neurodevelopmental disorders, impaired cognition and intelligence, hyperactive behavior, decreased motor function), but they also can act as mutagenic and carcinogenic agents, endocrine disrupters, etc.

Exposure to low-dose of metallic and metalloid elements in non-occupational settings, together with their accumulative capacity in target organs, is becoming a serious problem, especially for pregnant women, breast-feeding mothers, elderly people and children as they are considered as the most vulnerable subgroups of population (Gil and Pla, 2001; Grandjean and Landrigan, 2014). Children are exposed to metallic and metalloid elements from early prenatal stages because of mother's exposure and the mobilization of these compounds from maternal tissues during pregnancy and breastfeeding. Exposure continues during childhood and pre-adolescence through food and water intake, inhalation of airborne pollution and/or dermal absorption of metallic and metalloid elements (Counter and Buchanan, 2004; Rodríguez-Barranco et al., 2013). In addition, the body burden of certain of these elements usually increases with advancing age as a result of their slow elimination from the body, as occurs with cadmium (Cd) and lead (Pb) (Gil, 2012; Grandjean et al., 1994). Nevertheless, elimination of metallic elements in humans varies considerably, from days to years, depending on their half-lives and the organ in which they accumulate, among other factors.

Early knowledge of the health effects of toxic metallic and metalloid elements is based on workers occupationally-exposed to relatively high levels in industry or in populations living in heavily polluted environments. Only in the last few years have studies concerning human biomonitoring (HBM) addressed the possible effects of chronic low environmental exposure to mixtures of these compounds in the general population of industrialized countries, especially those particularly susceptible, such as adolescents (Interdonato et al., 2014).

2. Biological samples useful for human biomonitoring

Biomonitoring has the advantage of providing unequivocal evidence that both exposure and uptake have taken place. Biological samples in HBM should be easily accessible under routine conditions and without health risk for the individual. For these reasons, blood and urine samples are the most widely used and accepted matrices for evaluating metallic and metalloid element levels in the human body in occupational and environmental toxicology.

Other less invasive biological samples, including saliva, placenta, meconium, hair, nails, teeth or breast milk have different toxicokinetic profiles and may prove to have practical advantages over classical biological fluids for the assessment of the internal dose of metallic and metalloid elements in exposed individuals (Table 1). Nevertheless, certain samples (e.g., hair) should be viewed only as a supportive tool and the analytical results put into perspective with other more reliable data (e.g., blood or urine concentrations) (Angerer et al., 2007; Harkins and Susten, 2003).

However, strict quality assurance during sampling and chemical analysis is extremely important. Analytical procedures must be standardized to help ensure more accurate and reliable results, so an adequate analytical validation of the methods is absolutely necessary.

The German Human Biomonitoring Commission has recommended two criteria to assess exposure: reference values and HBM values (Schulz et al., 2007). The reference values indicate the upper margin of background exposure to a given contaminant in a given population at a given time. By contrast, HBM values derive two different kinds of values: (a) HBM I, which represents the concentration of a substance in human biological material below which there is no risk for adverse health effects and, consequently, no need for action; (b) HBM II, which represents the concentration above which there is an increased risk for adverse health effects and then there is a need of reduced exposure. The latter can be considered as an intervention or action level. Adverse health effects should be considered for concentrations in the range between HBM I and HBM II (Schulz et al., 2007).

2.1. Blood

Metallic elements in blood are distributed between the non-cellular (plasma/serum) and intra-cellular compartments (essentially erythrocytes) and these compounds have different affinity for each compartment, depending on chemical properties (e.g. lead and erythrocytes). The serum/plasma fraction is the one filtered in the glomeruli, and therefore these compounds might accumulate in erythrocytes in subjects with poor kidney function. Thus, kidney function has a major physiological impact on the distribution of metallic elements between the red blood cell and serum compartment, resulting in concentrations higher in whole blood than in serum (Schultze et al., 2014).

Blood, as the traditional matrix for HBM of chemicals clearly reflects recent exposure to these compounds (Table 1). Whole blood must be taken with special tubes and bottles for metallic element measurements and vacutainer needles used for venipuncture should not add measurable levels of these elements to the collected blood. Furthermore, currently available anticoagulants have drawbacks as most of them are either polyanions (e.g., heparin) or metal chelators (e.g., EDTA or citrate) and therefore have a high affinity for metals (De Cremer, 2003). If an anticoagulant is used, it must be rigorously controlled, and heparin is the most frequently used for metallic and metalloid elements analysis. Recent exposures to Cd, Pb and mercury (Hg) by any route (digestive, respiratory and dermal) can be assessed by determining their levels in blood; however, a positive finding does not necessarily have to be related with any adverse effects (D'Ilio et al., 2013).

Analysis of Pb in whole blood is the most common and accurate method of assessing Pb exposure as blood Pb levels reflect recent exposure. The extensive use of blood Pb as a dose metric indicates the greater feasibility of incorporating blood Pb measurements into clinical or epidemiological studies, compared to other potential dose indicators, such as Pb in kidney, plasma, urine, or bone. Hg levels in the blood provide more useful information after recent exposures than after long-term exposures (ATSDR -Agency for Toxic Substances and Disease Registry-, 2007). Except for methylmercury, blood is considered useful if samples are taken within a few days of the exposure as most forms of Hg in the blood decrease by one-half every three days if exposure has ceased.

As for manganese (Mn), systemic homeostasis of this essential element is tightly maintained under normal dietary consumption by both its rate of intestinal absorption and its efficient removal by the liver. As these processes keep Mn levels in an optimum range for nutritional requirements of the body, blood or urine biomonitoring can be considered unreliable. However, this delicate system for *in vivo* Mn regulation may fail under chronic high doses exposure conditions (Roth, 2006). In workers, group average blood levels appear to be related to Mn body burden, while group average urinary excretion levels are considered to be most indicative of recent exposures. Blood and urine levels may also be useful in detecting groups with above-average current exposure to Mn.