HUMAN BIOMONITORING FOR TOXIC METALS – A REVIEW OF THE CONTEMPORARY PERSPECTIVES

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Abstract: Exposure to excessive levels of toxic metals, resulting from both occupational and environmental pollution, is a global problem that is increasingly drawing attention. Measures related to the reliable evaluation of their impact on human health provide opportunities for the effective implementation of health policies aimed at reducing high exposures to these xenobiotics. Along with toxic metals, the role of inorganic nanoparticles (iNPs) as another potential pollutant is increasingly being discussed in this context. Nanomedicine has made revolutionary progress in the development of various applications of iNPs over the past decade. NPs are used in the production of antibacterial and antiviral agents, contrast agents, drug carriers, and in the process of photothermal anticancer therapies. In this regard, human biomonitoring (HBM) studies are increasingly planned as a preventive measure, providing continuous observation, control, and prognosis of the population's exposure to environmental pollutants. According to the World Health Organization, lead (Pb), cadmium (Cd), arsenic (As), and mercury (Hg) are among the most hazardous xenobiotics for human health. Children and adolescents are at particularly high risk of neurotoxic effects due to increased permeability of the blood-brain barrier. Besides, the level of respiratory and gastrointestinal absorption by children is higher per unit of body weight than in adults. This facilitates accumulation, especially in neural tissue, whereby even low-dose exposure is clinically significant. It is scientifically proven that neurological and behavioral disorders manifested as a result of heavy metal intoxication are dose-dependent and irreversible. They are expressed in learning deficits, mental retardation, and reduced intelligence quotient. Aim: The aim of the following review is to focus on the available analytical laboratory methods and biomarkers for the evaluation of intoxication with Pb, Cd, As, Hg, and iNPs. Additionally, the review aims to summarize the contemporary challenges to clinical-laboratory practice in this regard, including gaps in the availability of a harmonized diagnostic approach and quality assurance tools. Conclusion: The analysis of previous studies reporting the results of the first harmonized HBM studies in Europe emphasizes the importance of implementing measures to overcome the variability in interlaboratory methodological approaches. The continued development of efficient analytical methods and fit-for-purpose biomarkers is of leading importance for the reliability of conducting HBM research and integrating it into health policies.
Keywords: biomonitoring, toxic metals, biomarkers, ICP-MS methods, nanoparticles.

1. INTRODUCTION

Heavy metals such as lead (Pb), cadmium (Cd), arsenic (As), and mercury (Hg) are among the most toxic elements for human health (Jomova, 2024). It is estimated that approximately 13% of the world's arable land and 40% of lakes and rivers are contaminated by heavy metals, and the contamination of food, especially in polluted agricultural regions, is a particularly concerning fact (López-Alonso, 2025). Toxic elements exhibit specific toxicokinetics, which are strongly dependent on the form, dose, and exposure period (Xie, 2021; Słowik, 2025). The pathogenetic mechanisms by which Pb, Cd, As, and Hg induce multi-organ toxicity are based on oxidative stress, mitochondrial dysfunction, and impaired autophagy and apoptosis (Zhang, 2016; Paduraru, 2022). There are lots of scientific data confirming the relationship between heavy metal intoxication and the risk of neurodegenerative, cardiovascular, and reproductive diseases (Siblerud, 2019; Bakulski, 2020). Children are particularly vulnerable to heavy metal exposure due to some specific physiological characteristics. The blood-brain barrier (BBB) in infants and adolescents is not fully developed, and besides, the level of respiratory and gastrointestinal absorption is higher per unit of body weight than in adults (Olatomide, 2019; Ramírez Ortega, 2021). This facilitates accumulation, especially in neural tissue, resulting in clinically significant disorders even by low-dose exposure. In this context, the role of inorganic nanoparticles (iNPs) as another potential pollutant is increasingly being discussed. Nanomedicine has made revolutionary progress in the development of various applications of iNPs over the past decade, such as the production of antibacterial and antiviral agents, drug carriers, and in the process of anticancer therapies (Percoco, 2025). The reliable evaluation of the exposure to xenobiotics and its biological impact on organisms is an essential prerequisite for the quantitative measurement of risk to human health. Biomonitoring (BM) is a complex system for continuous monitoring and prognosis, which has wide application in the framework of occupational exposure to health-hazardous xenobiotics. BM studies are increasingly planned as a preventive measure to control population exposure to environmental pollutants, including heavy metals. In the Environment and Health Action Plan 2004–2010, the European Commission defined a number of actions, including the development of environmental health indicators and the development of a coherent approach to biomonitoring in Europe (Joas, 2012). According to the plan, the European Commission has funded several large-scale studies, through which the development of a harmonised approach to conducting BM in Europe was initiated (Joas, 2012;Vorkamp, 2023). Harmonization of BM studies aims to overcome the variability of the interlaboratory methodological approaches. A partical issue targeted is the gap regarding quality control tools. (Tadic, 2025). Another problem that still has no solution concerns the validation of harmonized biomarkers. The ideal biomarker must meet several defining criteria, namely high specificity and sensitivity, minimal invasiveness, and cost-effectiveness (López-Alonso, 2025). Blood biomarkers are established as the most relevant for scientific purposes, while urine biomarkers are less frequently published. Elemental analysis of hair and nails is an attractive non-invasive option that is particularly felicitous for large screening studies. The low concentration of toxic elements, as well as the complexity of matrices analyzed, requires highly specialized methods for trace element analysis. Inductively coupled plasma mass spectrometry (ICP-MS) is a powerful and high-throughput method for multi-element analysis, with a wide working range of concentrations, high specificity, and an easy-to-interpret spectrum (Rivas, 2025). Its scope is further increased with the ability to analyze iNPs, using single particle ICP-MS (spICP-MS). The aim of the following review is to focus on the available analytical laboratory methods and biomarkers for the evaluation of intoxication with Pb, Cd, As, Hg, and iNPs. Additionally, the review aims to summarize the contemporary challenges to clinical-laboratory practice in this regard, including gaps in the availability of harmonized diagnostic approach and quality assurance tools.

2. TOXIC ELEMENTS AND iNPs - IMPACT ON HUMAN HEALTH

Hg is a toxic microelement which exists in different forms in the environment: i) elemental Hg (Hg0), ii) inorganic Hg (Hg^{2+}), and iii) organic Hg, methylmercury (MeHg) (Paduraru, 2022). Its concentration in air, water sources, and soils increases as a result of occupational and environmental pollution, followed by long-term bioaccumulation and biomagnification. A common source of Hg poisoning is cosmetics, where, despite restrictions on the use of Hg, compliance with the rules is not always observed, especially outside the European Union and the United States (Słowik, 2025).

MeHg is the most common form of Hg. It enters the body mainly through the alimentary route through the consumption of fish, seafood, cereals, etc. (Xie, 2021). Once absorbed in the gastrointestinal tract, MeHg can migrate via the bloodstream to all tissues and organs, including the central nervous system (CNS), by crossing the blood-brain barrier (BBB) (Słowik, 2025). MeHg has a relatively long half-life in humans, ranging from 44 to 80 days. Excretion occurs via feces, breast milk, and urine (Adriano, 2001). The clinical picture of acute MeHg poisoning is associated with sensory disturbances, ataxia, dysarthria, narrowing of the visual field, hearing impairment, and tremor (Paduraru, 2022). Experimental models have shown that oxidative stress, mitochondrial dysfunction, and impaired autophagy are involved in the molecular pathogenesis of Hg intoxication (Zhang, 2016; Paduraru, 2022). There is currently sufficient data from clinical studies that link Hg toxicity and the risk of neurodegenerative, cardiovascular, and reproductive diseases (Siblerud, 2019).

Pb is a highly toxic element, which is non-biodegradable, reaching an alarming rate of environmental accumulation due to industrial pollution (Liu, 2025). Pb intoxication can occur through inhalation of Pb particles, consumption of water, food, and tobacco, or through dermal absorption by using cosmetics and paints (Joo, 2017). After absorption, 99% of Pb binds to hemoglobin in erythrocytes and is transported to soft tissues, the liver, and the kidneys. Due to its structural similarity to calcium, dental and bone tissue exhibit a high affinity for Pb. In adults, over 90% of Pb is stored in bones and teeth for up to 30 years (Ramírez Ortega, 2021). Remobilization of Pb from bone may occur in conditions associated with increased bone turnover, such as osteoporosis, pregnancy, and lactation, leading to transport to soft tissues and reintoxication (Ettinger, 2014). Pb toxicity is based on ionic mimicry, whereby Pb^{2+} competitively replaces essential divalent cations such as Ca^{2+}, Mg^{2+}, Zn^{2+}, and Fe^{2+} at binding sites in proteins and enzymes (Generalova, 2025; Witkowska, 2021). As a result, the processes of neurotransmission, neuronal signaling, and autophagy are compromised, stimulating neuroinflammation and immune response (Virgolini, 2021). Dose-dependent symptoms of systemic Pb toxicity are manifested, such as those associated with the nervous system, hematopoiesis, osteogenesis, respiratory, cardiovascular, and reproductive systems, liver, and kidney function. Children are the most vulnerable population group in terms of the risk of Pb intoxication. They have a less developed BBB, which allows various xenobiotics, including Pb, to enter and accumulate in the tissues of the nervous system. In addition, the intensive processes of cell proliferation, differentiation, and synaptogenesis, typical for this period, are a prerequisite for deepening the effects of intoxication on brain tissue (Ramírez Ortega, 2021).

Neurological and behavioral disorders manifested as a result of Pb intoxication are dose-dependent and irreversible, resulting in learning deficits, mental retardation, and reduced intelligence quotient (Mehri, 2020).
According to the WHO, there is no known safe concentration of Pb in blood. The United Nations Environment Programme (UNEP) initiated a global phase-out of leaded petrol in 2002, with a goal of total worldwide elimination by 2021 (Sprong, 2023). According to data compiled in a recent review, mean blood Pb levels in the population have been significantly reduced. However, despite progress, Pb exposure is estimated to cause more than 33 million years of disability-adjusted life years lost worldwide in 2021 (Angrand, 2022).
Cd is a trace element that is widely distributed in soil, sediments, air, and water and is categorized by the WHO as one of the most dangerous toxic metals for human health (Valacchi, 2023). For smokers, regular use of tobacco products is a major source of Cd, while for nonsmokers, it is the consumption of contaminated food products. Data from a number of epidemiological and experimental studies highlight the association between Cd exposure and the risk of neurodegenerative diseases, chronic lung disease, hypertension, as well as carcinogenesis in the lung, prostate, kidney, breast, bladder, nasopharynx, pancreas, and hematopoietic system (Bakulski, 2020; Parida, 2023). The pathogenetic mechanisms of damage are associated with redox imbalance, impaired autophagy processes, and ATP synthesis. Cd crosses the placenta freely and has teratogenic effects on fetal development (Rasin, 2025). Cd exposure causes skeletal demineralization, resulting in osteoporosis associated with pain, physical disability, and reduced quality of life.
Arsenic (As) is a highly toxic trace element, a metalloid, that is released into the environment from natural sources and anthropogenic activities (López-Alonso, 2025). Major food sources at risk of As contamination are cereals, especially rice, due to their higher iAs content compared to other crops, as well as fish and seafood, which accumulate organic As species (López-Alonso, 2025, Visciano, 2025). As has important medical applications forasmuchas arsenic trioxide is approved by the Food and Drug Administration (FDA) in the treatment of patients with acute promyelocytic leukemia (Emadi, 2015).
As enters the body mainly through the gastrointestinal tract, lungs, and skin, whereafter reaches peripheral tissues via the bloodstream. As is an epigenetic factor that increases the risk of lung, skin, liver, kidney, and bladder cancer (Ozturk, 2022). Its toxic and carcinogenic effects are manifested by impaired regulation of signaling pathways of gene expression, DNA repair, proliferation, and apoptosis (Palma-Lara, 2020). As crosses the BBB, exerting neurotoxic effects on the processes of neurotransmission and apoptosis of brain cells, and induces oxidative stress and epigenetic modifications (Chakraborty, 2022). It crosses the placental barrier unhindered and reaches fetal tissues, which increases the risk of pregnancy and birth complications, such as miscarriage, premature birth, fetal death, and low birth weight (López-Alonso, 2025; Ortiz-Garcia, 2023). There is increasing epidemiological evidence suggesting a link between As exposure and disorders related to neuropsychological development, cognitive development, intelligence, and memory (Notario-Barandiaran, 2025).
Nanomedicine has made significant progress in the development of various applications of nanoparticles (NPs) over the past decade. NPs are used in the production of antibacterial and antiviral agents, contrast agents, drug carriers, and in the process of photothermal anticancer therapies. (Percoco, 2025). However, the long-term use of NPs is associated with the risk of exposure through various routes (e.g., ingestion, inhalation, and dermal contact) during the production, use, and disposal of NPs (Yang, 2017). The toxic effects of NPs may be related to cell surface damage, ROS generation and oxidative stress, or interactions of NPs with cellular proteins and enzymes. Furthermore, NPs may disrupt normal biochemical functions, such as ATP synthesis, DNA replication, and gene expression.

3. HARMONIZATION OF HBM STUDIES IN EUROPE

Reliable evaluation of the exposure to xenobiotics and its biological impact on organisms is an essential prerequisite for the quantitative measurement of risk to human health. Biomonitoring (BM) is a complex system for continuous monitoring and prognosis, which has wide application in the framework of occupational exposure to health-hazardous xenobiotics. BM studies are increasingly planned as a preventive measure to control population exposure to environmental pollutants, including heavy metals. In the Environment and Health Action Plan 2004–2010, the European Commission defined a number of actions, including the development of environmental health indicators and the development of a coherent approach to biomonitoring in Europe (Joas, 2012). According to the plan, the European Commission has funded several large-scale studies, through which the development of a harmonised approach to conducting BM in Europe was initiated (EU, 2004; Sprong, 2023). The projects Expert Team to Support Biomonitoring in Europe (ESBIO), European Coordination Action on Human Biomonitoring (COPHES), and its demonstration project DEMOCOPHES involve several thousand participants from 17 European countries. Later, the European Human Biomonitoring Initiative (HBM4EU) ran from 2017 to 2022 with the aim of further advancing and harmonizing human biomonitoring in Europe (Sprong, 2023,Vorkamp, 2023). In the list of substances analyzed in different HBM studies in HBM4EU, Cd (urine, blood), Hg (hair), and As (urine) were included. Additionally, a quality assurance and control programme was designed in HBM4EU, provided for European laboratories offering HBM analyses (Sprong, 2023, Esteban Lopez , 2021). The 7-year initiative "Partnership for the Assessment of Risks in Chemicals (PARC)" announced in 2022 aims to methodologically upgrade this support for EU countries (Tadić, 2025)

Since 2018, the European chapter of the International Society of Exposure Science Human Biomonitoring Working Group (ISES Europe HBM WG) provides harmonized and transparent HBM metadata, as well as guide Ortiz-Garcia nes for environmental specialists. Since 2025 the ISES Europe HBM WG collaborates with the HBM Global Network, promoting worldwide policy integration (Zare Jeddi, 2026).

Organizing an HBM study requires multidisciplinary teams of specialists in different areas, including epidemiology, toxicology, statistics, laboratory etc. engaged in specific stages of the study. A very recent review summarizes the methodological and organizational challenges resulting in variability of the results in different HBM studies. For instance, there are still gaps concerning quality assurance/quality control tools, as well as harmonized protocols encompassing preanalytical and analytical stages (Tadic, 2025). For what concern methodology, the Joint Committee for Traceability in Laboratory Medicine database lists reference methods for metals, i.e., Cd in blood and urine, Hg in urine and blood, Pb in urine and blood, and As in serum and urine (Tadić, 2025). There are several commercially available certified reference materials (CRMs) for toxic elements in human blood, urine, and hair provided by the National Institute of Standards and Technology (NIST), National Institute of Minamata Disease (NIMD), Joint Research Centre of the European Commission (JRC), and LGC Standards (LGC) (Tadic, 2025). Laboratories involved in HBM studies could apply for two proficiency testing schemes for environmental toxicological analyses in human matrices, namely the Centre de Toxicologie du Québec (CTQ) and the German External Quality Assessment Scheme (G-EQUAS) (Tadić, 2025).

4. LABORATORY METHODS AND BIOMARKERS FOR HBM

The availability of reliable laboratory biomarkers provides an opportunity to study general exposure to toxic elements, as well as to manage population risk by developing strategies to improve public health. The ideal biomarker must meet several defining criteria, namely high specificity and sensitivity, minimal invasiveness, and cost-effectiveness (López-Alonso, 2025). From a clinical-laboratory perspective, a top priority is to provide clinicians with biomarkers that reliably reflect the dose-dependent impact on the elemental status of the patient. Blood biomarkers are established as the most relevant for scientific purposes, while urine biomarkers are less frequently published. Elemental analysis of hair and nails is an attractive no-invasive option in large screening studies. For instance, the measurement of Pb exposure is recommended in whole blood, as the most relevant biomarker for acute and chronic intoxication. The recommendable laboratory indicators for Hg exposure are blood and hair, whereas Cd and As are usually assessed by quantification in urine and blood. However, a careful evaluation of the advantages and disadvantages of the available biomarkers shows that none of the mentioned meets all of the above criteria and cannot be classified as "ideal" (López-Alonso, 2025).

Over the past decade, significant progress has been made in the development of new highly specialized methods for trace element analysis, which are increasingly entering routine clinical and laboratory practice. Numerous methods have been developed that meet the requirement of working in the ppb/ppt concentration range. Inductively coupled plasma mass spectrometry (ICP-MS) is one of the most powerful and high-throughput methods for multi-element analysis, with a wide working range of concentrations, high specificity, and an easy-to-interpret spectrum (Gregar, 2025). Compared to all other analytical methods, ICP-MS has the lowest limits of detection and quantification. From a laboratory perspective, an outstanding advantage of the method is the ability to work with micro amounts of biological material and analyze various matrices (exhaled air, biological fluids, tissue samples) (Rivas, 2025). Moreover, single-particle ICP-MS (spICP-MS) provides additional opportunities for measurement of a various metal-containing NPs in human matrices (Gregar, 2025). Serious challenges in using ICP-MS are the spectral and non-spectral interferences, which are a typical characteristic of the method by analysis of complexed matrices. This requires highly specialized training of personnel, which, along with the high cost of the equipment, makes it difficult for ICP-MS to enter routine clinical laboratory practice.

7. CONCLUSIONS

The results of the first harmonized BM studies across Europe demonstrate the success of the coordinated approach to implementing BM in Europe and are a basis for continuing actions to unify BM programs. The development of efficient analytical methods and fit-for-purpose biomarkers is of leading importance for the reliability of conducting HBM research and integrating it into health policies.

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