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BIOMONITORING OF HUMAN EXPOSURE TO LEAD: A REVIEW OF THE SCIENTIFIC LITERATURE

BIOMONITORIZAREA EXPUNERII UMANE LA PLUMB: O ANALIZĂ A LITERATURII ȘTIINȚIFICE

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ABSTRACT

Objectives. Lead remains one of the most hazardous and persistent environmental toxicants and continues to pose a major public health concern, particularly for children and women of reproductive age. The harmonization of national legislation with European Union standards necessitates the establishment and implementation of an effective human lead biomonitoring system in the Republic of Moldova. This review aimed to synthesize current scientific evidence on lead exposure, toxicity, endocrine-disrupting effects, and human biomonitoring approaches to support the development of a national protocol for human lead biomonitoring in the Republic of Moldova.

Methods. A review of the scientific literature was conducted using the HINARI (WHO), PubMed/MEDLINE, ScienceDirect, Cochrane Library, Medscape, and Google Scholar databases. The search strategy employed combinations of the following key terms: *lead, lead exposure, lead toxicity, endocrine disruption, human biomonitoring, biological matrices, biomarkers, human exposure, and public health*. The search was limited to English-language publications published between January 1993 and June 2026. The final search was conducted on September 9, 2026. The review included original research articles, systematic and narrative reviews, guidelines issued by international organizations, and official documents relevant to the aim and objectives of the review.

Results. Current scientific evidence on human lead biomonitoring was reviewed, with a focus on environmental sources and exposure pathways, mechanisms of toxicity, adverse health effects, relevant biological matrices and biomarkers, and the role of biomonitoring in identifying high-risk populations and informing evidence-based public health strategies.

Conclusions. Lead continues to pose a major public health challenge because it affects virtually all organ systems, no safe level of exposure has been established, children are particularly vulnerable to its toxic effects, and lead exposure imposes a substantial socioeconomic burden. Human lead biomonitoring is essential for strengthening and harmonizing Moldova's public health surveillance system with European standards. Current priorities include the implementation of standardized human lead biomonitoring protocols and the identification of the most informative biological matrices and relevant biomarkers according to age-specific characteristics and health-based exposure reference values.

Keywords: lead exposure, lead toxicity, endocrine disruption, human biomonitoring, biological matrices, biomarkers

REZUMAT

Obiective. Plumbul rămâne unul dintre cei mai periculoși și persistenți poluanți toxici din mediu și continuă să reprezinte o preocupare majoră pentru sănătatea publică, în special în cazul copiilor și al femeilor de vârstă reproductivă. Armonizarea legislației naționale cu standardele Uniunii Europene impune instituirea și implementarea unui sistem eficient de biomonitorizare a expunerii populației la plumb în Republica Moldova. Prezenta analiză a avut drept scop sintetizarea dovezilor științifice actuale privind expunerea la plumb, toxicitatea acestuia, efectele de perturbare endocrină și abordările de biomonitorizare umană, în vederea sprijinirii elaborării unui protocol național de biomonitorizare a expunerii umane la plumb în Republica Moldova.

Metode. A fost realizată o analiză a literaturii științifice prin efectuarea unei căutări în bazele de date HINARI (OMS), PubMed/MEDLINE, ScienceDirect, Cochrane Library, Medscape și Google Scholar. Strategia de căutare a utilizat combinații ale următorilor termeni-cheie: *plumb, expunere la plumb, toxicitatea plumbului, perturbare endocrină, biomonitorizare umană, matrici biologice, biomarkeri, expunere umană și sănătate publică*. Căutarea a fost limitată

la publicațiile în limba engleză, publicate în perioada ianuarie 1993 – iunie 2026. Căutarea finală a fost efectuată la 9 septembrie 2026. În analiză au fost incluse articole de cercetare originale, studii de sinteză sistematică și narativă, ghiduri elaborate de organizații internaționale, precum și documente oficiale relevante pentru scopul și obiectivele lucrării.

Rezultate. Au fost analizate dovezile științifice actuale privind biomonitorizarea plumbului la om, cu accent pe sursele de origine ambientală și căile de expunere, mecanismele toxicității, efectele adverse asupra sănătății, matricele biologice și biomarkerii relevanți, precum și rolul biomonitorizării în identificarea populațiilor cu risc crescut și în fundamentarea strategiilor de sănătate publică bazate pe dovezi.

Concluzii. Plumbul continuă să reprezinte o problemă majoră de sănătate publică, deoarece afectează practic toate sistemele de organe, nu a fost stabilit niciun nivel sigur de expunere, copiii sunt deosebit de vulnerabili la efectele sale toxice, iar expunerea la plumb generează o povară socioeconomică semnificativă. Biomonitorizarea expunerii umane la plumb este esențială pentru consolidarea și armonizarea sistemului de supraveghere a sănătății publice din Republica Moldova cu standardele europene. Prioritățile actuale includ implementarea unor protocoale standardizate de biomonitorizare a plumbului la om și identificarea celor mai informative matrice biologice și a biomarkerilor relevanți, în funcție de particularitățile specifice vârstei și de valorile de referință pentru expunere stabilite în funcție de efectele asupra sănătății.

Cuvinte-cheie: expunerea la plumb, toxicitatea plumbului, perturbarea endocrină, biomonitorizarea umană, matrice biologice, biomarkeri

Introduction

Throughout life, humans are exposed to a complex and cumulative combination of environmental, lifestyle, and social factors that influence health and contribute to disease development from conception onward. This concept is referred to as the exposome [1–3]. The exposome encompasses cumulative environmental exposures experienced throughout the life course, including chemical, physical, biological, lifestyle, and social factors that may influence human health [4, 5]. Among these exposures, environmental metals such as lead, mercury, and arsenic have been investigated for their potential to disrupt endocrine signaling and hormone-regulated biological processes [6–9].

Lead (Pb), mercury (Hg), and arsenic (As) may interfere with endocrine signaling through multiple mechanisms, including alterations in hormone synthesis and secretion, disruption of steroidogenesis, interference with hormone receptors and receptor-mediated gene expression, and dysregulation of the hypothalamic–pituitary–thyroid and hypothalamic–pituitary–gonadal axes [10–13]. The evidence base concerning endocrine-disrupting chemicals (EDCs) has expanded substantially, with an increasing number of human studies examining exposure–outcome associations and their potential implications for human health [14].

Among toxic metals, lead (Pb) is a widespread and persistent environmental contaminant with well-established adverse effects on human health [15–18]. Its extensive use over several decades has resulted in widespread environmental contamination, and lead exposure remains an important public health concern [15, 17, 19].

Lead exposure is associated with a broad spectrum of adverse health effects involving multiple organ systems, including the neurological, hematological, gastrointestinal, cardiovascular, and renal systems [15, 18, 20]. Recent estimates from the Institute for Health Metrics and Evaluation (IHME), as reported by the World Health Organization (WHO), indicate that lead exposure was associated with more than 3.5 million deaths worldwide in 2023, primarily attributable to cardiovascular effects [19]. Despite reductions in lead use in many applications, lead persists in contaminated soil,

air, and water and remains present in a variety of consumer and industrial products [15, 17]. Electronic waste recycling, particularly when conducted informally or under unsafe conditions, represents an important contemporary source of environmental lead contamination [19, 21, 22].

Consequently, human exposure to lead remains a significant environmental and public health concern [15, 17, 19, 23]. Important uncertainties remain regarding the assessment of recent versus cumulative lead exposure, the long-term health consequences of low-level exposure, and the selection and interpretation of biological matrices and biomarkers for human biomonitoring [24, 25]. These knowledge gaps, together with limitations in the existing evidence, underscore the need for a comprehensive evaluation of current knowledge on lead exposure, toxicity, and biomonitoring. Such an evaluation could provide an evidence base for the development, harmonization, and implementation of a standardized human biomonitoring protocol for lead in the Republic of Moldova.

Materials and Methods

This narrative review incorporates recent evidence on pathways of human exposure to lead, lead toxicity—with particular emphasis on endocrine effects—associated health consequences, and the selection of relevant biomarkers for exposure assessment. The objective of this review was to support the development and implementation of an effective human lead biomonitoring protocol for public health practice in the Republic of Moldova, with the aim of assessing population health risks associated with lead exposure.

A literature search was conducted using the bibliographic and full-text databases PubMed/MEDLINE, ScienceDirect, the Cochrane Library, HINARI, Medscape, and Google Scholar. Various combinations of keywords and search terms were used, including lead, lead exposure, lead toxicity, endocrine disruption, human biomonitoring, biological matrices, and biomarkers. Additional terms included lead biomarkers, human exposure, and public health, as well as relevant synonyms, variations, and combinations of these terms.

The search included English-language publications addressing human exposure to lead, its toxicokinetics and toxicity, clinical and subclinical health effects, endocrine disruption, biomonitoring, and the use of biological matrices and biomarkers for the assessment of exposure and/or biological effects. Priority was given to original research studies, systematic and narrative reviews, guidelines issued by international organizations, and official public health documents. The search covered publications published between January 1993 and June 2026. The final literature search was conducted on September 9, 2026.

Publications were excluded if they were not directly related to human exposure to lead; focused exclusively on experimental animal studies or in vitro research without direct relevance to human health risk assessment; lacked information relevant to the toxicological, endocrine, or biomonitoring aspects addressed in this review; or were duplicates. Additional publications identified through screening the reference lists of included articles were also assessed according to the predefined eligibility criteria. The source selection process was conducted in two stages. First, the titles and abstracts of identified publications were screened for relevance. Second, the full texts of potentially eligible publications were assessed against the predefined inclusion and exclusion criteria, taking into account the objectives and scope of the present review.

To minimize the risk of selection bias, a publication authored by members of the review team was assessed using the same predefined eligibility criteria applied to all other publications and was not automatically included. The publication was retained in the final analysis because it met the eligibility criteria and provided relevant evidence concerning the health effects of endocrine-disrupting substances. Following duplicate removal, title and abstract screening, and full-text assessment, 104 unique sources met the predefined inclusion criteria and were included in the final analysis.

Results and Discussion

Environmental sources and pathways of lead exposure

Lead is a naturally occurring toxic metal that has been widely used in industry and has contributed substantially to environmental contamination through mining, smelting, manufacturing, recycling, and the use of lead-containing products [17, 18, 26]. Lead occurs naturally in the Earth's crust, with an average abundance of approximately 0.0016%. Lead is rarely found in its metallic form in nature and commonly occurs in minerals containing sulfur or oxygen. Galena (PbS) is the most important lead-bearing mineral. Lead occurs in both inorganic and organolead forms [18]. Natural background concentrations of lead in soil derived from crustal rock typically range from <10 to 30 mg/kg. However, lead concentrations in surface soils can vary substantially because of atmospheric deposition and accumulation from anthropogenic sources; substantially elevated concentrations may occur near mining, smelting, and other lead-emitting sources [18]. Lead, particularly in its inorganic forms, is a

major environmental pollutant that is widely distributed in environmental media, including air, water, soil, and sediment [27–29]. The principal anthropogenic sources of lead contamination include battery manufacturing, metal smelting, electronic-waste recycling, lead-based paints, ceramics and pottery, mining and other industrial activities, as well as agricultural inputs such as fertilizers, plant-protection products, and contaminated irrigation water [16, 23, 28, 30]. The presence of lead-containing plumbing fixtures, lead service lines, and lead solder, particularly in older buildings, can contribute to elevated lead concentrations in drinking water [15, 31–33]. Industrial activities and the use of lead-containing products contribute to environmental lead contamination of soil, water, and air and can facilitate the transfer of lead into food chains [15, 34]. Sewage sludge may contain lead and other potentially harmful metals, and its agricultural use therefore requires monitoring of metal concentrations and compliance with applicable regulatory limits to minimize risks to soil, crops, and the environment [35–37]. Discharge of untreated industrial wastewater and improper disposal of hazardous materials can contribute to soil contamination, while the accumulation of heavy metals in sewage sludge and its application to agricultural land may increase metal concentrations in soils and crops, thereby increasing ecological and potential human health risks [35–38]. These contaminants, including lead, may enter the food chain through soil–plant transfer and the consumption of contaminated food, thereby contributing to human exposure and potentially increasing human health risks [23, 30, 39, 40].

Global demand for lead remains strongly associated with lead-acid batteries, which account for more than 80% of global demand for refined lead. Most lead-acid batteries are used in automotive applications, while lead batteries are also used extensively for industrial and stationary energy storage [41–43]. Lead remains an important component of lead-acid battery technology because of the technology's established performance, long cycle and calendar life, economic effectiveness, and highly developed recycling infrastructure [42].

Lead compounds were widely used in paints as pigments and drying agents, contributing to properties such as durability, corrosion resistance, and faster drying [44, 45]. As lead-based paint deteriorates, peels, chips, or is disturbed, it can generate lead-contaminated dust and paint particles that may be ingested or inhaled, particularly by children, potentially contributing to adverse neurodevelopmental, cognitive, and behavioral outcomes [46, 47].

The canning industry may contribute to dietary lead exposure because lead-soldered cans can increase lead concentrations in canned foods, particularly in older cans manufactured using lead-containing solder [18, 48]. Lead may contaminate canned foods through migration from lead-containing tin coatings or solder. Light-colored fruits and fruit juices may be of particular concern because they have historically been packaged in lacquered tin-coated cans lacking an internal synthetic coating [49, 50]. Lead may also be present

in some ceramic, glazed-clay, glass, and metal food containers and cooking utensils, particularly those manufactured, glazed, or soldered using lead-containing materials [51–53].

Lead concentrations in Ayurvedic medicines may exceed recommended permissible exposure limits for pharmaceutical impurities by several orders of magnitude. In an investigation of 252 Ayurvedic medicine samples, lead was detected in 65% of the samples. Among the lead-containing samples, 36% had estimated per-pill lead exposures exceeding the United States Pharmacopeia (USP) recommended oral Permissible Daily Exposure (PDE) for pharmaceutical impurities, in some cases by several thousand-fold [54]. Clinically significant lead poisoning has also been reported in association with lead-containing Ayurvedic medicines; in one Canadian investigation, 11 of 17 visually distinct Ayurvedic pills tested contained detectable lead, and one pill contained 129,000 µg/g of lead (approximately 13% by weight) [55].

Tetraethyl lead (TEL) was introduced as an antiknock additive to gasoline in the early 1920s, with the first commercial sale of leaded gasoline occurring in February 1923 in Dayton, Ohio. Its subsequent widespread use contributed substantially to environmental lead pollution [56, 57]. Leaded petrol was used worldwide for decades and contributed to environmental contamination, including air and soil pollution [56, 58].

Both organic and inorganic forms of lead are toxic; however, organic lead compounds, particularly alkyl lead compounds, are generally more toxic than their inorganic counterparts, partly due to their greater lipophilicity and more efficient absorption [59, 60]. The International Agency for Research on Cancer (IARC) classifies inorganic lead compounds as Group 2A agents (probably carcinogenic to humans), whereas organic lead compounds are classified as Group 3 agents (not classifiable as to their carcinogenicity to humans) [60, 61].

The progressive phase-out of leaded gasoline and the implementation of other lead-control measures, including restrictions on lead-containing paints, plumbing materials, and solder, have contributed to substantial declines in population blood lead concentrations in many countries [19, 26]. In the United States, the geometric mean blood lead level among children aged 1–5 years declined by 94.5%, from 15.2 µg/dL in 1976–1980 to 0.83 µg/dL in 2011–2016 [62]. Nevertheless, residual environmental contamination from legacy sources, including lead-based paint, contaminated soil, and lead-containing plumbing materials, continues to pose a risk to human health [62, 63]. Despite extensive efforts to reduce environmental lead exposure, lead remains a persistent, non-biodegradable toxicant that is widely distributed in the environment [64].

Absorption, toxicokinetics, and health effects

Human exposure to lead occurs primarily through ingestion of contaminated food, drinking water, and soil, as well as through inhalation of contaminated dust and fumes [17, 18]. The gastrointestinal absorption of ingested lead varies considerably according to age, nutritional status,

fasting, and the physicochemical characteristics of the lead compound [17, 18]. In adults, approximately 5–15% of ingested lead is absorbed under fed conditions, whereas absorption may increase substantially during fasting, reaching approximately 45% or higher [17]. In infants and young children, gastrointestinal absorption of water-soluble lead is considerably higher than in adults, with approximately 40–50% of an ingested dose being absorbed; absorption may be further increased by fasting and deficiencies of iron or calcium [17]. Lead absorption, an important determinant of internal dose and toxicity, is influenced by particle characteristics, route of exposure, age, nutritional status, and physiological conditions. Gastrointestinal absorption may increase during fasting and in individuals with iron or calcium deficiency [23, 65–67].

As a cumulative toxicant, lead can adversely affect multiple organ systems, including the nervous, cardiovascular, renal, hematological, and reproductive systems. Fetuses, infants, and children are particularly vulnerable to its adverse effects [15, 16]. Lead accumulates over time in mineralized tissues, particularly bones and teeth. In chronically exposed adults, more than 90% of the total body burden may be stored in the skeleton, which serves as a long-term reservoir of cumulative exposure [16, 66].

Maternal bone lead stores may be mobilized during pregnancy as physiological changes in calcium and bone metabolism can increase the transfer of lead from the maternal skeleton into the circulation [67, 68]. Mobilized lead can subsequently contribute to fetal exposure through placental transfer [67–69]. Maternal lead exposure has been associated with increased risks of spontaneous abortion, preterm birth, reduced fetal growth, and adverse neurodevelopmental outcomes [47, 69]. Even low-level lead exposure is increasingly recognized as an important risk factor for cardiovascular disease [70–72]. According to the World Health Organization, the latest Institute for Health Metrics and Evaluation estimates indicate that lead exposure was responsible for more than 3.5 million deaths worldwide in 2023, primarily due to cardiovascular effects [19]. Global costs associated with lead exposure were estimated at US\$6.0 trillion (range, US\$2.6–9.0 trillion) in 2019, equivalent to 6.9% (range, 3.1%–10.4%) of global gross domestic product. Of these costs, 77% was the welfare cost of cardiovascular disease mortality, and 23% was the present value of future income losses from IQ loss [73]. Chronic lead exposure is associated with hypertension, atherosclerosis, and other cardiovascular outcomes, with evidence suggesting adverse effects on vascular function and involvement of inflammatory and oxidative stress pathways [16, 70, 71, 74].

Chronic exposure to elevated lead concentrations can contribute to immune dysfunction, including altered cytokine profiles, inflammatory responses, and impairment of cell-mediated and humoral immunity, with oxidative stress proposed as an important underlying mechanism [75, 76]. Lead acts as an immunotoxicant that can dysregulate immune function and may increase susceptibility to hypersensitivity

and allergic responses, infections, autoimmune diseases, and cancer through alterations in immune-cell function and immune regulation [77, 78].

Survivors of severe childhood lead poisoning may experience permanent intellectual disability, behavioral disorders, and other neurological sequelae [19]. Neurodevelopmental consequences of lead exposure include reduced intelligence quotient (IQ), impaired learning and academic performance, attention and behavioral problems, impulsivity, and hyperactivity, including symptoms resembling those observed in attention-deficit/hyperactivity disorder (ADHD) [79–81]. Lead exposure is associated with cognitive impairment, including reduced IQ, diminished attention span, memory deficits, and learning difficulties [80, 82, 83]. As a potent neurotoxicant, lead can impair normal brain development in children and has also been associated with cognitive impairment in adults [19, 80, 82].

Endocrine and neurodevelopmental effects

Lead is an endocrine-disrupting toxicant capable of interfering with endocrine function, including at relatively low levels of exposure [84, 85]. It can affect the hypothalamic-pituitary axis, thyroid function, adrenal glucocorticoid regulation, and reproductive endocrine function [84]. Human evidence also indicates associations between blood lead levels and alterations in thyroid hormones, insulin, and testosterone, with potential endocrine effects occurring at relatively low blood lead concentrations [85]. Lead exposure has also been associated with elevated prolactin concentrations and disturbances in thyroid and adrenal endocrine function [84, 85]. Epidemiological evidence further suggests adverse effects of lead exposure on male reproductive function, including reduced sperm count and motility and increased serum prolactin concentrations, whereas evidence for alterations in testosterone and other reproductive hormones remains inconclusive [86].

These endocrine and reproductive disturbances have been linked to impaired fertility, altered reproductive hormone profiles, thyroid dysfunction, skeletal effects, and metabolic disturbances [84–86]. Lead exposure has also been associated with delayed pubertal development, particularly in girls [87, 88]. Children are particularly vulnerable to the neurodevelopmental effects of lead because the developing brain and nervous system are highly susceptible to its toxic effects. Adverse effects on IQ and cognitive function have been documented at blood lead concentrations below 10 µg/dL [89, 90], including concentrations below 5 µg/dL [91, 92]. Low-level lead exposure has also been associated with deficits in attention, executive function, and behavior [92, 93].

Population reference values and global disease burden

The Centers for Disease Control and Prevention (CDC) blood lead reference value (BLRV) of 3.5 µg/dL is a population-based reference value used to identify children with blood lead concentrations higher than those of most U.S. children and to guide appropriate medical and environmental follow-up; it is not a health-based standard or a toxicity threshold [62]. According to the World Health Organization (WHO),

the Institute for Health Metrics and Evaluation (IHME) estimated that lead exposure accounted for approximately 540,000 deaths globally in 2016 [94].

Earlier WHO assessments estimated that lead exposure was responsible for approximately 143,000 deaths and 8.98 million disability-adjusted life years (DALYs) globally in 2004, corresponding to approximately 0.6% of the global burden of disease, primarily through cardiovascular disease in adults and lead-associated intellectual impairment in children [95]. More recent estimates indicate that the global burden attributable to lead exposure may be substantially greater than previously recognized. The World Health Organization (WHO), citing estimates from the Institute for Health Metrics and Evaluation (IHME), reports that more than 1.5 million deaths globally were attributable to lead exposure in 2021, primarily due to cardiovascular effects [15].

In addition, a health-impact modelling study published in *The Lancet Planetary Health* in September 2023 estimated that lead exposure contributed to approximately 5.5 million adult deaths from cardiovascular disease globally in 2019, more than six times the corresponding estimate reported in the Global Burden of Disease (GBD) 2019 study [73]. The same study estimated the global economic cost of lead exposure at approximately US\$6.0 trillion in 2019, equivalent to 6.9% of global GDP, with 90.2% of lead-attributable cardiovascular disease deaths occurring in low- and middle-income countries (LMICs) [73]. This comprehensive estimate included both the welfare costs of premature cardiovascular disease mortality and the present value of future income losses associated with childhood IQ loss.

In contrast, an earlier study by Attina and Trasande focused specifically on the neurodevelopmental consequences of childhood lead exposure in LMICs and estimated approximately \$977 billion in annual losses in lifetime economic productivity, expressed in international dollars and based on 2011 estimates [96]. According to a large-scale epidemiological analysis based on the GBD 2019 framework, the global number of deaths and disability-adjusted life years (DALYs) attributable to lead exposure increased by 70.19% and 35.26%, respectively, between 1990 and 2019 [97].

Human biomonitoring: biological matrices and interpretation

The World Health Organization has also issued evidence-based clinical guidance for the diagnosis and management of lead exposure [98]. Exposure to inorganic lead remains a major public and occupational health concern because of its neurological, renal, and cardiovascular toxicity [99, 100]. Inorganic lead compounds are classified by the International Agency for Research on Cancer (IARC) as probably carcinogenic to humans (Group 2A) [60].

Human biomonitoring plays a central role in assessing lead exposure and associated health risks [83]. Blood lead concentration is the primary and best-validated biomarker for assessing internal lead exposure and is widely used in both environmental and occupational settings [79, 83, 100]. Human biomonitoring provides a measure of internal lead

exposure and is therefore an important tool for identifying populations with elevated exposure, including children [79, 83]. Even low-level lead exposure has been associated with adverse neurological, cognitive, and behavioral effects in children [79]. Biomonitoring methods are also valuable tools for environmental health risk assessment because they provide information on internal exposure and the biological uptake of lead [79, 83]. Because no safe blood lead level has been identified in children, early identification of children with lead exposure is important for preventing further exposure and enabling timely medical, environmental, and public health interventions to reduce the risk of adverse developmental and health effects [62, 83]. In 2021, the CDC lowered the blood lead reference value (BLRV) from 5.0 to 3.5 $\mu\text{g}/\text{dL}$ to identify children with blood lead levels higher than those of most U.S. children and to facilitate earlier follow-up and exposure-reduction measures [62].

Lead biomonitoring can provide information on recent exposure and, depending on the biological matrix and sampling strategy, cumulative exposure and body burden. Lead can be measured in various biological matrices, including blood, bone, urine, hair, nails, and saliva, although these matrices differ substantially in their ability to reflect recent exposure, cumulative body burden, and internal dose [83]. Whole-blood lead is the most widely used and best-validated biomarker of lead exposure, whereas bone lead provides information on cumulative exposure and long-term body burden [83, 101]. Biomarkers of effect, including alterations in heme biosynthesis, can complement exposure biomarkers by providing insights into the biological responses associated with lead toxicity [83]. Appropriate selection of biological matrices and biomarkers is therefore important for accurate exposure assessment and interpretation of lead-related health risks. Whole-blood lead concentration remains the primary biomarker for assessing recent or ongoing lead exposure, whereas bone lead measurements are better suited for evaluating long-term cumulative exposure [83, 101].

Lead exposure can also be assessed through analysis of teeth, nails, hair, and other biological matrices, although their interpretation depends on the exposure window and matrix-specific limitations [83, 102]. For historical and chronic exposure assessment, *in vivo* bone lead measurement by X-ray fluorescence (XRF) provides a valuable approach for estimating cumulative lead body burden [93, 103]. Saliva has been investigated as a potential non-invasive surrogate matrix for lead biomonitoring; however, its correlation with blood lead appears to vary with exposure level and sampling methodology, limiting its use as a direct substitute for blood lead measurement [83, 104]. Although whole-blood lead is the established and best-validated biomarker for lead exposure, no

single biological matrix can capture all exposure windows and aspects of lead body burden. Alternative matrices, including bone and saliva, may provide complementary information, but their interpretation and application are subject to important methodological limitations [83, 102, 104].

Conclusions

Inorganic lead remains a persistent environmental, occupational, and public health hazard despite the substantial global reduction in its use. Current evidence indicates that human exposure continues to occur through multiple environmental pathways, and no safe level of lead exposure has been established. Even low-level exposure has been associated with adverse neurological, cardiovascular, renal, hematological, reproductive, endocrine, and developmental effects. Fetuses, newborns, children, and pregnant women represent the most vulnerable population groups because of physiological immaturity and the heightened susceptibility of the developing nervous system.

Human biomonitoring plays a central role in assessing lead exposure, monitoring temporal trends, identifying vulnerable populations, and supporting evidence-based public health interventions. Whole blood lead concentration remains the primary biomarker of recent exposure, whereas bone lead provides valuable information on cumulative body burden and long-term exposure. The selection of appropriate biological matrices should be guided by the objectives of the study, the characteristics of exposure, and the target population.

Despite substantial advances in the understanding of lead toxicology, important challenges remain regarding the interpretation of biomonitoring data, the establishment of health-based reference values, the selection and validation of biomarkers, and the assessment of long-term health outcomes associated with chronic low-level exposure. Addressing these challenges requires standardized methodologies, harmonized quality assurance and quality control procedures, and continued international collaboration.

For the Republic of Moldova, the development and standardization of a national human biomonitoring protocol for lead, aligned with European human biomonitoring standards and internationally recognized best practices, represent an important step toward strengthening environmental surveillance, improving chemical risk management, and supporting evidence-based public health policy. Such a framework would facilitate the early identification of populations at increased risk and contribute to reducing the long-term health burden associated with lead exposure.

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