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Priority toxic metals arsenic, cadmium, mercury, and lead in ecosystems: A review of sources, toxicity, and regulatory approaches

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ABSTRACT

Heavy metals pose a persistent and escalating threat to ecosystems and human health due to their environmental persistence, bioaccumulative potential, and pronounced toxicity. This systematic review synthesizes current knowledge on the distribution, mechanisms of toxicity, regulatory approaches, and analytical strategies concerning four priority toxic metals: arsenic (As), cadmium (Cd), mercury (Hg), and lead (Pb). Relevant literature published between 2020 and 2025 was retrieved from Scopus, Web of Science, and PubMed, focusing on peer-reviewed studies. Included publications address contamination sources, toxicodynamics, international standards (WHO, EFSA, EU, Codex), and monitoring practices. Marked discrepancies in permissible exposure limits were identified across jurisdictions, while the neurotoxic, nephrotoxic, and carcinogenic effects of these metals are well documented. Particular concern arises from chronic low-dose exposure, combined metal exposure, and the emergence of nanoparticulate forms—areas where regulatory frameworks remain insufficient. The findings highlight the urgent need for harmonized standards, expanded biomonitoring efforts, and improved risk assessment methodologies to better safeguard environmental and public health.

1. Introduction

Environmental pollution by heavy metals remains one of the most pressing global challenges due to their persistence, bioaccumulative potential, and high toxicity to humans and ecosystems [1, 2]. According to the World Health Organization (WHO), approximately 1.4 million premature deaths each year are associated with exposure to chemicals, including toxic metals, through contaminated water, air, and soil [3, 4]. The problem is particularly acute in low- and middle-income countries, where sanitation infrastructure is underdeveloped and environmental quality monitoring is limited [5, 6]. Among the ten chemicals of greatest public health concern identified by WHO, four are heavy metals: As, Cd, Hg, and Pb [7]. These elements have been recognized by the World Health Organization (WHO), the United Nations Environment Programme (UNEP), the International Agency for Research on Cancer (IARC), and the U.S. Agency for Toxic Substances and Disease Registry (ATSDR) as among the most hazardous due to their toxicity, widespread presence, and significant health risks [5, 8-11].

Human exposure occurs via ingestion, inhalation, or dermal absorption and contributes to carcinogenesis as well as neurotoxic, nephrotoxic, and hepatotoxic outcomes [5, 9-11].

Vulnerable populations – including children, pregnant women, the elderly, and residents of heavily industrialized regions – are at particularly elevated risk [4, 5]. Recent WHO estimates indicate that the highest

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mortality rates associated with unsafe water sources are observed in African and South Asian regions, where populations simultaneously face high heavy metal exposure, limited wastewater treatment infrastructure, and poor access to clean water [4, 9]. The visualization in Figure 1 was created by the authors based on data from WHO [4, 9].

Heavy metal-based nanomaterials are increasingly used in cosmetics, packaging, pharmaceuticals, and agriculture, thereby amplifying exposure pathways and expanding their environmental distribution [12–15]. Evaluating heavy metal toxicity requires careful consideration of chemical speciation, as organic and nanoparticulate forms (e.g., MeHg, As_2O_3 nanoparticles) exhibit significantly higher bioavailability and toxicity than their ionic counterparts [13, 14].

This review synthesizes current data on the toxicity, environmental distribution, carcinogenicity, and human exposure pathways of four priority heavy metals (As, Cd, Hg, and Pb), along with an evaluation of international and national regulatory frameworks. Covering the period 2020–2025, the review emphasizes peer-reviewed publications, systematic reviews, and assessments by WHO, UNEP, EFSA, and IARC, as well as emerging studies on mixed exposures, nanoparticulate forms, and epigenetic mechanisms. The objective of this review is to provide an integrated and systematic analysis of the toxicity, biological effects, and regulatory inconsistencies related to As, Cd, Hg, and Pb. By consolidating recent toxicological, epidemiological, and policy-related evidence, this review identifies key scientific gaps and outlines priority directions for environmental health research and chemical risk governance.

2. Materials and Methods

2.1. Literature search strategy

This systematic review was conducted in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [16], as illustrated in the PRISMA diagram. The aim of the search was to consolidate recent evidence on four priority heavy metals – As, Cd, Hg, and Pb – with a focus on pollution sources, exposure pathways, toxicity, bioaccumulation, carcinogenicity, and regulatory frameworks.

The literature search was performed across major international bibliographic databases, including Scopus, Web of Science, PubMed, Google Scholar, DOAJ, and CyberLeninka (restricted to Scopus- and VAK-listed journals). Search queries were constructed using relevant keywords and Boolean operators: “heavy metals” AND (“arsenic” OR “cadmium” OR “mercury” OR “lead”) AND (toxicity OR regulation OR exposure OR risk), with adaptations made for each database.

In addition, a manual search was performed in key environmental journals, including Environmental Research, Science of the Total Environment, Environmental Geochemistry and Health, Toxics, IJERPH, ESPR, and other high-impact journals in the fields of environmental toxicology and regulatory science.

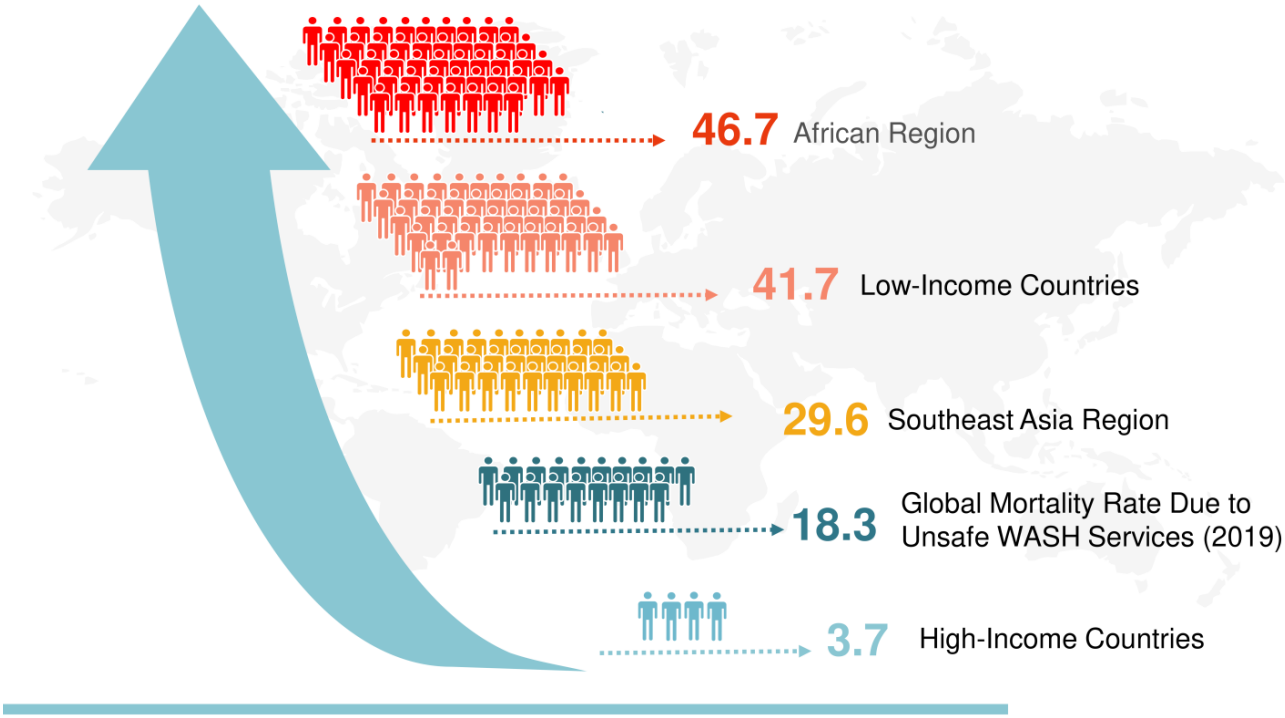

Fig. 1. Mortality rates associated with unsafe water sources by global region (per 100,000 population).

2.2. Inclusion and exclusion criteria

This review included peer-reviewed articles published between 2020 and 2025 and indexed in international databases such as Scopus, Web of Science, and PubMed. Reports from authoritative organizations (WHO, UNEP, EFSA, IARC, CDC), regulatory documents, and open-access systematic reviews were also considered.

The primary inclusion criteria were as follows: a clear focus on As, Cd, Hg, or Pb; content addressing toxicological effects, sources of pollution, exposure pathways, regulatory thresholds, or mechanisms of action; and the presence of quantitative or qualitative data related to human health or the environment. Particular attention was given to systematic reviews, meta-analyses, and original research that met established standards of scientific rigor (transparent methodology, representative samples, and appropriate statistical analysis).

Geographical diversity of publications was also taken into account to enable comparison of global and national-level risks. Excluded from the analysis were duplicate records, non-peer-reviewed publications, outdated sources (pre-2020), and studies unrelated to the selected metals. Priority was given to publications focusing on vulnerable populations – children, pregnant women, the elderly, and individuals with chronic health conditions – who are known to be more sensitive to heavy metal exposure. While peer-reviewed articles were strictly limited to the 2020–2025 period, a small number of regulatory documents published before 2020 were retained due to their continued relevance or official status. These exceptions were limited to normative sources from international organizations and did not include scientific studies.

2.3. Source selection process

A total of 1,248 records were initially identified. After removing duplicates and irrelevant publications, 936 sources remained. During the screening stage, studies focusing on unrelated metals, non-peer-reviewed materials, and outdated publications were excluded. Following full-text assessment and evaluation against quality criteria, 129 sources were included in the final review. These comprised: 72 peer-reviewed journal articles, including 24 systematic reviews and meta-analyses, and 57 authoritative sources from international organizations and regulatory agencies, including official reports, guidelines, web resources, and public data repositories.

2.4. Source reliability

All included scientific publications were peer-reviewed and published in journals indexed in Scopus or Web of Science, primarily within the Q1–Q2 quartiles. Documents from international organizations – including WHO, UNEP, EFSA, IARC, Codex Alimentarius, CDC, and EPA – further ensure a high level of credibility and comprehensive coverage.

2.5. Visualization of the selection process

The overall process of identification, screening, eligibility assessment, and inclusion of sources is presented in the PRISMA 2020 flow diagram (Figure 2). This visual summary enhances transparency and reproducibility of the review, in accordance with the PRISMA reporting standards.

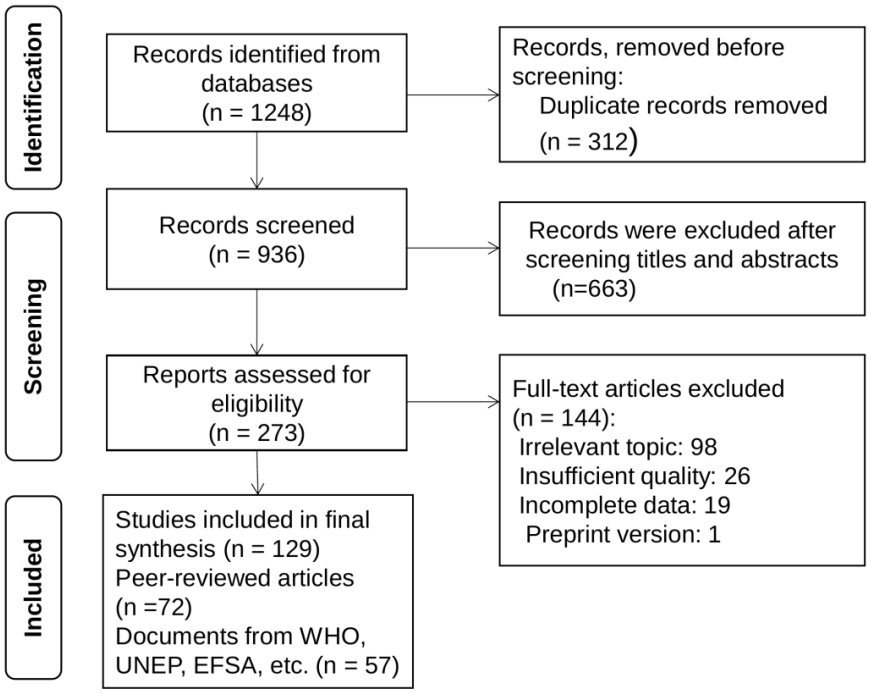

Fig. 2. PRISMA 2020 flow diagram illustrating the systematic selection and screening process for eligible sources.

3. Results and Discussion

Heavy metals are among the most persistent environmental pollutants. They remain in ecosystems for extended periods, exhibiting high toxicity, bioaccumulative potential, and the ability to undergo transboundary migration. Understanding their contamination pathways, environmental behavior, and health impacts is essential for effective risk assessment and the development of regulatory measures.

3.1. Sources of pollution

Environmental contamination by heavy metals originates from both natural and anthropogenic sources. Natural inputs include the weathering of rocks, volcanic activity, and diffuse runoff from soils and groundwater [13]. However, the primary contributors are anthropogenic activities – such as metallurgy, mining and ore processing, coal combustion, transportation, fertilizer and pesticide use, and industrial waste disposal [8, 17]. According to Ogwu et al. [8], the major pathways of As, Cd, Hg, and Pb contamination include industrial emissions, agricultural runoff, and uncontrolled waste disposal.

Agriculture is a significant source of heavy metal pollution, particularly in developing countries. The use of phosphate fertilizers, pesticides, and sewage sludge contributes to the accumulation of Cd and Pb in arable soils and can result in contamination of surface water bodies [18, 19].

The contribution of transport and energy sectors remains substantial. Pb was widely used in automotive fuel for decades, and despite regulatory bans, elevated concentrations of this metal persist along highways [20]. As for Hg, coal combustion continues to be the dominant global source of emissions: the United Nations Environment Programme (UNEP) [21] indicates that the energy sector accounts for up to 40% of annual atmospheric mercury releases. Recent quantitative assessments show that transportation remains the primary source of heavy metal pollution in urban ecosystems. According to Wang et al. [22], traffic contributed 58.2% to heavy metal contamination in road dust in Xi'an (China), while industrial sources accounted for 11.5%, and the remaining share originated from mixed natural and anthropogenic inputs. Moderate to high contamination levels were observed for Cd and Hg, with significant carcinogenic risks associated with As. These findings underscore the importance of considering local specificities when assessing pollution sources in urban environments [22]. Figure 3 presents the structure of anthropogenic sources of pollution, compiled from WHO, UNEP, EFSA, JRC, and publications from 2023–2024 [1, 2, 5, 8, 17–23]. The study by Du et al. [23] demonstrated that in Hg mining areas in China, Hg concentrations in soil and water significantly exceed background levels and are accompanied by marked alterations in microbial communities. This highlights the importance of incorporating bioindicators into environmental monitoring and land reclamation efforts.

Modern approaches to pollution assessment include both conventional and remote sensing methods. Lovynska et al. [24] reviewed the use of remote sensing technologies for monitoring heavy metal concentrations in soils and vegetation, recommending the integration of satellite data with ground-based measurements.

Artisanal gold mining remains a particularly hazardous local practice. In eastern Cameroon, Mimba et al. [25] reported significant contamination with Hg and Pb, causing severe damage to soil and aquatic ecosystems.

Identifying the sources of contamination provides a foundation for analyzing the migration, transformation, and accumulation of heavy metals in the environment, which are addressed in the next section.

3.2. Biogeochemical behavior of heavy metals: bioaccumulation, cycling, and ecosystem impact

Heavy metals are characterized by their persistence, toxicity, and long-term accumulation in various components of the biosphere. Their key environmental properties – bioaccumulation and biomagnification – are responsible for their long-lasting ecological impacts [8, 26-28]. The biogeochemical behavior of these elements varies: As, Cd, and Hg exhibit high mobility, whereas Pb has low migration potential [26, 29]. In living organisms, heavy metals disrupt enzymatic activity, photosynthesis, respiration, and membrane permeability. Aquatic and soil ecosystems are especially sensitive, exhibiting reduced productivity and altered microbial communities [8, 27].

At the global scale, heavy metals cycle through the atmosphere, hydrosphere, lithosphere, and biosphere. Natural sources include rock weathering, volcanic activity, and forest fires, while anthropogenic sources comprise industrial emissions, fossil fuel combustion, and agrochemical inputs [8, 18, 30].

The reuse of fertilizers and sewage sludge contributes to long-term metal contamination. For instance, the prolonged application of phosphate fertilizers increases Cd and Pb concentrations in arable soils, leading to their accumulation in food crops [8, 19]. Transformational processes are of particular toxicological importance: As and Hg undergo methylation, forming highly toxic species (MeHg, DMA) with elevated bioavailability and biomagnification potential. Pb is less prone to transformation but accumulates extensively in bones and internal organs [27, 28, 30]. Table 1 summarizes the primary sources, migration pathways, transformation forms, and biological accumulators of priority heavy metals based on data from WHO [31], EFSA [26], UNEP [21, 27, 28].

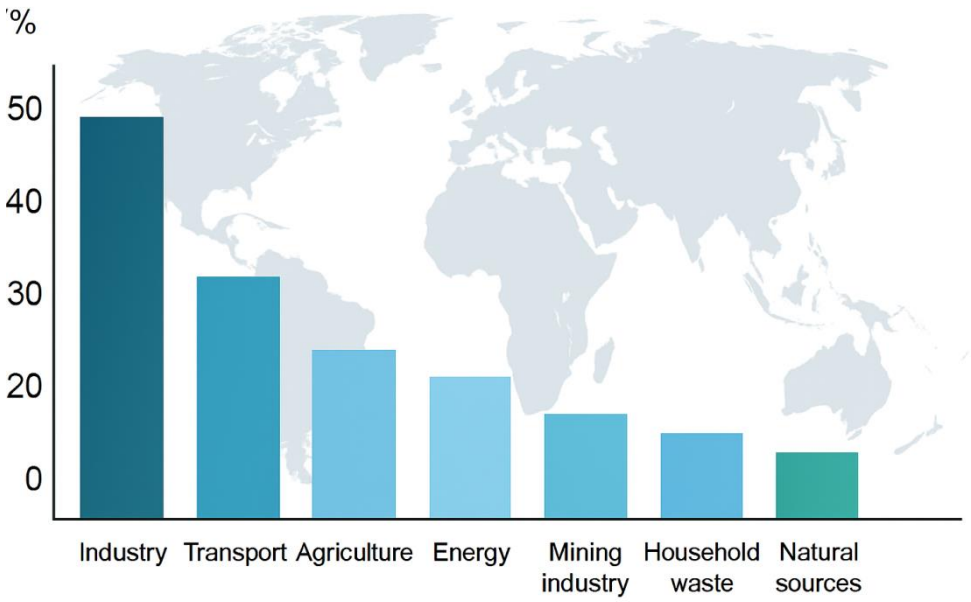

Fig. 3. Distribution of major sources of environmental contamination by heavy metals.

Table 1. Primary pathways of migration, transformation, and accumulation of priority heavy metals in ecosystems.

Metal	Primary Sources	Migration Pathways	Transformation Forms	Biotic Accumulators	Key Features
As	Pesticides, metallurgy, coal	Water → soil → plants → animals	Methylation (MMA, DMA)	Fish, rice, leafy vegetables	High mobility, carcinogenicity
Cd	Fertilizers, metallurgy	Soil → plants → humans	Complexation	Grains, vegetables, liver	Soil accumulation, nephrotoxicity
Hg	Gold mining, coal combustion	Air → deposition → water → biota	Methylation (MeHg)	Predatory fish, shellfish	Most toxic form is MeHg
Pb	Industry, transportation	Air, soil → water → plants	Limited transformation	Kidneys, bones, plants	High persistence, cumulative effects

Thus, the ecological behavior of heavy metals is governed by their chemical form, mobility, transformation processes, and tendency to bioaccumulate. Aquatic and soil systems are especially vulnerable, where even low concentrations can trigger toxic cascades. This underscores the importance of considering chemical speciation, methylation dynamics, and trophic transfer when managing contamination and designing biomonitoring strategies.

3.3. Impact on soil ecosystems

The entry of heavy metals into soil significantly disrupts its biological functions. It reduces microbial diversity, inhibits enzymatic activity, suppresses plant growth, and slows organic matter decomposition. Agroecosystems are particularly vulnerable, as even low concentrations of As, Cd, and Pb reduce crop yields and nutrient bioavailability [8, 26]. According to Hou et al. [32], approximately 17% of the world's arable land is contaminated with at least one heavy metal, affecting around 1.4 billion people. Major sources include industrial activities, mining, fertilizers, atmospheric deposition, and waste incineration [19, 20, 21, 25].

In the European Union, more than 2.5 million potentially contaminated sites have been identified, with 340,000 officially confirmed as contaminated by metals [18, 20]. Cd accumulation in EU agricultural soils has been documented with adverse effects on agricultural productivity [33]. Examples of regional contamination are summarized in Table 2, including data from China, Cameroon, Nigeria, Russia, and South Asia [8, 18-20, 25, 32, 34].

Of particular concern is the rise of antibiotic resistance in contaminated soils. Studies have demonstrated co-selection of resistance to both heavy metals and antibiotics in microbial communities [35, 36]. Common toxicity assessment methods include tests using earthworms (Eisenia fetida), microalgae, plants, and the collembolan Xenylla welchi, which exhibits strong stress responses to Pb [37]. Additionally, sequential extraction techniques – such as the BCR scheme – are widely used in environmental research to evaluate the mobility and potential bioavailability of metals in soils and sediments. In conclusion, heavy metal contamination undermines

soil ecosystem resilience and calls for integrated monitoring approaches that combine bioindicators, chemical analysis, and geospatial assessment tools.

3.4. Background concentrations in water and phytotoxicity

The background concentrations of heavy metals in aquatic environments play a critical role in determining their bioavailability, accumulation, and transfer through trophic chains. Metals enter water bodies from both natural sources – including rock weathering, volcanic activity, and groundwater infiltration – and anthropogenic activities such as industrial and municipal wastewater discharge, agrochemical runoff, and atmospheric deposition [29, 38].

Cd, Hg, and Pb are particularly phytotoxic. Even at low concentrations, they disrupt photosynthesis, membrane permeability, energy metabolism, and growth in aquatic vegetation, inducing oxidative stress and tissue damage [38, 39]. A systematic review by Zeb et al. [40], covering 52 river systems across Asia and Europe, identified bottom sediments as key reservoirs of heavy metals, reflecting both current and historical pollution sources. The highest concentrations of Cr, Co, Mn, Ni, Zn, Cd, Cu, and Pb were recorded in Indian rivers, followed by those in Iran, Turkey, Spain, and Vietnam. The Pollution Load Index (PLI) reached a peak value of 6.512 in Turkey, indicating critical environmental pressure. The Potential Ecological Risk Index (PERI) also highlighted Vietnam, Spain, and Turkey as regions with the greatest ecological risk, primarily due to elevated levels of Cd, Pb, Ni, and other toxic metals. Major sources of contamination included industrial activities, mining, agrochemicals, and wastewater discharge. Table 3 presents background concentrations of priority heavy metals in marine and freshwater systems, based on the generalized data from Vinogradov, Grushko, and Bockris (as cited in SEBIZ [41]), along with their phytotoxic effects as reported by WHO [29], UNEP [38], Mansoor et al. [39], and Zeb et al. [40].

Thus, even at background concentrations, As, Cd, Hg, and Pb can induce both phytotoxic and ecotoxic effects. Universal molecular mechanisms of toxicity – including cytotoxicity, oxidative stress, and metabolic inhibition – have been observed in both plant and animal systems, including humans [39]. This underscores the need for a more in-depth analysis of each of the four priority metals – As, Cd, Hg, and Pb – which is provided in the following sections of the article.

Table 2. Soil contamination by heavy metals in different world regions.

Region / Country	Main Metals	Sources of Contamination	Key Effects / Risks	Quantitative Data
China	As, Cd, Pb, Cr	Industry, fertilizers, waste incineration	Contamination of arable land affecting a large population (Hou et al., 2025)	17% of arable land contaminated
Nigeria	Pb, Cd, Zn, Ni	Battery dumping sites	Co-selection of resistance to antibiotics and heavy metals (Joseph et al., 2023)	Pb – 2596.8; Zn – 1445.1; Cd – 34.97; Ni – 50.05 mg/kg
Austria	Pb, Cd	Metallurgy, mine water	Spread of multidrug resistance genes in bacteria (Prochaska et al., 2025)	Concentrations not specified
Eastern Cameroon	As, Pb, Cu, Zn	Artisanal gold mining	Enrichment of metals in soils and sediments (Mimba et al., 2023; Doumo et al., 2022)	Pb – 18.04; Cu – 24.22; Zn – 96.22; As – 1.93 mg/kg
South Asia	Cd, Pb	Phosphate fertilizers, agricultural runoff	Accumulation in food crops; reduced food quality and safety (Angon et al., 2024)	Cd — up to 2.3; Pb – up to 70 mg/kg
European Union	Cd, Pb	Industry, transport, agrochemicals	Over 2.5 million potentially contaminated sites, 340,000 confirmed (JRC, 2023; Vieira et al., 2024)	See text
Russia	Pb	Industrial and transport emissions	Elevated Pb levels in urban and industrial soils (Ivanishchev and Sigolaeva, 2024)	Pb – 500–1000 mg/kg
Global overview	Cd, Pb, As, Hg	Industry, agrochemicals, atmospheric deposition	Cumulative toxicity; persistent contamination (Ogwu et al., 2025; Hou et al., 2025)	2–50 times above background levels

Table 3. Background concentrations of priority heavy metals in marine and freshwater and their phytotoxic effects.

Metal	Marine water (µg/L)	Freshwater (µg/L)	Phytotoxic effects
As	10.0	30.0–64.0	Disruption of water balance, tissue necrosis, biomass reduction
Cd	0.1	0.1–1.3	Inhibition of photosynthesis, oxidative stress, tissue accumulation
Pb	0.03	1.0–23.0	Disruption of chlorophyll synthesis, growth inhibition
Hg	0.03	0.03–2.8	Inhibition of mitosis and enzymatic activity, tissue damage

4. Priority toxic metals: Ecological and toxicological characteristics

4.1. Vulnerable populations and sensitivity to heavy metal exposure

Heavy metals pose the greatest threat to specific population groups, including children, pregnant women, the elderly, individuals with chronic health conditions, and workers subject to occupational exposure. Vulnerability is determined by physiological characteristics such as immature barrier systems, specific metabolic pathways, and hormonal shifts, combined with cumulative exposure through food, air, and dermal contact.

Current data from WHO, EFSA, CDC, IARC, and UNICEF, along with recent epidemiological studies, demonstrate that heavy metals can cause persistent cognitive, endocrine, and metabolic disorders even at low-level exposures [42–47].

Table 4 below summarizes key vulnerable groups, routes of exposure, and characteristic health effects associated with each of the four priority metals, based on data from WHO, EFSA, the European Commission, IARC, UNICEF, and peer-reviewed studies [1, 6, 23, 26, 30, 31, 33, 42–47].

The impact of heavy metals depends not only on their chemical form and dose but also on individual sensitivity. Even low levels of contamination can trigger severe health effects in vulnerable groups, especially under conditions of chronic or combined exposure. This highlights the importance of element-specific toxicological assessments and source attribution, which are addressed in the following subsections.

4.2. Arsenic (As)

4.2.1. Sources and exposure routes

Arsenic is a naturally occurring metalloid with high toxicity, particularly in its inorganic forms As(III) and As(V), which dominate in both natural and anthropogenically altered environments. Natural inputs of arsenic result from the weathering of sulfide ores, volcanic activity, and geochemical release from sedimentary rocks, especially under reducing conditions in groundwater [31, 38, 48, 49].

Anthropogenic activity significantly amplifies the global arsenic cycle. Major sources include mining and smelting industries, the use of arsenic-based pesticides, coal combustion, and the production of glass and pharmaceuticals [50]. According to Schlesinger et al. [51], anthropogenic mobilization of arsenic through coal, ore, and phosphate mining is estimated at 1500–5600 $\times 10^9$ g/year – approximately ten times higher than natural sources (60–544 $\times 10^9$ g/year). Atmospheric emissions from non-ferrous metal smelting contribute an additional 17–38 $\times 10^9$ g/year, compared to a background level of 10–25 $\times 10^9$ g/year.

The greatest health threat from arsenic arises from contaminated groundwater, particularly in regions with intensive agricultural and industrial land use. Arsenic contamination is often accompanied by elevated levels of other toxic metals, creating complex risks for agroecosystems and food security [32]. Inorganic arsenic is naturally present at high concentrations in groundwater in several countries, including Argentina, Bangladesh, Cambodia, Chile, China, India, Mexico, Pakistan, the United States, and Vietnam) [32, 52].

Thus, arsenic contamination is both global and transboundary in nature. This necessitates regionally adapted strategies for monitoring, exposure reduction, and regulatory improvement, as emphasized in reports and studies by JRC [18], WHO [31], UNEP [38, 32, 50, 51].

4.2.2. Mechanisms of toxicity

Arsenic exerts systemic toxic effects, impacting the respiratory, hematopoietic, hepatic, renal, endocrine, and nervous systems. Key mechanisms include the generation of reactive oxygen species (ROS), oxidative damage to biomolecules, inhibition of DNA repair, and mitochondrial dysfunction – particularly associated with As(III) [53–55].

Epigenetic alterations also play a significant role, including DNA methylation, histone modifications, and microRNA dysregulation, all of which influence cell cycle regulation, apoptosis, and immune response, especially during prenatal and early postnatal development [55–57]. In addition, arsenic disrupts endocrine regulation, including the hypothalamic–pituitary–gonadal axis and the synthesis of thyroid hormones and sex steroids, thereby increasing the vulnerability of sensitive populations [55, 56].

4.2.3. Carcinogenicity

The inorganic forms of arsenic – As(III) and As(V) – are classified by the International Agency for Research on Cancer (IARC) as proven human carcinogens (Group 1) [10]. According to the World Health Organization (WHO) [31], chronic consumption of water containing arsenic at concentrations within current regulatory limits is associated with an increased risk of cancers of the skin, lungs, liver, and bladder [50, 52].

The carcinogenic effects are attributed to a combination of genotoxicity, epigenetic alterations, impaired antioxidant defense, and oxidative stress. The underlying mechanisms vary depending on the chemical species of arsenic.

Table 5 summarizes the toxicological characteristics of major arsenic species based on assessments by IARC, WHO, and the U.S. EPA from 2021 to 2024.

Table 4. Vulnerable populations, exposure pathways, and characteristic effects of priority heavy metal exposure.

Metal	Vulnerable Groups	Major Health Effects	Exposure Sources / Risk Contexts
As	Children, pregnant women, newborns	IQ reduction, endocrine disruption, immunodeficiency	Contaminated drinking water, rice, groundwater
Cd	Children, pregnant women, elderly, individuals with CKD	Nephrotoxicity, hepatotoxicity, osteoporosis, developmental impairment	Food (rice, vegetables), smoking, soil, industrial areas
Hg	Fetuses, children, pregnant women, elderly, occupational groups, high fish consumers	CNS damage, dementia, IQ decline	Seafood, Hg vapors, cosmetics, dental amalgams
Pb	Children, pregnant women, elderly, occupational groups	Cognitive impairment, ADHD, nephrotoxicity	Drinking water, aging infrastructure, dust, soil, lead-based paints

Table 5. Carcinogenicity and toxicological characteristics of arsenic forms based on evaluations.

Arsenic form	Example compounds	Bioavailability	Toxicity	IARC classification	Primary mechanism of action
Inorganic As(III)	As_2O_3, $AsCl_3$	Very high	Very high	Group 1	Genotoxicity, hypomethylation of oncogenes
Inorganic As(V)	Na_2HAsO_4, As_2O_5	High	High	Group 1	DNA repair inhibition, oxidative stress
Methylated arsenic	MMA, DMA	Moderate	Moderate	Group 2B	Moderate genotoxicity, epigenetic alterations
Organic arsenic	Arsenobetaine, arsenocholine	Low	Low	Not classified	No substantial evidence

The systematic review by Khoshakhlagh et al. [56] identified a dose–response relationship between arsenic exposure and increased risk of bladder, thyroid, and leukemia cancers. However, evidence concerning prostate and breast cancer remains inconsistent and calls for further research considering tissue specificity and genetic susceptibility. Hasan et al. [58] confirmed a significantly elevated risk of renal cell carcinoma even at low concentrations of arsenic in drinking water.

Special attention is given to epigenetic mechanisms of arsenic-induced carcinogenesis, including altered DNA methylation and microRNA expression [59]. Of additional concern are arsenic nanomaterials (e.g., As_2O_3 nanoparticles), which exhibit high bioavailability and have been shown to induce mitochondrial dysfunction, apoptosis, and epigenetic remodeling [60–62]. Their carcinogenic potential warrants targeted toxicological evaluation and inclusion in biomonitoring and environmental surveillance programs.

4.2.4. Research gaps and scientific priorities

Despite extensive evidence of arsenic (As) toxicity, several critical scientific and regulatory gaps persist. Current standards often overlook the diversity of chemical species, regional exposure patterns, and vulnerable populations.

Key gaps include: insufficient understanding of methylated arsenic species (MMA, DMA), particularly their nephrotoxic and epigenetic effects [53, 56]; lack of reliable data on dietary exposure, especially with regard to arsenic concentrations in staple crops from endemic regions [32]; absence of biomonitoring systems in countries with high geochemical arsenic mobility and weak public health infrastructure [31, 38]; limited validation of experimental models for assessing epigenetic and cellular mechanisms of arsenic-induced carcinogenesis [53, 56]; insufficient data on vulnerable populations, including children, pregnant women, and the elderly [31, 63–66].

Research priorities include: development and validation of epigenetic and metabolomic biomarkers of exposure; integration of analytical, toxicological, and digital tools to track As migration and speciation in ecosystems; creation of global biomonitoring networks that reflect regional risk factors and resource limitations.

Addressing these gaps is essential to improve regulatory standards, risk assessment accuracy, and prevention strategies for arsenic-related health effects.

4.3. Cadmium (Cd)

4.3.1. Sources and exposure routes

Cadmium is a highly toxic heavy metal that enters the environment from both natural sources – such as volcanic activity and rock weathering – and, more predominantly, from anthropogenic activities. Major industrial sources

include non-ferrous metal smelting, coal combustion, battery manufacturing, pigment and plastic stabilizer production, and the use of phosphate fertilizers in agriculture [19, 67, 68]. According to estimates by Yang et al. [45], approximately 22,000 tons of Cd are released into soils annually.

The highest levels of contamination are observed in industrial zones and agricultural regions with intensive agrochemical inputs. Petruzzelli et al. [33] reported that Cd concentrations in soils range from 0.01 to 0.7 mg/kg, but may exceed background levels by several orders of magnitude near metallurgical and chemical facilities.

Cd enters the human body primarily through dietary and inhalation exposure. Major dietary sources include cereals, vegetables, seafood, and organ meats [26, 68, 69]. The widespread occurrence of Cd in agroecosystems has been documented by the WHO [2], the UNEP [5], the EFSA [26], the Codex Alimentarius [67], and multiple recent studies [19, 33, 45, 68, 70]. These findings underscore the global relevance of cadmium pollution and the urgent need for prioritized monitoring of Cd in food chains.

4.3.2. Toxicity and mechanisms of action

Cadmium (Cd) exerts systemic toxicity through the induction of oxidative stress, mitochondrial dysfunction, and inhibition of antioxidant enzymes [44, 70]. By displacing Zn^{2+} and Ca^{2+} in metalloproteins, Cd induces cytotoxic and mutagenic effects. Chronic exposure is associated with nephropathy, osteoporosis, type 2 diabetes, and several malignancies [45, 71].

Cd tends to bioaccumulate in the liver and kidneys, with slow excretion leading to prolonged and often irreversible toxic effects. Even low-level exposure significantly increases the risk of chronic kidney disease through proximal tubule injury and reduced glomerular filtration rate [71, 72].

The dermal route is also toxicologically relevant: in vitro studies have shown Cd accumulation in the epidermis, modulated by concentration, pH, and chemical form [73]. Cd exposure induces the expression of metallothioneins, which serve as sensitive biomarkers of cadmium burden [74].

A recent study by Saah et al. [75] reported that cadmium levels in commercial lipstick samples exceeded safety thresholds, indicating potential risks of chronic dermal and oral exposure and underscoring the need to revise current cosmetic safety standards.

4.3.3. Dietary contamination and exposure

The dietary pathway is the primary route of cadmium (Cd) exposure in humans. Even at moderate levels in food products, daily Cd intake can exceed tolerable limits, particularly in countries with high consumption of rice, vegetables, and seafood [45, 68, 69]. In Europe, the main dietary sources include cereals, leafy vegetables, offal, mushrooms, and mollusks. According to FoodEx data, the largest contributions come from grain products (26.9%), vegetables (16.0%), and root crops (13.2%) [76].

Regional patterns have been observed: in Western countries, major contributors include bread, cereals, vegetables, and potatoes; in Eastern countries, rice, mollusks, and tobacco dominate. In China, rice accounts for 58.6% of dietary Cd intake, followed by tobacco (25%) and mollusks (13.2%); in South Korea, rice (40.3%) and seafood are the main contributors. In the United States, the average Cd intake is estimated at 0.54 µg/kg body weight per week. Figure 4 presents a summary of dietary Cd contributions, derived from the analysis by Kuzmin et al. [76].

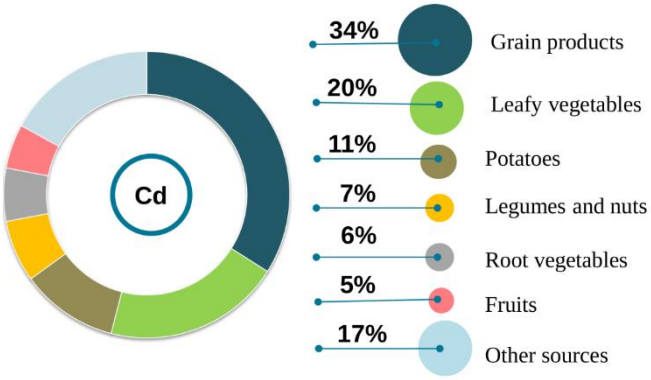

Fig. 4. Contribution of various food groups to total cadmium intake

Despite this diversity of sources, EFSA emphasizes that the greatest cadmium burden results from regular consumption of foods with moderate Cd levels. This highlights the need to revise regulatory thresholds and refine carcinogenic risk assessments under conditions of widespread population exposure.

4.3.4. Carcinogenicity

Cadmium has been classified by the International Agency for Research on Cancer (IARC) as a confirmed human carcinogen (Group 1) [10]. Its carcinogenicity is mediated through oxidative stress, DNA damage, epigenetic modifications – including hyper- and hypomethylation of tumor suppressor genes – as well as disruptions in cell cycle regulation and apoptosis [44, 57, 70].

Cd accumulates in target organs such as the lungs, liver, and kidneys, where its carcinogenic effects are manifested. Epidemiological studies indicate a consistent association between chronic Cd exposure and increased risks of lung, kidney, liver, and prostate cancers, particularly among occupationally exposed populations [45]. According to Peana et al. [74], Cd has been linked to more than 12 types of malignancies, including cancers

of the breast, pancreas, bladder, and prostate. Disruption of the metalloproteome – via displacement of Zn^{2+}, Fe^{2+}, and Cu^{2+} – impairs antioxidant defenses, promotes lipid peroxidation, and inhibits DNA repair.

A systematic review by Khoshakhlagh et al. [56] confirmed associations between Cd exposure and elevated risks of lung, breast, and bladder cancers, although evidence for kidney and prostate cancer remains inconclusive, warranting consideration of dose–response relationships and individual susceptibility.

A meta-analysis by Soleimani et al. [77] reported a significantly increased risk of pancreatic cancer (OR = 2.01; 95% CI: 1.30–2.72), while Florez-Garcia et al. [78] identified a moderate increase in breast cancer risk (OR = 1.13; 95% CI: 1.00–1.28). Data on other cancer sites remain inconclusive and require further investigation, accounting for tissue specificity and genetic predisposition.

4.3.5. Research gaps and scientific priorities

Despite the well-documented toxicity and widespread environmental occurrence of Cd, important knowledge and regulatory gaps remain. Current risk models often underestimate chronic and cumulative exposures.

Key gaps include: limited investigation of chronic low-dose Cd exposure, particularly in vulnerable populations, and insufficient attention to long-term health effects [70, 71]; lack of distinction between chemical forms of Cd^{2+} with varying bioavailability and toxicity [74]; limited application of validated biomarkers, such as β_2-microglobulin, metallothioneins, and indicators of hepatic and renal damage [44]; insufficient data on epigenetic, neurotoxic, and endocrine-disrupting effects of Cd [56, 70].

Research priorities include: development of rapid detection methods and novel molecular biomarkers; implementation of molecular-epidemiological models integrating susceptibility and total toxic burden; multicenter studies on Cd bioavailability in diverse environmental contexts; integration of cumulative exposure assessment for Cd, Pb, and As in agricultural and industrial regions.

Filling these gaps will support more accurate risk assessments and strengthen environmental health policies targeting cadmium exposure.

4.4. Mercury (Hg)

4.4.1. Sources and exposure routes

Mercury is one of the most toxic heavy metals, entering the environment from both natural and anthropogenic sources. Natural inputs include volcanic activity, rock weathering, and biogeochemical processes in the hydrosphere [2, 27, 79]. However, the dominant burden originates from anthropogenic activities such as coal combustion, artisanal and small-scale gold mining (ASGM), metallurgy, cement production, and the processing of mercury-containing waste [23, 80, 81].

According to UNEP [82], ASGM accounts for up to 37% of global Hg emissions, making it the largest source of anthropogenic mercury release. Approximately 20 million people are employed in this sector – including women and children – with signs of chronic intoxication observed in nearly one-third of workers. In mining-intensive areas such as eastern Cameroon, severe watershed contamination and ecosystem disruption have been documented [25].

The second-largest source of emissions is coal combustion (≈21%), particularly in countries with outdated flue gas treatment systems [82, 83]. Dietary exposure is also of critical importance: methylmercury (MeHg), formed in aquatic ecosystems, bioaccumulates in predatory marine species such as tuna, shark, and swordfish. According to BLOOM Association [80], over 50% of canned tuna in the European Union exceeds allowable Hg concentrations.

Wu et al. [83] report that the largest regional contributors to global Hg emissions include East and Southeast Asia (38.6%), South America (18.4%), Sub-Saharan Africa (16.2%), and South Asia (10.1%).

Additional exposure routes involve inhalation of elemental mercury (Hg^0) during coal combustion, e-waste recycling, chlorine production, disposal of fluorescent lamps, and dental amalgams [81]. Mercury also enters the body through contaminated water, food crops, and skin-lightening cosmetics [84].

Even in the absence of direct occupational contact, Hg is detected in the majority of the global population, with levels varying by region, occupation, and diet [1, 30, 79]. Due to its high volatility, Hg^0 undergoes long-range atmospheric transport, making mercury a global pollutant and the subject of international regulation [79, 82, 83, 85].

4.4.2. Mechanisms of toxicity

The toxicity of mercury (Hg) depends on its chemical form – elemental (Hg^0), inorganic (Hg^{2+}), or organic (methylmercury, MeHg) – which differ in their bioavailability and ability to cross biological barriers [79, 83]. Elemental mercury (Hg^0) readily volatilizes and is primarily absorbed through inhalation. Due to its lipophilicity, it crosses the blood–brain barrier, where it is oxidized to Hg^{2+} and accumulates in tissues, exerting prolonged neurotoxic effects [81, 86]. MeHg is formed under anaerobic conditions and enters the human body mainly through dietary intake, particularly via seafood. It crosses both the blood–brain and placental barriers, disrupting neurogenesis and neural network development in the fetus [79, 87]. Its toxicity is mediated by oxidative stress, mitochondrial dysfunction, DNA damage, and calcium imbalance [8, 86]. At the molecular level, Hg binds to protein sulfhydryl (SH) groups, altering protein

structure and gene regulation. MeHg affects epigenetic processes, including DNA methylation and histone modification, particularly during prenatal exposure [79, 88].

According to a review by Kang et al. [86], all mercury species induce apoptosis via the MAPK, PI3K/Akt, and Nrf2 signaling pathways, and are associated with immunosuppression and autoimmune responses. Inorganic mercury predominantly targets the kidneys – especially the proximal tubules – leading to proteinuria and impaired glomerular filtration [83]. Due to its slow elimination (lasting several months for MeHg and over a year for Hg^{2+}), mercury exerts cumulative, multisystemic toxicity, which poses a particular threat to the developing brain.

4.4.3. Carcinogenicity

The carcinogenicity of mercury, particularly methylmercury (MeHg), remains a subject of scientific debate. According to the International Agency for Research on Cancer (IARC), MeHg is classified as Group 2B – possibly carcinogenic to humans [10].

Proposed mechanisms of carcinogenicity include epigenetic alterations, oxidative stress, DNA damage, and apoptosis suppression [83, 88, 89]. MeHg activates proliferative signaling pathways (ERK1/2, JNK, Nrf2), interacts with estrogen receptors, reduces antioxidant defenses, and affects the methylation of tumor suppressor genes [86].

A review by Kang et al. [86] emphasizes the role of Hg in dysregulation of the cell cycle and calcium homeostasis. A systematic analysis by Khoshakhlagh et al. [56] reported that in 62.5% of studies, Hg concentrations in biological samples of cancer patients exceeded those of control groups, particularly in thyroid, prostate, breast, lung, and brain cancers. In prostate cancer cases, blood Hg levels were 2.43 times higher than in controls. Despite the heterogeneity of data and interindividual variability in Hg metabolism, MeHg demonstrates molecular features of carcinogenicity even at low exposure levels. This underscores the need to revisit regulatory thresholds and strengthen monitoring of mercury levels in the environment and food products [83, 89].

4.4.4. Research gaps and scientific priorities

Despite global regulations and extensive toxicological data, significant scientific and policy gaps remain regarding mercury (Hg). Current frameworks often fail to reflect regional dietary habits and exposure pathways.

Key gaps include: insufficient understanding of chronic Hg exposure in vulnerable populations, including children, pregnant women, artisanal miners, and workers in e-waste recycling facilities [30, 81]; limited epidemiological evidence on Hg carcinogenicity (e.g., in thyroid, breast, and prostate cancers), due to variability in biological matrices and analytical methodologies [56, 89]; lack of validated biomarkers for neurotoxicity, apoptosis, and epigenetic effects in environmental and human biomonitoring programs [83, 86]; inability of regulatory standards to distinguish between mercury species (MeHg, Hg^{2+}, Hg^{0}), which differ significantly in bioavailability and toxicokinetics [90]; underestimation of combined exposure to MeHg, Pb, and Cd in agro-industrial regions.

Research priorities include: application of multi-omics tools (e.g., transcriptomics, proteomics, metabolomics) to identify MeHg-specific biomarkers; validation of molecular indicators for neuro-, cardio-, and immunotoxicity; large-scale longitudinal studies on chronic Hg exposure effects; development of techniques to differentiate Hg species in biological and food matrices; implementation of sensor-based technologies for real-time exposure detection and contamination control.

Bridging these gaps is crucial for updating international standards and reinforcing strategies to mitigate mercury-related health risks.

4.5. Lead (Pb)

4.5.1. Sources and Exposure Routes

Lead is recognized as a priority pollutant by the World Health Organization (WHO), the United Nations Environment Programme (UNEP), and the U.S. Centers for Disease Control and Prevention (CDC), and is subject to regulatory control in soil, water, air, and food [5, 7, 21, 91-93]. Major sources of Pb contamination include metallurgical activities, battery production, leaded gasoline, paints, lead pipes, and fertilizers [19, 20, 94]. In several countries, the use of leaded fuel persists, and waste management practices remain inadequate – particularly in residential areas with aging infrastructure [66, 91]. According to WHO and UNEP estimates, Pb accounts for up to 10% of heavy metal contamination, especially near industrial facilities and roadways [20, 93]. Average Pb concentrations in soils range from 6.8–12 mg/kg in agricultural areas, up to 200 mg/kg in urban zones, 500 mg/kg in industrial zones, and as high as 1000 mg/kg near thermal power plants and mining sites [40, 94]. Despite reductions in blood lead levels (BLLs) among children in the United States, millions remain at risk. In 2021, the CDC lowered the reference BLL from 5.0 to 3.5 μg/dL, emphasizing that no safe exposure threshold exists [92, 95]. According to the Institute for Health Metrics and Evaluation (IHME) [96], Pb was responsible for over 1.5 million premature deaths globally in 2021, primarily from cardiovascular diseases.

In low-income countries, exposures are even higher: over 800 million children are estimated to have BLLs exceeding 5 μg/dL, largely due to informal battery recycling and the continued use of Pb-based paints [97,

98]. WHO and UNEP advocate for the global phase-out of lead paints, a policy now implemented in 48% of countries [99].

The magnitude of the Pb pollution crisis is further supported by systematic reviews and meta-analyses [93, 100–102], as well as global epidemiological data from WHO, CDC, and IHME [91, 92, 96].

4.5.2. Mechanisms of toxicity

Lead exerts pronounced toxic effects on the nervous, hematopoietic, renal, hepatic, and cardiovascular systems. At the molecular level, it inhibits enzyme activity, induces the formation of reactive oxygen species (ROS), disrupts mitochondrial function, calcium homeostasis, and epigenetic regulation [11, 42].

Neurotoxicity is particularly severe in children: even low levels of Pb exposure are associated with reduced IQ, attention deficits, and persistent neurocognitive impairments [43, 92, 103, 104]. Combined exposure to Pb, Cd, and Hg has also been linked to cognitive dysfunction in children [46]. The hematotoxic effects of Pb are mediated through the inhibition of δ-aminolevulinic acid dehydratase (δ-ALA-D) and ferrochelatase, disrupting heme synthesis and contributing to anemia [11]. Pb accumulates in the renal proximal tubules, leading to reduced glomerular filtration rate and proteinuria [92, 102].

Systematic reviews confirm a broad spectrum of health effects, including impaired neurodevelopment [100], an association with attention-deficit/hyperactivity disorder (ADHD) [101], and reduced renal function in adults [102]. According to Song et al. [105], margin of exposure (MOE) values for children in China were below 1, indicating an unacceptable level of risk even under typical dietary conditions.

4.5.3. Carcinogenicity

Inorganic lead (Pb) compounds are classified by the International Agency for Research on Cancer (IARC) as probably carcinogenic to humans (Group 2A) [10, 11]. Chronic inhalation and oral exposure are associated with an increased risk of cancers of the kidney, lung, and stomach. The carcinogenicity of Pb is mediated by oxidative stress, DNA damage, and epigenetic modifications – particularly hypermethylation of tumor suppressor genes such as MLH1 and MGMT – as well as disruptions in cell cycle control and apoptosis [11, 15]. Vulnerable populations, including children and pregnant women, are especially sensitive to low levels of Pb exposure due to the immaturity of their antioxidant defenses and immune systems [42, 43]. Lead nanoparticles (PbNPs), due to their high cellular penetration, may further enhance carcinogenic potential by inducing mitochondrial dysfunction and activating oncogenes such as KRAS and BRAF [106].

A systematic review by Khoshakhlagh et al. [56] confirmed associations between Pb exposure and a broad spectrum of malignancies, including tumors of the brain, thyroid, breast, stomach, testes, bladder, and hematological malignancies such as leukemia. Epigenetic alterations and activation of the RAS/RAF/MAPK signaling pathway have been observed in individuals with occupational exposure. Evidence regarding prostate cancer remains inconclusive and calls for further investigation, with consideration of dose–response relationships and genetic susceptibility.

4.5.4. Research Gaps and Scientific Priorities

Despite its recognized toxicity and global prevalence, lead (Pb) remains inadequately addressed in many regulatory and research systems. Emerging evidence suggests that even very low levels may cause lasting harm.

Key gaps include: lack of a safe threshold for Pb exposure: blood lead levels (BLLs) below 3.5 µg/dL have already been associated with cognitive and epigenetic impairments [100–102]; limited monitoring capacity in low-resource settings: data on Pb concentrations in blood, soil, and household dust remain fragmented [92, 93]; inconsistencies across regulatory frameworks (WHO, EFSA, CDC, EPA), hindering global harmonization [91, 92, 106]; insufficient data on long-term consequences of chronic exposure, such as neurodegeneration and cardiovascular disease in older populations [11, 100, 105]; underutilization of non-invasive biological matrices (e.g., hair, tooth enamel, nails) and digital tools such as geographic information systems (GIS) in exposure assessment [5, 13]; neglect of the carcinogenic potential of low-level Pb exposure, particularly in relation to kidney, lung, stomach, and breast cancers [56]; absence of regulatory consideration for lead nanoparticles (PbNPs), despite their high bioavailability and enhanced toxicokinetic properties [13, 106].

Research priorities include: validation of biomarkers such as hair, nails, and tooth enamel; population-level studies on neuro- and cardiotoxicity of chronic exposure; integration of GIS and digital platforms for exposure mapping; revision of regulatory values toward a “no safe level” paradigm; assessment of global Pb phase-out strategies, with equity-based policies for low-income countries. Filling these gaps is vital to improving Pb risk governance and ensuring effective long-term health protection.

5. Regulation of toxic metal contamination

5.1. International and national standards: a comparative analysis

The regulation of toxic metal concentrations in water, air, soil, and food products is governed by international, regional, and national normative frameworks that

establish maximum permissible limits. These threshold values aim to reduce health risks, particularly among vulnerable populations, and to support the resilience of ecosystems. In addition to international and regional guidelines, many countries have developed their own national standards to regulate acceptable concentrations of heavy metals in environmental media and food. In some cases, international benchmarks – such as those established by the World Health Organization (WHO) or the European Union – are adopted. In others, national thresholds are set independently, reflecting local environmental conditions, patterns of exposure, and socio-economic factors. The differences span not only the threshold values themselves but also the methodologies used for risk assessment and the robustness of environmental monitoring systems, resulting in a diverse and often fragmented global regulatory landscape.

To facilitate comparative analysis and visualization, this section adopts a standardized approach to aligning drinking water standards, based on the systematic review by Mukherjee et al. (2021) [107] and supplemented with up-to-date information from official international, regional, and national sources, including: the European Union (Directive (EU) 2020/2184) [108], the United States Environmental Protection Agency (EPA, 2023) [109], Health Canada (Guidelines for Canadian Drinking Water Quality, 2025) [110], the National Health and Medical Research Council of Australia (NHMRC, 2024) [111], China's national standard GB 5749-2022 (USDA FAS, 2023) [112], the South African Bureau of Standards (SABS, 2015) [113], the Ministry of Health of Brazil (GM/MS Ordinance No. 888, 2021) [114], the Russian Sanitary Rules and Norms (SanPiN, 2021), the Resolution of the Republic of Uzbekistan No. 861 (2019) [115-117], and recent WHO recommendations (WHO, 2022a; WHO, 2024d) [29,31]. This comparative framework highlights the geographical and socio-economic diversity in risk management practices. Table 6 presents the maximum permissible concentrations of selected heavy metals in drinking water as established by international, regional, and national regulations in effect as of 2023–2024. The comparison includes values for As, Cd, Pb, and Hg, reflecting the toxicological relevance of these elements. The international limits for As and Pb are relatively consistent. However, considerable discrepancies exist for Cd and particularly for Hg. For example, the WHO allows 0.006 mg/L of Hg in drinking water, whereas the EU sets a much stricter limit of 0.001 mg/L. The U.S. standard lies in between at 0.002 mg/L. Russia and Uzbekistan enforce even more stringent limits of 0.0005 mg/L, while in some countries, allowable levels are 2 to 10 times higher.

These divergences reflect differences in risk assessment practices, public health priorities, and monitoring capabilities. Such inconsistencies underscore the need for harmonized regulatory approaches that account for local conditions, exposure profiles in vulnerable groups, and the latest scientific evidence.

5.2. Beyond drinking water: air and soil standards for heavy metals

Unlike drinking water, regulatory frameworks for heavy metal concentrations in ambient air remain fragmented and vary considerably across regions. In many countries, binding Ambient Air Quality Standards (AAQS) have been established only for Pb, with typical values ranging from 0.15 to 0.5 μg/m³. For example, the United States enforces a limit of 0.15 μg/m³ under the National Ambient Air Quality Standards (NAAQS), calculated as a three-month rolling average but interpreted on an annual basis (EPA, 2024) [117]. In the European Union, an annual limit of 0.5 μg/m³ is in effect, as stipulated in Directive (EU) 2024/2881 [118]. Comparable thresholds are enforced in Australia (NEPC, 2016) [119] and South Africa (Department of Environmental Affairs, 2009) [120]. Several post-Soviet countries, including Russia (Chief Sanitary Inspectorate, 2021) [115] and Uzbekistan (Ministry of Health, 2024) [121], apply a stricter annual limit of 0.15 μg/m³, consistent with the U.S. standard. This reflects a broad international consensus regarding the high toxicity of Pb and the relevance of inhalation as a major exposure pathway.

For other priority metals – Cd, As, and Hg – regulatory coverage is significantly less consistent. In the EU, long-term air quality standards are set at 0.5 μg/m³ for Pb, 5 ng/m³ for Cd, and 6 ng/m³ for As, as defined in Directive 2024/2881 (European Parliament and Council, 2024) [118]. These thresholds are being transposed into national legislation across all EU member states and form the basis for harmonized monitoring and policy enforcement. No official AAQS has been established for Hg in the EU; however, mandatory atmospheric monitoring and deposition tracking are required.

Table 6. Maximum permissible concentrations (MPC) of heavy metals in drinking water (mg/L) according to international, regional, and national standards.

Me	WHO	EU	USA	Canada	Australia	China	South Africa	Brazil	Russia	Uzbekistan
As	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Cd	0.003	0.005	0.005	0.007	0.002	0.005	0.003	0.003	0.003	0.001
Pb	0.01	0.005	0.01	0.005	0.01	0.01	0.01	0.01	0.01	0.01
Hg	0.006	0.001	0.002	0.001	0.001	0.001	0.006	0.001	0.0005	0.0005

A similar situation is observed in Canada and China, where no binding air quality standards exist for Hg, but concentration guidelines for Cd and As are applied near industrial emission sources. These include provincial-level benchmarks in Ontario (Ontario Ministry of the Environment, Conservation and Parks, 2020) [122] and national air quality limits in China (Ministry of Ecology and Environment, 2012) [123]. According to comparative data from Copernicus CAMS, WHO guidelines specify thresholds of 0.5 μg/m³ for Pb, 5 ng/m³ for Cd, and 6.6 ng/m³ for As (Copernicus CAMS, 2024).

Several Central Asian and Eastern European countries, including Uzbekistan and Russia, have established hygienic air quality standards for all four metals – Pb, Cd, As, and Hg – which include daily, short-term peak, and annual concentration limits [115, 121]. These standards are generally more conservative than international benchmarks and are widely used in environmental impact assessments and public health surveillance.

In countries with emerging environmental governance systems, the regulatory landscape is even more fragmented. A global review by the United Nations Environment Programme (UNEP, 2021) [124] and a regional analysis in the Eastern Mediterranean [125] indicate that only 19 of 54 African UN member states have formally adopted AAQS. These include Algeria, Egypt, Ghana, Kenya, Morocco, Nigeria, Rwanda, Senegal, South Africa, Tunisia, and Tanzania. Greenpeace Africa has also highlighted the widespread absence of air quality regulations for heavy metals associated with fossil fuel combustion across much of the continent (Greenpeace Africa and Greenpeace MENA, 2024) [126].

Despite the existence of partial frameworks and global treaties – such as the Minamata Convention on Mercury [127] – most countries still lack comprehensive standards for Cd, As, and Hg in ambient air. This limits the feasibility of integrated health risk assessments and underscores the need to harmonize regulatory approaches. Thus, the regulatory framework for heavy metal concentrations in ambient air remains fragmented and inconsistent at the global level. While legally binding standards for Pb are established in many countries, thresholds for Cd, As, and Hg vary widely or are entirely absent. This heterogeneity hinders cross-country data comparability and limits the capacity for comprehensive risk management, particularly in countries with underdeveloped emission control and air quality monitoring systems.

Compared to water and air, regulatory frameworks for heavy metal concentrations in soils are even more fragmented. International organizations such as WHO and UNEP do not provide universal soil quality standards, and national thresholds are typically established based on local geochemical baselines, land use categories, or indicative risk levels. In many countries, binding limits exist only for Pb, while values for Cd, As, and Hg are either absent or issued as non-binding guidelines. This regulatory heterogeneity hampers data comparability, ecosystem-based assessments, and the implementation of preventive environmental policies.

These regulatory gaps highlight the urgent need to revise and modernize heavy metal standards based on contemporary toxicological data, molecular epidemiology, and the precautionary principle.

5.3. Regulatory and scientific-analytical gaps

Despite the existence of an extensive regulatory framework for heavy metals, substantial gaps remain that limit the effectiveness of chemical risk management and the implementation of preventive public health strategies.

Key issues include:

Methodological heterogeneity: Regulatory limits are based on different risk assessment models – such as PTWI, RfD, MOE, and BMD – which complicates international harmonization and cross-country comparisons (WHO, 2024 [91]; EFSA, 2023 [69]; EPA, 2023 [109]).

Lack of consideration for chemical speciation: Most standards account only for total metal concentrations, without distinguishing between toxicologically distinct forms (e.g., MeHg vs. Hg^{2+}, As(III) vs. As(V), Cd^{2+} vs. organometallic complexes) [53, 79, 89].

Absence of regulation for nanomaterials: Highly bioavailable nanoparticulate forms—such as PbNPs and As_2O_3-NPs – are still not recognized as a separate category in most legal frameworks [15, 60, 106].

Insufficient protection of vulnerable populations: Existing maximum permissible concentrations (MPCs) are not adjusted for the increased sensitivity of children, pregnant women, or the elderly, despite growing evidence of sub-threshold health effects (UNICEF, 2024 [63]; CDC, 2024 [92]; WHO, 2024 [31]).

Weak monitoring systems: In many countries, large-scale biomonitoring programs for vulnerable populations are lacking or underdeveloped (Pure Earth, 2020 [100]; WHO, 2024 [31]; UNEP, 2023 [38]).

Disconnect between experimental and population-based risk assessments: Biomarkers such as KIM-1, metallothioneins, and microRNAs are not yet integrated into regulatory practice due to a shortage of validated epidemiological data [53,56, 86]. For instance, a systematic review by Hu et al. [128] found a significant increase in cardiovascular mortality associated with chronic mercury exposure, highlighting the need for more stringent exposure thresholds and their formal incorporation into regulatory documents.

Underestimation of cumulative exposure risks: Evaluating metals in isolation overlooks synergistic or additive effects. In Spain, for example, children exposed

simultaneously to Pb, Cd, and Hg exhibited persistent cognitive impairments, despite exposure levels below current regulatory [46].

These gaps highlight the necessity for revising current regulatory approaches by integrating emerging scientific evidence, enhancing exposure assessment methodologies, and prioritizing at-risk populations.

5.4. Priorities for advancement: from regulation to ecosystem-based risk management

Transitioning to a sustainable and science-driven framework for regulating heavy metals requires a fundamental revision of current risk assessment and management approaches. This review has highlighted persistent regulatory fragmentation, underdeveloped biomonitoring systems in high-exposure regions, and the neglect of chemical speciation and cumulative toxicity in existing standards. Addressing these challenges necessitates the integration of toxicological evidence, digital technologies, and adaptive policy instruments into a unified risk governance architecture.

Key strategic priorities include: international harmonization of regulatory thresholds, accounting for differences in the toxicity of specific chemical forms (e.g., MeHg, As(III), PbNPs), exposure profiles in vulnerable populations, and the effects of combined metal toxicity; validation of sensitive biomarkers for chronic and mixed exposure – such as KIM-1, β_2-microglobulin, epigenetic indicators, and markers of dysbiosis or microbiome disruption – across both human and animal populations [53, 56]; integration of sensor technologies and artificial intelligence to enable real-time detection of metal species in environmental and biological matrices, particularly in emergency contamination scenarios; development of global monitoring platforms that combine GIS-based systems, pollutant databases, epidemiological indicators, and predictive modeling tools; construction of multifactorial risk models that incorporate cumulative exposure, age, genetic predisposition, lifestyle factors, and socioeconomic vulnerability – with particular emphasis on children and the elderly. A notable example is the study by Wang et al. [129], which applied a probabilistic risk model and source apportionment analysis in an urban setting to identify priority metals (Hg, Cd, As) and propose targeted mitigation strategies based on ecological and public health criteria; localization of international initiatives in resource-limited settings through the implementation of safe technologies, educational outreach, and support for basic sanitation infrastructure. An example of successful multilevel coordination is the Global Alliance to Eliminate Lead Paint, spearheaded by WHO and UNEP, which integrates regulatory reform, technical assistance, and public information campaigns (WHO, 2023). Expanding such platforms to reflect regional risk profiles and institutional capacities is key to translating scientific knowledge into effective policy.

Thus, ecosystem-based risk governance for heavy metals requires comprehensive, cross-sectoral solutions grounded in scientific evidence, principles of equity, and regional adaptability. The transition from fragmented regulation to a globally coordinated approach is a critical prerequisite for ensuring ecosystem resilience and protecting public health.

6. Conclusion

This review presents a comprehensive synthesis of current evidence on the distribution, toxicity, biogeochemical behavior, and regulatory challenges related to four priority toxic metals: As, Cd, Hg, and Pb. These elements are environmentally persistent, bioaccumulative, and exert a broad spectrum of toxic effects, including neurotoxicity, nephrotoxicity, hepatotoxicity, and carcinogenicity. Their biological impact depends on chemical speciation (e.g., MeHg, MMA, DMA, ionic forms), exposure routes, and individual susceptibility, particularly among vulnerable populations. A comparative assessment of international and national standards (e.g., WHO, EU, EPA, Codex, FSSAI) revealed significant fragmentation and inconsistency. Regulatory thresholds often differ by orders of magnitude, lack consideration of chemical forms, and fail to reflect cumulative exposure, low-dose chronic effects, and region-specific risks. Many remain based on outdated toxicological data, with limited responsiveness to emerging contaminants and synergistic toxicity. Key gaps include the absence of standards for nanoparticulate and methylated metal species, limited biomonitoring in high-risk regions, underuse of molecular biomarkers in public health, and insufficient international coordination in harmonizing safety thresholds.

To advance chemical risk governance, modern regulatory frameworks should incorporate findings from molecular toxicology, multi-omics, and digital monitoring technologies, with a focus on the bioactivity and combined toxicity of metal species. Recent dose-response meta-analyses confirm that even low-level exposures may cause significant health effects, challenging long-held assumptions of safety.

Addressing legacy contamination and preventing future risks require investment in evidence-based mitigation strategies, including phytoremediation, advanced filtration, substitution of hazardous materials, and public education. Bridging the gap between scientific evidence and policy action is critical to reducing environmental injustice and protecting human and ecosystem health. This review provides a timely foundation for globally coordinated, science-driven approaches to heavy metal risk management and regulatory modernization.

Data availability statement:

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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