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Review article

From contamination to detection: The growing threat of heavy metals

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ABSTRACT

Heavy metals like lead, mercury, cadmium, and arsenic are environmental pollutants that accumulate in ecosystems and pose significant health risks to humans and wildlife, primarily through food chain contamination where plants absorb heavy metals, affecting their growth and threatening consumer health. Cognitive and cardiovascular functions are particularly affected by exposure to heavy metals even at low concentrations through the induction of oxidative stress. Various analytical techniques are used in measuring heavy metals in different environmental and biological samples. The atomic absorption spectroscopy (AAS) offers low cost, simplicity, and portability but lacks sensitivity for certain metals. Although more sensitive, the high cost of inductively coupled plasma mass spectrometry (ICP-MS) may limit laboratory accessibility. The inductively coupled plasma with atomic emission spectrometry (ICP-AES) is known for its broad dynamic linear range and ability to identify minute variations in concentration. Atomic fluorescence spectrometry (AFS) is considered a powerful tool for quantifying heavy metals due to its high sensitivity, low detection limits, and wide linear range. The current article reviews heavy metal pollution's impact on health and spectrometric techniques for the detection of these contaminants. This may help efforts of international, and regional policies towards preventing this health hazard problem.

1. Introduction

Heavy metals exposure represents a major health hazard to human well-being, constituting a significant threat as environmental pollutants (approximately one-fourth of human diseases). Being non-biodegradable, they accumulate in the environment and infiltrate the food chain, posing multiple health-related risks to animals and humans [1]. Heavy metals are described as metals with a density greater than 4.5 g/cm^3 and atomic weight larger than calcium (i.e. higher than 40.04) [2]. The most widely identified elements that largely contribute to pollution are lead (Pb), mercury (Hg), and cadmium (Cd). They are largely found in ecosystems including atmosphere, soil, and water, particularly from industrial exhaust wastes and mining processing [3]. Their penetration into the food chain

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in, inhalation, ingestion, or physical contact poses a significant threat to public health [4]. In 2001, As, Pb, Hg, and Cd were listed among the “Top 20 Hazardous Substances” reported by the U.S. Environmental Protection Agency [the Agency for Toxic Substances and Disease Registry-ATSDR] [5] that may lead to various pathological consequences on the skeletal, circulatory, nervous, endocrine, immune systems and may lead to life-threatening diseases such as cancer [1]. Moreover, exposure to Pb during pregnancy can lead to major prenatal fetal impairments [4].

Heavy metals originate from various sources. Pb commonly arises from fossil fuel combustion, leaded gasoline, paints, pigments, fertilizers, industrial waste incineration, ceramics, dishware, industrial dust and fumes, lead-acid battery manufacturing, pesticides, mining, metallurgy, certain types of PVC, and urban runoff [6,7]. Hg is found in industrial wastewater, fossil fuel combustion, fluorescent bulbs, chlor-alkali plants, scientific instruments, chemical production, mercury arc lamps, industrial dust, and fumes, municipal waste incineration, pesticides, fertilizers, smelting, mining, electrical switches, explosives, rubber and plastics, mercury products (e.g., thermometers, amalgams, batteries), and cellulose production [8]. Cd sources include polyvinyl chloride (PVC) products, phosphate fertilizers, color pigments, electronics, industrial and incineration dust and fumes, pesticides, paints, batteries, mining, metallurgy, and wastewater. As is associated with industrial dust and waste, gold and lead smelting, mining, pharmaceuticals, textiles, wastewater, metal hardening, pesticides, paints, copper and nickel production, steel and iron manufacturing, phosphate fertilizers, and fossil fuel combustion [7–9].

Heavy metals are most likely absorbed in the soil through the roots and may reach the leaf surface via the polluted atmosphere which consequently build up high levels in plants. Some plant species such as *Cedrus deodara* and *Cupressus arizonica* absorb heavy metals through their leaves, alternatively, *Nerium indicum*, *Platanus acerifolia*, and *Pittosporum tobira* uptake heavy metals through trichomes, mucous layer, or stomata. These elements can negatively affect vital processes such as photosynthesis and respiration, they can also cause damage to the stomata structurally and functionally [10].

Studying the spatial distribution pattern and properties of regional heavy metal pollution is highly crucial for heavy metal pollution evaluation, prevention, and management. Several advanced spectrometric techniques are currently utilized to monitor heavy metal content in environmental and biological samples including atomic absorption spectroscopy (AAS), inductively coupled plasma mass spectrometry (ICP-MS), atomic emission spectrometry (ICP-AES), and atomic fluorescence spectrometry (AFS) as shown in Table 1 [4,11,12].

Maintaining suitable freshwater quality is becoming a vital need for both aquatic and terrestrial life. There are relevant bioindicators that provide valuable information about the effective evaluation and monitoring of the environmental status with respect to marine life [13]. One of the frequently used bioindicators is macroinvertebrates, they provide a reliable assessment tool for monitoring alterations in water conditions representing areas of potential contamination. The most commonly used species for biomonitoring studies belong to crayfish as they occur in most ecosystems, and most importantly, the accumulation of pollutant elements in their body tissues is found to be a valid reflection of pollution levels in specific environments [14]. Although fish are mobile and might avoid contaminated areas, it is still reported that they can be also successfully used in biomonitoring programs, while algae can sometimes serve the same purpose despite some difficulties in detection. Heavy metals accumulation in target organisms and certain tissues is directly proportional to the contamination caused by a specific element in the water area. Several studies support the same finding where heavy metals’ bioaccumulation in aquatic biota, such as crayfish and fish, has provided useful data. The usefulness of crayfish is not only limited to being a reliable bioindicator of water contamination, they are considered an important source of food, which further enhances their relevance in monitoring contamination levels of certain elements in both animals and human populations [15,16].

The migration of heavy metals after entering the soil (heavy metal transport in different crops) occurs horizontally and vertically, thus showing different spatial distribution characteristics of pollution. The migration process in the horizontal direction is detected by obtaining samples of surface soil, where the increase in distance from point sources of pollution results in a general decrease in the content of heavy metal elements. Regarding the vertical direction, most of the soil samples showed a gradual decrease from the surface to the bottom in the content of soil heavy metals [4,17]. The control of heavy metals accumulation in medicinal plants and food crops is particularly critical. The proper understanding of the biological and physiological processing of plants which involve the different

Table 1
Comparison between principles and applications of spectrometric techniques used in metal analysis.

Analyticaltechnique	Principle	Multi/single-element technique	Applications
Atomic Absorption spectrometry (AAS)	All atoms absorb light at unique wavelengths and the amount of the absorbed light is proportional to the concentration of the absorbing atoms.	Multi and single-element analysis. *“Quantification is based on reference standard calibration”*	The gold standard technique.
Inductively coupled plasma with atomic emission spectrometry (ICP- AES)	It uses an optical spectrometer to measure the light emitted from elements as they pass through the plasma.		Widely used method for analyzing trace elements in environmental samples
Inductively coupled plasma with mass spectrometry (ICP- MS)	Ions are separated according to their mass-to-charge ratio (m/z) using argon plasma.		Commonly used for determination of isotopes.
Atomic fluorescence spectrometry (AFS)	A light source excites the element of interest to a higher electronic energy level while the sample is transformed into gaseous atoms. A photon is released once the atoms are excited, leading to their deactivation. This emission process is the measured fluorescence.		Particularly useful with the measurement of mercury and arsenic.

processes of heavy metals absorption, transport, accumulation, and detoxification should secure the cultivation of medicinal and edible plants with reduced levels of heavy metals and promote the employment of hyperaccumulators for treatment of excessively polluted soils [10].

The safety of foodstuffs became a major concern about public health. Some countries face a serious problem with metal pollution of soil, where approximately 82.8 % of the soil samples have exceeded the maximum allowed limit for heavy metals in soil [18]. More than 70 % of dietary intake of cadmium is attributed to contamination sources along the food chain, therefore the extensive consumption of the crops cultivated on contaminated land over long periods may increase the risk of heavy metals accumulation in the human population and animals [18,19].

In conclusion, this article sheds light on the neural and cardiovascular health hazards associated with exposure to heavy metals like As, Pb, Hg, and Cd. Additionally, it highlights the most common spectrometric techniques used for quantitative analysis of those elements in different biological and environmental samples including atomic absorption spectroscopy (AAS), inductively coupled plasma mass spectrometry (ICP-MS), inductively coupled plasma with atomic emission spectrometry (ICP-AES), and atomic fluorescence spectrometry (AFS). Moreover, rehabilitation approaches and policies have also been discussed, where regulatory authorities have collaboratively worked with scientific communities to develop a solid legal framework and efficient strategies for removing and monitoring heavy metals to mitigate health hazards and promote environmental sustainability worldwide. Fig. 1 depicts the outline of the current review paper.

2. Health hazards related to heavy metal exposure

2.1. Entry of heavy metals into the food chain

When soil is contaminated by lead (Pb), it is passively absorbed by roots and accumulates either in the plant roots (more than 95 %) or is transported through the xylem to the aerial plant parts (APP). In general, plant roots uptake metal ions from soil. Once absorbed, it binds to rhizoderm uronic acid/polysaccharide and moves through the water stream by apoplast to the endodermis. The xylem acts as a metal transporter, with the help of transpiration, from plant roots to shoots [20]. A previous study performed an x-ray mapping of mosquito plants and highlighted that a significant amount of Pb was accumulated in the xylem and phloem cells. Once it reaches the stem's central cylinder, it can be transported to leaf areas using the apoplastic pathway through vascular flow [21]. Accidental soil ingestion constitutes a significant pathway of Pb exposure for individuals residing in Pb-polluted areas. Additionally, ingesting plants

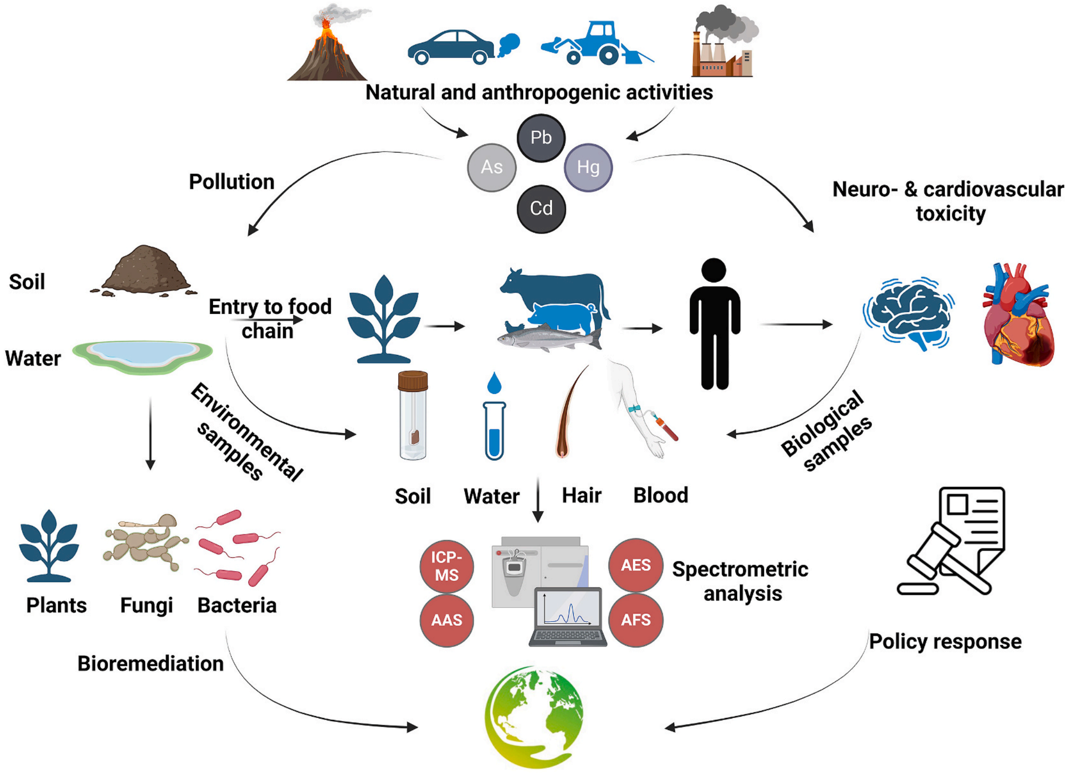

Fig. 1. Schematic outline of the data collected in this paper. As: Arsenic, Pb: Lead, Hg: Mercury, Cd: Cadmium, AAS: Atomic Absorption Spectrometry, ICP-MS: Inductively Coupled Plasma Mass Spectrometry, AES: Atomic Emission Spectrometry, AFS: Atomic Fluorescence Spectrometry.

contaminated with Pb is considered a risk to humans and animals. Plants, whether edible or wild, grown near phosphate industries can be biological indicators of Pb contamination. Individuals living or working in these industrial areas may face Pb exposure. Levels of Pb blood concentration among populations at risk fluctuate with industrial activity and season. During summer and early fall, blood Pb levels (BLLs) of children tend to be higher, with levels increasing notably in 2-year-old children compared to other age groups [22].

Mercury (Hg) undergoes biomagnification in the food chain once it leaches from its different sources to the water, with fish at higher trophic levels having concentrations significantly higher by 105–106 fold than the water they inhabit. Humans are exposed to Hg through the consumption of contaminated seafood which contains ethyl, dimethyl, and methyl Hg (CH_3Hg). These forms of Hg are also naturally present in low concentrations in oceans, lakes, and rivers but are absorbed by algae, which are then consumed by fish and other organisms higher up the food chain. Predatory fish like tuna, swordfish, and sharks tend to have the highest concentrations of CH_3Hg, accounting for more than 90 % of the total Hg in fish muscle. As fish consume prey, Hg bioaccumulates in their tissues, resulting in higher concentrations at each trophic level. Larger and longer-living predators generally have higher Hg levels than smaller or shorter-lived species [23]. On the other hand, it was reported that people residing in inland regions of China are exposed to CH_3Hg through the consumption of contaminated rice from areas polluted with Hg and highlight rice as a primary CH_3Hg source in regions with substantial inorganic Hg pollution [24].

Besides possible sources of soil contamination with cadmium (Cd), it is found in trace amounts in all crops within the food chain due to its natural presence in soil, even in minute quantities [25]. Initially, Cd absorbed from the soil is stored in plant roots before being transported to aboveground parts via xylem sap, influenced by respiratory power. Upon reaching the leaves, metals spread to leaf cells through the apoplast and symplast. Cd distribution in the leaf is facilitated by its binding to chelators in tissues, with phytochelatins and metallothioneins (MT) being the primary chelators involved in Cd retention due to their cysteine sulfhydryl groups, which form stable complexes [26]. Cd accumulates in different parts of plants in varying degrees. Generally, it accumulates mostly in roots, followed by leaves, and least in grains [27,28].

Arsenic (As) is naturally present in a concentration ranging from 5 to 10 mg/kg of agricultural soil. As exists in various forms in nature, including As(III), As(V), monomethylarsonous acid (MMA(III)), dimethylarsinous acid (DMA(III)), monomethylarsonic acid (MMA(V)), monomethylarsinic acid (DMA(V)), and other compounds. Plants uptake As differently depending on its chemical form. As (V) enters plant cells through inorganic phosphate channels, while As(III) is absorbed using specific proteins and transporters. As typically accumulates in the vacuoles of root or shoot tissues of plants and can be transferred to the food chain. Excessive consumption of crops grown in As-contaminated soil can pose health risks [29,30]. Water sources can be contaminated with As through both natural sources and human activities. The presence of As in aquifers can be influenced by the chemical properties of groundwater and the form in which As is found. In aerobic environments, As(V) is the predominant form, while in anaerobic environments, As(III) is more common. Factors like higher organic content and alkaline conditions in groundwater and aquifers can also contribute to the release of As. As undergoes biomagnification in different aquatic organisms with studies showing elevated levels in fish, crabs, eels, and other aquatic life. This not only impacts the ecosystem but also poses potential health risks for humans consuming contaminated seafood [29, 30].

2.2. Impact of lead exposure on nervous and cardiovascular systems

The central nervous system (CNS) is the first affected system by Pb toxicity, making the brain the most extensively studied organ in this regard. Pb disrupts normal CNS activity and causes damage to its structure and function. Pb neurotoxic effects include alterations in mitochondria, neurotransmitter receptors, cerebrovascular endothelial cells, astroglia, and oligodendroglia. It also induces cell apoptosis and causes an imbalance in neurotransmitter storage and release. Clinical manifestations of Pb neurotoxicity may be delayed or appear immediately after exposure. Symptoms include visual impairment, memory loss, cognitive and behavioral problems, and brain damage. Previous studies focused on the relationship between Pb exposure and neurocognitive diseases while current research studies have correlated between Pb exposure and other morbidities such as violence, delinquency, and antisocial behavior [31]. Pb exposure harms the brain, especially in children whose developing brains are highly affected by Pb exposure. Pb disrupts various aspects of brain development, including neurochemical development, synapse formation in the cerebral cortex, and the organization of ion channels. Additionally, Pb poisoning leads to neuron myelin sheath loss, reduction in neuron count, interference with neurotransmission, and decreased neuronal growth. Even in adults who have a history of elevated Pb exposure levels during childhood, there is evidence of reduced brain volume, especially in the prefrontal cortex as observed on MRI scans. Pb can penetrate the blood-brain barrier by substituting calcium ions and being transported by calcium-ATPase pumps which block synapse formation [32].

Recent meta-analyses have indicated a 1 to 5-point decline in IQ for every increase in BLLs by 10 μg/dL. A threshold for the Pb effects on IQ has not been reported, suggesting that cognitive function can be affected by even low levels of Pb exposure. Additionally, analysis of further studies has reported a relationship between children with BLLs below 10 μg/dL and impaired cognitive functions [33]. Moreover, for every 5–35 μg/dL increase in BLLs, there is a reported decrease of 2–4 IQ points in children. Elevated BLLs are also linked to diminished cognitive function and psychiatric conditions like depression and anxiety. Increased Pb exposure has been linked to antisocial behavior and attention deficit hyperactivity disorder (ADHD) in children. Prenatal and early childhood Pb exposure correlates with violent crimes in adulthood. In adults, an increase in BLLs from 50 to about 100 μg/dL is associated with permanent impaired function of CNS [34]. A previous study reported computed tomography (CT) results of 3 adults suffering from cerebellar and cerebral calcification who had been exposed to Pb for over 30 years, with admission BLLs ranging from 54 to 72 μg/dL. Various patterns of calcification including curvilinear, punctiform, and diffuse were observed in the basal ganglia, subcortical area, cerebellum, and vermis. These patients suffered from loss of visual acuity, dementia, and peripheral neuropathy [35].

Prolonged Pb exposure causes oxidative stress in vascular and endothelial smooth muscle cells causing persistent hypertension

(HTN) that may lead to atherosclerosis [36]. A previous study on rats showed that HTN in rats exposed to Pb was associated with decreased cGMP levels in plasma [37].

2.3. Impact of mercury exposure on nervous and cardiovascular systems

CH_3Hg is the primary compound of Hg that alters neurogenesis in experimental animals and humans. CH_3Hg causes a disruption of cell signaling leading to impaired cell proliferation. Changes in the proliferation of neural stem cells (NSC) cause decreased neuron numbers and microcephaly [38]. The molecular mechanisms underlying the disruption of cell proliferation by low Hg concentrations include inhibition of DNA synthesis, alterations in gene expression, disturbances in the homeostasis of intracellular calcium ion (Ca^{+2}), changes in protein phosphorylation, and increased neurodegenerative diseases associated with oxidative stress such as Parkinson's disease, Alzheimer, and amyotrophic lateral sclerosis. A previous study reported that pre-treating bovine cells with pyrroloquinoline quinone (PQQ), an antioxidant, mitigates CH_3Hg-induced cytotoxicity. PQQ lowers ROS generation, diminishes the proportion of apoptotic cells, inhibits lipid peroxidation, and enhances the antioxidant enzyme activity in CH_3Hg-exposed cells [38,39].

Exposure to different Hg compounds causes an increase in arterial blood pressure (BP). A previous study showed an elevation in pulse pressure, as evidenced by 24-h ambulatory blood pressure monitoring which was correlated with blood Hg levels in a cohort of Greenlanders who consumed more fish compared to a group of Danes [40]. Prenatal exposure to CH_3Hg from seafood consumption has been linked to increased BP in children. Exposure to different forms of Hg has been shown to increase oxidative stress which eventually produces ROS. Hg binds to selenium and molecules containing thiol, reducing the antioxidant enzyme activity and increasing cardiovascular disease risks [41].

2.4. Impact of cadmium exposure on nervous and cardiovascular systems

Exposure to Cd induces damage in cerebral micro-vessels associated with oxidative stress. This exposure initially triggers an increase followed by a subsequent decrease in micro-vessel enzymes involved in cellular redox reactions. Eventually, there is a depletion of antioxidant enzymes and an elevation in lipid peroxidation leading to micro-vessel damage. Additionally, Cd exposure prompts the induction of MT proteins, particularly MT-III in the brain, contributing to Cd accumulation in the choroid plexus. Also, neuronal toxicity induced by the activation of mammalian target of rapamycin (mTOR) and mitogen-activated protein kinases (MAPKs) signaling pathways leads to ROS induction, oxidative stress, and apoptosis of neuronal cells. Cd also disrupts intracellular calcium homeostasis, leading to apoptosis in various cells, including neurons. Cd may also block calcium influx through membrane channels into nerve terminals, altering transmitter release [42].

A previous study reported that when a rat brain endothelial cell line (RBE4) was exposed to Cd chloride ($CdCl_2$), the onset of oxidative stress was swift leading to the production of ROS, triggering an endoplasmic reticulum (ER) signaling cascade that broke down cytoskeletal and tight junction proteins in the blood-brain barrier (BBB). The study revealed a dual response to acute Cd exposure, with ROS levels peaking at 5 min, returning to baseline at 10 min, and then rising again after 2 h, indicating both short- and long-term oxidative stress reactions. Additionally, oxidative stress caused by exposure to $CdCl_2$ triggered an ER stress response followed by apoptotic protein caspase-3 increase and abnormal staining patterns for filamentous actin microfilament (F-actin), vimentin, and zonula occludens-1 (ZO-1) that are important for BBB integrity [42,43].

Once Cd diffuses to endothelial cells after disrupting their integrity, it primarily accumulates in smooth muscle cells. Its effects on these cells include disrupting ion balance, altering calcium ion flow, causing cell toxicity, and promoting smooth muscle cell proliferation leading to lipid buildup in vessel walls and changing lipid profiles towards a more atherogenic state. It also has the potential to inhibit endothelial nitric oxide synthase (NOS), which can lead to the suppression of acetylcholine-induced vascular relaxation, leading to HTN. Cd accumulation is associated with elevated levels of pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, and IL-8, exacerbating inflammation in atherosclerosis. A study on ApoE−/− mice indicates that chronic exposure to Cd increases total cholesterol levels and reduces nitric oxide (NO) availability. These findings highlight the potential mechanisms of atherosclerosis and cardiovascular damage caused by Cd [44]. A cross-sectional study on patients suffering from coronary artery disease (CAD) and peripheral artery disease (PAD) revealed that the accumulation of Cd could be considered a biomarker for the onset of symptomatic PAD in the lower extremities. The study indicated a spectrum of risks, ranging from low Cd burden in CAD patients to high Cd burden in CAD patients suffering from critical limb ischemia [45].

2.5. Impact of arsenic exposure on nervous and cardiovascular systems

As crosses BBB and accumulates in the brain leading to impaired brain function and increased risk for neurological disorders. Individuals exposed to As during early life usually suffer from cognitive impairment. These effects may not be immediately apparent but can manifest later in life, permanently affecting intellectual function and memory. As exposure has been linked to an increased risk of mood disorders, Parkinson's, and late-life Alzheimer's diseases [46]. As exposure is known to cause oxidative stress which can lead to mitochondrial dysfunction, alterations in proteins and DNA, changes in neurochemistry, and neuronal death leading to cognitive impairments. The high content of polyunsaturated fatty acid content and oxygen consumption of the brain make it a highly susceptible organ to changes in the redox environment upon As exposure [46–48].

As also alters the balance of neurotransmitters and synaptic plasticity in the brain, causing a decrease in dopaminergic receptor expression, dopamine levels, and its metabolites (homovanillinic and 3,4-dihydroxyphenylacetic acids); acetylcholinesterase activity and production are decreased; N-methyl-D-aspartate receptor (NMDAr) subunits NR1, NR2A, and NR2B are diminishedly expressed;

the α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid receptor (AMPAr) is also diminished [46]. The alterations of NMDAr and AMPAr expression indicate the effect of As exposure on synaptic plasticity and cognitive function. In vitro research highlights the impact of As exposure on CNS cells (including neurons, primary astrocytes, microglia, and brain microvascular endothelial) damage and its mechanisms [49]. As exposure has been found to decrease AMPAr expression in primary cortical neurons leading to an inhibition in neurite growth and differentiation [46].

Peripheral neuropathy can be caused also by chronic As exposure. A cross-sectional study was designed to conduct medical examinations on 1867 residents in Myanmar. Results showed that residents with As concentration in drinking water (ACDW) levels of 10 ppb or higher reported experiencing feelings of weakness and chronic numbness or pain more frequently than those with ACDW levels below 10 ppb. Residents with ACDW levels of 50 ppb or higher also exhibited three types of sensory disturbances more frequently than those with ACDW levels below 50 ppb [50].

As directly damages the heart and impairs the function of blood vessel lining cells as it modulates activator protein 1 (AP-1) and NF-κB proteins activities leading to disruptions in the production of inflammatory proteins including vascular cell adhesion protein 1 (VCAM-1) and TNF-α. Additionally, As impacts vascular function by reducing the availability of NO, inhibiting NOS, activating Nox2 enzyme, and promoting oxidative stress leading to oxidized lipids accumulation [51,52]. As was also found to cause heart damage via several routes, such as activating the signaling pathways for c-Jun N-terminal kinase (JNK), MAPK38, and epidermal growth factor (EGF), which in turn stimulates endothelial cell death. Additionally, it has been found that vascular damage occurs through the neurogenic release of substance P and activation of neurokinin 1 (NK-1) receptors. Lastly, direct harm to cells is caused by the inactivation of protein kinase B/Akt [51,52]. As has also been linked to potentially harmful effects on the heart, including QT prolongation leading to arrhythmias and ischemic heart disease. Studies have shown that As affects calcium and potassium currents in the heart causing an increase in the risk of QT prolongation. Additionally, As is toxic for peripheral blood vessels leading to ischemic heart disease. Chronic As exposure to high levels of As causes increased arterial stiffness, systolic blood pressure, and decreased diastolic blood pressure. Diseases like the Taiwanese “blackfoot disease” highlight the connection between As exposure and arterial diseases. Studies have also demonstrated a dose-response relationship between As exposure and the incidence of ischemic heart disease [51,52].

3. Analytical methods for determination of heavy metals

3.1. Sample preparation

Sample digestion can be done in several ways, falling into two categories: dry ashing method and wet digestion. In the dry ashing, the sample is burnt and the resultant ash is dissolved in nitric acid. The main drawback of this method is the high energy demand. In wet digestion, samples are combined with a potent acid and heated to create a clear solution. Microwave digestion is considered an advanced form of wet digestion and is known for its efficiency in saving time and energy. It involves subjecting the sample to microwave radiation in a controlled environment with a mineral acid [53].

3.2. Instrumental techniques

3.2.1. Atomic absorption spectrometry (AAS)

There are four key components of AAS: a light source, a light modulation, a sample atomization, and a light selection measuring system. The target element absorbs specific wavelengths produced by the light source (electrodeless discharge lamp or hollow cathode). The light modulation device (chopper) allows for accurate intensity variation monitoring by separating the released light from excited atoms in the sample cell. The sample atomization system uses thermal energy to change molecules into gaseous atoms that can absorb the necessary light energy. This system often consists of a flame, an electrically heated graphite furnace, or a heated quartz CDL. The light-selection measurement system manages wavelength selection, light intensity variance monitoring, electrical signal amplification, and data recording using components such as slits, monochromators, photomultiplier-amplifier systems, and read-out

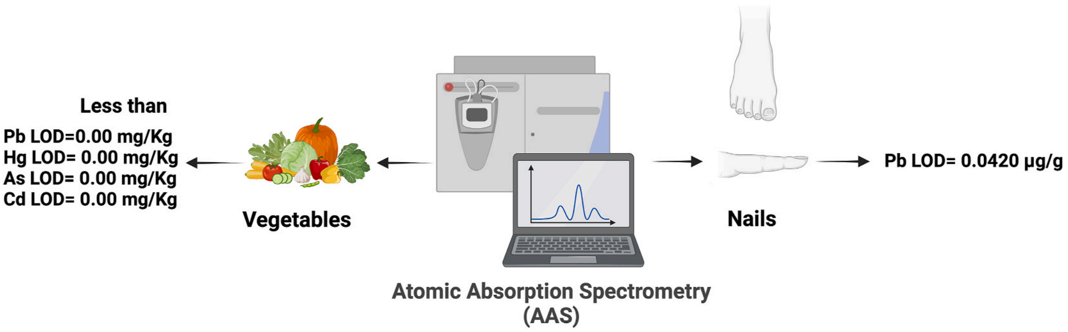

Fig. 2. Application of atomic absorption spectrometry in the detection of lead, mercury, cadmium, and arsenic in biological samples. A summary of the lowest reported limit of detection (LOD) of atomic absorption spectrometry (AAS) for lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (As) in various biological samples (vegetables, nails).

systems. The process of flame AAS involves aspirating a sample into a flame and atomizing it. The amount of light absorbed by the atomized element in the flame is measured by a detector, where a light beam is focused through the flame, into a monochromator, and then onto the detector. Worth noting, that the atomic absorption technique shows better sensitivity than flame emission for some metals [54]. An electrodeless discharge lamp or hollow cathode lamp, which emits the line spectrum of a particular element, is a common light source for AAS. Other components include a flame for sample vaporization, a monochromator filter and slip for isolating an absorption line, and a photoelectric detector with related electronic measuring and amplifying apparatus. To eliminate big droplets, the device additionally has a premix burner, which introduces spray into the condensing chamber. Various burner types can be employed, including a one-slot conventional head, a three-slot head for direct aspiration using an air-acetylene flame, and a specialized

Table 2
Comparison between different spectrometric techniques in the detection of lead, mercury, cadmium, and arsenic in biological and environmental samples.

Analytical method	Sample	Heavy metal	Detection limit	References
Atomic absorption spectrometry (AAS)				
Gas chromatography (GC) coupled to atomic absorption spectrometry (AAS)	Crops and vegetables	Lead (Pb), mercury (Hg), arsenic (As), and cadmium (Cd)	0.00 mg/kg	[57]
Graphite furnace atomic absorption spectrometry (GFAAS)	Nail	Pb	0.0420 μg/g	[59]
Inductively coupled plasma mass spectrometry (ICP-MS)				
Inductively coupled plasma mass spectrometry (ICP-MS)	Urine	Cd	0.06 ng/mL	[73]
		Pb	0.1 ng/mL	
		Hg	0.04 ng/mL	
Femtosecond laser ablation-inductively coupled plasma-mass spectrometry (fs LA-ICP-MS)	Brown rice	As	0.087 μg/kg	[76]
High-performance liquid chromatography (HPLC) with inductively coupled plasma mass spectrometry (ICP-MS)	Human serum and urine		0.3–1.5 ng/mL	[74]
	Blood		1.66–10 ng/mL	[77]
	Urine		0.5–10 ng/mL	
Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES)				
Inductively coupled plasma atomic emission spectrometry (ICP-AES)	Water	Pb	0.07 μg/L	[85]
	Glomerular mesangial cells	Cd	0.1 mg/L	[84]
	Freshwater	As	0.1 μg/L	[87]
Axially-viewed sequential ICP-AES in combination with ion exchange chromatography	A mixture of organic and inorganic arsenic compounds		10–20 μg/L	[86]
Hydride generation-microwave plasma atomic emission spectroscopy (HG-MP-AES)	Wine		43.8 mg/L	[88]
Atomic Fluorescence Spectrometry (AFS)				
Cold vapor atomic fluorescence spectrometry (CV-AFS)	Chinese medicine injections	Hg	0.061 mg/L	[92]
	Tobacco leaves		4.3 ng/L	[95]
Hydride generation atomic fluorescence spectrometry (HG-AFS)	Chinese herbal medicines		0.44 mg/mL	[93,94]
Vapor generation non-dispersive atomic fluorescence spectrometry (VG-AFS)	Chinese medicines		0.019 mg/L	
CV-AFS combined with combustion-AAS instrument	- Biological samples: Hair and nails - Environmental samples: raisins, coal, carrots, tea, tobacco, and tomato leaves.		2–1000 ng/g	[96]
	Blood		4.9 ± 1.5 ng/g	
Slurry CV-AFS	Human serum		25 ng/L	[99]
Chemical vapor generation atomic fluorescence spectrometry (CVG-AFS)	Canned sardines		0.33 ng/g	[102]
	Soil		0.00047 mg/kg	[103]
		As	0.53 mg/kg	
Hydride generation atomic fluorescence spectrometry (HG-AFS)	Wastewater		0.09 μg/L	[107]
	Sewage sludge		0.01 mg/kg	
	Poultry and calf meat		0.3 ng/g	[106]
Slurry sampling hydride generation (SLS-HG) system in conjunction with in-situ dielectric barrier discharge atomic fluorescence spectrometry (DBD-AFS)	Hair		14 pg/2 mL	[108]
	Real paramecium and micro diatom		8 pg/2 mL	
Cold vapor atomic fluorescence spectrometry (CV-AFS)	Tobacco leaves	Cd	2.8 ng/L	[95]
Vapor generation non-dispersive atomic fluorescence spectrometry (VG-AFS)	Chinese medicines		0.010 mg/L	[93,94]
Solid sampling electrothermal vaporization atomic fluorescence spectrometry (SS-ETV-AFS)	Grains and vegetables	Pb	50.2–223.8 μg/kg	[104]
Flow injection-hydride generation-atomic fluorescence spectrometry (FI-HG-AFS)	Blood, serum, and human plasma		0.117–10.25 μg/L	[105]
	Rain, tap, ground, spring, and drinking water		0.16–2.5 μg/L	

head designed for the use of nitrous oxide and acetylene [55]. To carry out analysis, a liquid sample is mixed with nitrous oxide and acetylene as well as other flammable gasses [56].

ICP-AAS has been used in detecting several heavy metals in biological and environmental samples as shown in Fig. 2 and Table 2. In a study that used gas chromatography (GC) in addition to AAS in identifying heavy metals, such as Pb, Hg, As, and Cd in Nigerian crops and vegetables, it was found that the heavy metals were within the accepted range with LODs of 0.00 mg/kg for the mentioned heavy metals [57]. In another study done in eastern Sudan, they considered gender variations and the results showed a stronger association between nail element levels in areas such as Port Sudan and Jabiat as well as a high degree of Pb environmental contamination [58]. In a study done on measuring Pb in human nail samples that were analyzed using GFAAS, Pb in the nail matrix was 0.0420 μg/g [59].

In addition to the previously mentioned biological samples, health hazards associated with exposure such as Pb, Cd, and Hg were assessed in agricultural soil in a previous study on 29 sites throughout Tuzla Canton, Bosnia, and Herzegovina. The study demonstrated Pb being more hazardous than Hg or Cd [60]. In a study on groundwater As levels in Bangladesh and West Bengal, AAS-VGA is used to measure total As levels. Sample preparation involves reduction with sodium borohydride and 10 M HCl. Acid concentration is important for sensitivity. A modified approach can reduce acid concentration and analysis time. Various analytical techniques are used for As quantification, with AAS-VGA being ideal for sensitive measurements. Neutron activation provides analysis at the ppt level but is costly. Speciation of As affects outcomes, with As(III) easily detected and As(V) requiring reduction to As(III) for measurement. AAS-VGA can detect total As by pre-reducing samples with KI or adding KI with sodium borohydride in the reduction channel [61]. Hydride generation is a common method used along with AAS to increase sensitivity in As detection instruments by creating As(III) hydroxide through a chemical reaction with sodium tetrahydroborate. However, using this method indiscriminately can compromise measurement accuracy. It is important to match standards to sample materials as the chemical form of As species greatly affects reaction efficiency and signal response. Transforming As compounds in samples to As(III) or (IV) salts is necessary to ensure accurate measurements. Certain organic molecules, especially those found in marine life or animal samples, are acid-resistant and may not fully break down during digestion. Failure to ensure the destruction of As compounds could lead to inaccurate analytical results using HG [62].

3.2.2. Inductively coupled plasma mass spectrometry (ICP-MS)

ICP-MS is used for the identification of a broad range of elements, including heavy metals. Plasma ionizes the sample, and ions are directed into ion optics, which directs them to the quadrupole mass analyzer to be sorted by their *m/z*. ICP is a "tough" ionization method compared to others like electrospray, and typically uses argon plasma, though helium is also used despite its cost. It can detect ultra-low amounts of elements at or below the part per trillion (ppt) range and perform isotope analysis [63–65]. Plasma is generated within the torch, which has three concentric quartz tubes. Argon gas flows through these tubes, with the innermost transporting the sample aerosol to the plasma. A copper induction coil connected to a radio frequency generator powers the torch, creating a high-temperature plasma (around 10,000 K). The stages of ICP-MS include ionization, interface, ion optics, mass analysis via the quadrupole, and detection [64,66,67]. After nebulization, the sample enters the plasma, vaporized, atomized, and ionized. Most elements form singly charged positive ions, but some may form doubly charged ions [64,66]. The interface stage uses two cones to separate the plasma from the vacuum chamber, allowing ions to pass into the mass analyzer. Electrostatic lenses behind the skimmer cone focus the ion beam while blocking neutral molecules from reaching the detector [67]. Using alternating and direct current potentials, the quadrupole mass analyzer separates ions based on their *m/z* ratio. Ions that follow a stable path are detected, while

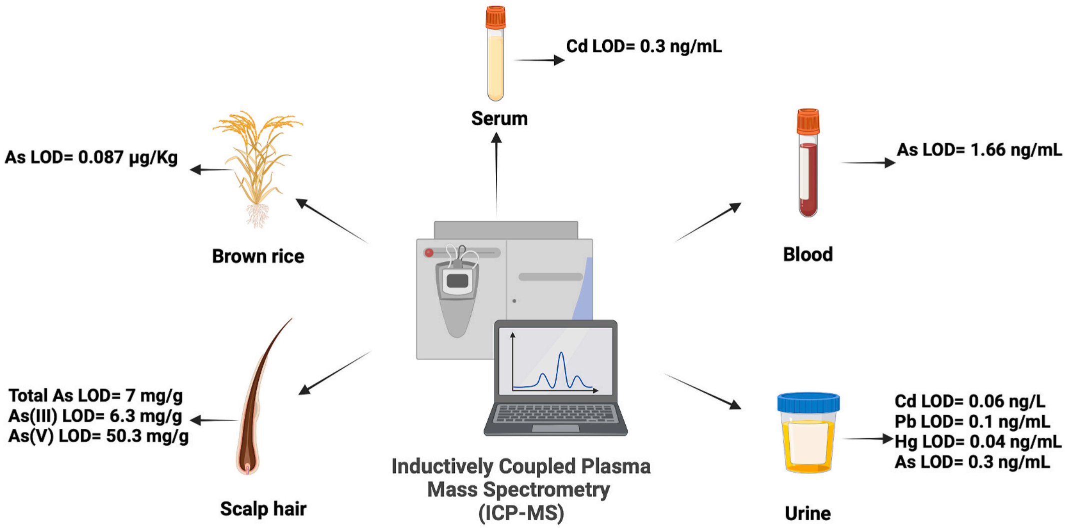

Fig. 3. Application of inductively coupled plasma mass spectrometry (ICP-MS) in the detection of lead, mercury, cadmium, and arsenic in biological samples. A summary of the lowest reported limit of detection (LOD) of Inductively coupled plasma mass spectrometry (ICP-MS) for lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (As) in biological samples (brown rice, scalp hair, blood, serum, and urine).

unstable ions crash into the rods. The detector amplifies the signal through secondary electron emission, providing high analytical sensitivity. ICP-MS offers detection limits in the nanomoles per liter range, influenced by various factors like the element, sample matrix, and operational parameters [66,68].

Since ICP-MS can study a wide spectrum of elements in addition to operating at lower temperatures, it is a better alternative than methods such as flame atomic absorption in studying refractory elements in oxide form. ICP-MS has rapid analysis, high sensitivity, outstanding spectral resolution, and multi-elemental technique and is known for having a pure spectrum. In addition to the previously mentioned advantages, it has specific benefits for detecting particles in terms of size and mass distributions, concentrations, stoichiometry, particle-matrix interactions, stability, dissolution, toxicity, biosafety, and destiny [69,70].

ICP-MS has been applied in heavy metal detection in different biological and environmental samples as shown in Fig. 3 and Table 2. ICP-MS was used in a study by Clases et al., in 2022 to examine water samples taken from two different lakes. In this study, they determined the concentrations of eight elements, including Cd [71]. This technique is good at detecting trace element abnormalities in newborns and infants suggesting potential detection of heavy metals in serum or whole blood for metals such as Cd, Pb, and Hg [72]. In a previous study published in 2020, urine and blood samples were collected from 1040 Puerto Rican pregnant women to screen for 16 metals using ICP-MS. Cd, Pb, and Hg were detected with a LOD of 0.06, 0.1, and 0.04 ng/mL in urine, respectively. The study discovered that most individuals have greater metalloid concentrations than the overall female population compared to the United States. Certain metalloids are accurate biomarkers of exposure, including Hg in blood. Various metal and metalloid indicators were linked to factors including consuming rice and seafood and using tap water [73].

The analysis of As compound speciation in urine and serum samples from Vietnam was conducted using high-performance liquid chromatography (HPLC) with ICP-MS as an elemental-specific detector. The five species of As examined were As(III), As(V), As(MMA), As(DMA), and arsenobetaine (AsB). The separation of these As species was achieved through chromatography with a gradient elution of ammonium carbonate, ethylenediaminetetraacetic acid disodium salt, and methanol at pH 9.0 utilizing a Hamilton PRP-X100 strong anion-exchange column. Samples of serum and urine underwent protein precipitation with trichloroacetic acid and solvent dilution for this investigation. In the analysis of the urine matrix, extraction efficiency exceeded 91 %, and recoveries of As species in human serum samples spiked with contaminants ranged from 94 % to 139 %. LOD and method quantitation limit (MQL) were determined to be 0.3–1.5 and 1.0–5.0 ng/mL, respectively, based on signal-to-noise ratio assessments [74].

In another study on biological samples, researchers identified and quantified six As compounds in seafood using advanced analytical methods. As species were extracted using microwave-assisted extraction and separated and quantified using ion exchange chromatography in combination with ICP-MS. Ammonium carbonate-based buffers were utilized to minimize interference with ICP-MS sensitivity, replacing commonly used phosphate buffers. These techniques are simple to implement, cost-effective, and suitable for the regular analysis of total As content and species in trace and ultra-trace levels across a range of seafood products [75].

In addition to the previously mentioned biological samples, there has been previous research on staple crops such as rice in Asian nations like China, Korea, and Japan to detect As. In this study, a quadrupole ICP-MS was used to measure the total As level of 200 white and 104 brown rice samples that were collected in Korea. A sample of rice grains was polished to 3, 5, 7, 9, and 11 degrees of milling, and the variation in As concentration between the outside and inner core regions was examined. Furthermore, femtosecond laser ablation-inductively coupled plasma-mass spectrometry (fs LA-ICP-MS) was used to determine the spatial distribution of As over the cross-section of a brown rice grain. LOD and LOQ values were estimated at 0.087 and 0.290 μg/kg, respectively [76]. Moreover, studies have developed analytical techniques utilizing high-performance liquid chromatography-inductively coupled plasma-mass spectrometry (HPLC-ICP-MS) for the detection of six As compounds (AsC, AsB, As (III), DMA, MMA, and As (V)) in blood and urine, and applying this method to real-life situations. Cell damage was induced with Triton, followed by complexation of As compounds using EDTA·2Na·2H_2O. The sample underwent pretreatment with sonication and protein deposition using acetonitrile. As compounds were extracted from the samples using gradient elution with ammonium carbonate and ultrapure water mobile phase, then analyzed using ICP-MS with a Hamilton PRP-X100 column. The study found that the lower blood quantification limits ranged from 5 to 30 ng/mL, with detection limits between 1.66 and 10 ng/mL. In urine, the lowest limits of quantification were 5–30 ng/mL, with detection limits of 0.5–10 ng/mL [77]. HPLC-ICP-MS is also reported in a study where it has been used in detecting hexavalent chromium (Cr(VI)) and inorganic As (iAs) in a liquid resulting in a severe poisoning incident. In this unique case, a liver transplant was deemed necessary for treatment. Procedures were developed and put into practice for utilizing ICP-MS to measure total Cr, As, and Cr (VI) levels in erythrocytes and blood, plasma, urine, and liver tissue. Identification of iAs species and their metabolites in urine through anion exchange HPLC-ICP-MS facilitated the diagnosis of iAs exposure. After consuming the liquid for three days, the entire blood and plasma had total Cr concentrations of 2180 and 1070 μg/L, respectively, while the erythrocytes had 4540 μg/L Cr(VI). The blood's As content was 206 μg/L. Urinary As species concentrations for arsenobetaine, As (III), As (V), methylarsonate (V), and dimethylarsinate (V) were <0.5, 109, 115, 154, and 126 μg/L, respectively. The explanted liver had total amounts of As of 0.9 mg/kg. Additional analytical findings from this case study are tallied, offering toxicologists and doctors useful information [78].

In human scalp hair, analytical techniques have been established for the determination of total As and As species, primarily As(III) and As(V). Total As and As species have been determined using ICP-MS and HPLC linked to ICP-MS, respectively. A "green", quick, highly effective, and automated pressurized hot water extraction (PHWE) species leaching process was one of the suggested methods. A concentration of 150 mM acetic acid and powdered hair samples thoroughly mixed with diatomaceous earth (DE) at a DE mass/sample mass ratio of 5 were recommended for best results. The extraction process involved four steps carried out in 5 min at 100 °C and 1500 psi of pressure. LOQ achieved were 7.0, 6.3, and 50.3 mg/g for total As, As(III), and As(V), respectively, under optimized conditions. The overall repeatability of the process was found to be 4.4 %, 7.2 %, and 2.1 % for total As, As(III), and As(V), respectively. Validation was conducted using GBW-07601 (human hair) reference material. The optimized procedure has now been successfully applied to several human scalp hair samples [79].

Over the last thirty years, ICP-MS has become a major tool in the field of current equipment advances. Even in small amounts, this extremely sensitive approach allows for the exact identification of the elemental composition in samples. These days, a broad spectrum of entities use it for analysis, which includes the examination of different chemical components in a variety of matrices, including water, rocks, soils, stone materials, and organic materials [71].

3.2.3. Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES)

One often-used method in emission spectroscopy is ICP-AES, sometimes referred to as ICP-optical emission spectrometry (OES). To deal with aqueous aerosols efficiently and to provide high energy for the analytes' atomization, ionization, drying, and dissociation, an argon-based plasma is employed. An argon ICP can reach temperatures of 5500–6500 K, which is high enough to ionize a wide range of elements. A high atomization yield and general high sensitivity are the results of this high excitation level. A spray chamber to filter out droplets larger than a specific size and a pneumatic nebulizer for aerosol generation are common components of an ICP setup. Due to the possibility of interferences from matrix components, a comprehensive evaluation is required to ensure precise outcomes. ICP-AES is a flexible analytical method that may identify several elements at once, however elemental speciation frequently uses it as a single-element detector. Because of its capacity to manage a continuous eluent flow, it can be seamlessly integrated online with Liquid Chromatography (LC). Nevertheless, there are several limitations to take into account, like the nebulizer's inefficiency and the plasma's susceptibility to organic solvents. The technique's usefulness may be limited by common mobile phases such as ion-pair reagents, which can also alter the plasma source. Furthermore, particular techniques are required to handle any variations in the analyte response during elution due to the varied nature of ion exchange chromatography elutions [80,81].

Even at extremely low concentrations in the ppb range, this technique is very successful and capable of detecting a wide spectrum of elements, allowing the simultaneous identification of up to seventy elements. It does not require multiple sets of calibration standards for sample preparation. Also, it offers many advantages compared to AAS, by guaranteeing that both the wet-ashed sample and calibration standards are prepared in a similar acid concentration. ICP-AES also permits interelement adjustments that improve analytical accuracy. However, the applicability of this technique in analyzing biological samples is still not guaranteed in terms of its repeatability and dependability, therefore it's rarely used for trace element investigation in the biomedical fields [82].

This approach has been applied in heavy metal detection in different environmental samples as shown in Fig. 4 and Table 2. Trace toxic elements such as Pb and Cd could be quantitatively determined using this method. ICP-AES was used to analyze minerals in a different investigation in which gum samples were dissolved at 180 °C in concentrated hydrochloric and nitric acids. Another study was conducted to analyze heavy metals, including Pb and Cd, in the wastewater of Kocabas Stream using ICP-AES. Samples were taken from nine stations along the Biga-Kocabas Stream for analysis using ICP-AES. Each sample's analysis was finished in around 15 min. The heavy metal contents in the wastewater samples ranged from 0.00001 to 77.69610 mg/L. The concentrations of Pb and Cd were 0.00001–0.0087 mg/L, respectively [83]. In another study, trace amounts of Pb were measured with LOD = 0.07 μg/L in water, and on soil samples switchable hydrophilicity solvent-based extraction (SHSE) in conjunction with ICP-AES was used. To evaluate Cd uptake in glomerular mesangial cells ICP-AES was used and successfully detected Cd in 0.3 mg/L with LOD = 0.1 mg/L [84,85].

As speciation can be efficiently conducted using HPLC and ICP-AES detection. The use of axially-viewed sequential ICP-AES in combination with ion exchange chromatograph allowed an effective separation of As(III), As(V), DMA, and MMA in a mixture of organic and inorganic arsenic compounds. A thorough investigation of the interface was conducted post-adjustment of chromatographic parameters such as pH and mobile phase concentration. Evaluation of three spray chambers and five nebulizers revealed the importance of selecting the appropriate nebulizer and spray chamber for optimal ICP reaction, while still maintaining consistent responses for all As species. The utilization of a cyclone spray chamber with a micro concentric nebulizer yielded the highest signal-to-noise ratios without compromising chromatographic resolution. Detection limits of less than 10 μg/L were achieved for As(III), DMA, MMA, and 20 μg/L for As(V), representing a significant enhancement compared to previous findings [86].

A flow-based method was developed along with ICP-AES to simultaneously detect As(III) and As(V) in freshwater samples. As

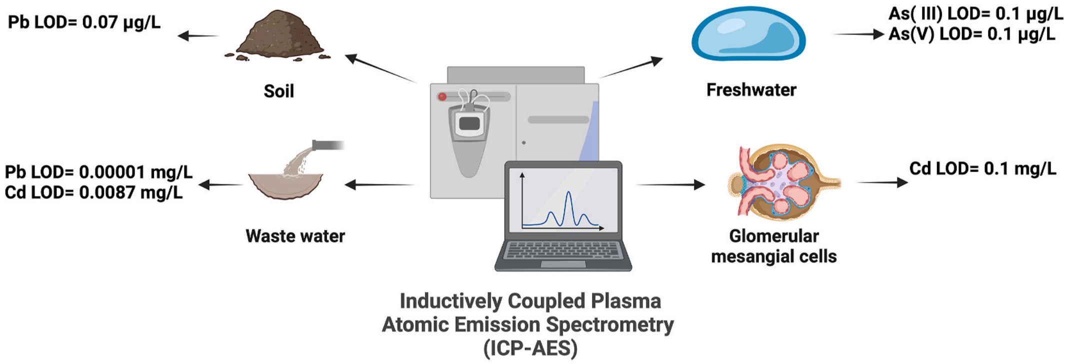

Fig. 4. Application of inductively coupled plasma atomic emission spectrometry (ICP-AES) in the detection of lead, mercury, cadmium, and arsenic in biological and environmental samples. A summary of the lowest reported limit of detection (LOD) of Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES) for lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (As) in biological samples (mesangial cells) and environmental samples (freshwater, wastewater, and soil).

species were collected and concentrated using solid phase anion exchange resin in micro columns. As(III) could be converted to As(V) with an oxidizing agent and then eluted with 2M nitric acid for analysis by ICP-AES. Potassium permanganate was explored as an oxidizing agent. Repeat analysis showed standard deviations of 3 % for As(III) and 5 % for As(V), with a detection limit of 0.1 μg/L for both species. The system performed well in analyzing inorganic As species in freshwater samples [87].

A novel analytical method known as hydride generation-microwave plasma atomic emission spectroscopy (HG-MP-AES) was utilized to assess the overall As levels in forty wine samples from California. Before analysis, As species were reduced with potassium iodide, resulting in the detection of gaseous As trihydride. The method's detection limit was determined to be 0.38 mg/L. Various wine styles (including white, rose, red, Port, and sparkling) were tested, revealing total As levels ranging from below LOD to 43.8 mg/L. This innovative approach enables rapid and precise quantification of total As content in different wine styles, even below the EPA drinking water standard of 10 mg/L [88].

3.2.4. *Atomic fluorescence spectrometry (AFS)*

AFS is considered one of the emission spectroscopy techniques used in the quantitative analysis of heavy metals. AFS consists of five major components: a light source, an atomization system, a spectroscopic system, a detecting system, and a display device. In brief, the sample is converted into atomic vapor by an atomizer followed by light absorption at a specific wavelength. Light absorption stimulates atoms' transition from their ground to an excited state for 8–10 s followed by fluorescence emission at the same or different wavelength. Then a photoelectric detector converts this fluorescence into an electrical signal, which is processed by a data processing system to generate readable data [89,90]. Cold vapor atomic fluorescence spectrometry (CV-AFS) and hydride generation atomic fluorescence spectrometry (HG-AFS) are two subtypes of AFS. AFS exhibits many advantages, including high sensitivity, low LOD (especially for Cd), a wide linear range, minimal spectrum interference, simple spectral lines, high accuracy (comparable to AAS), and the ability to simultaneously analyze multiple elements. Also, AFS is a more cost-effective and simpler technique compared to AAS. Research shows that AFS is often combined with chromatographic methods to analyze trace and ultra-trace elements in plants and assess their chemical compositions [89].

AFS has been applied in heavy metal detection in different biological and environmental samples as shown in Fig. 5 and Table 2. The technique sensitivity is enhanced through coupling with HG as the HG separates the target analyte from the matrix for hydride generation under ambient conditions [91]. CV-AFS can be used to quantify Hg in different samples including traditional Chinese medicine injections by utilizing cold Hg vapor at room temperature with Hg LOD of 0.061 mg/L [92]. Additionally, the HGAFS method has been developed with a recovery rate of 94.7–105.4 % and LOD at 0.44 mg/mL for detecting small amounts of Hg in Chinese herbal medicines. Also, Intermittent flow in vapor generation non-dispersive atomic fluorescence spectrometry (VG-AFS) was used in

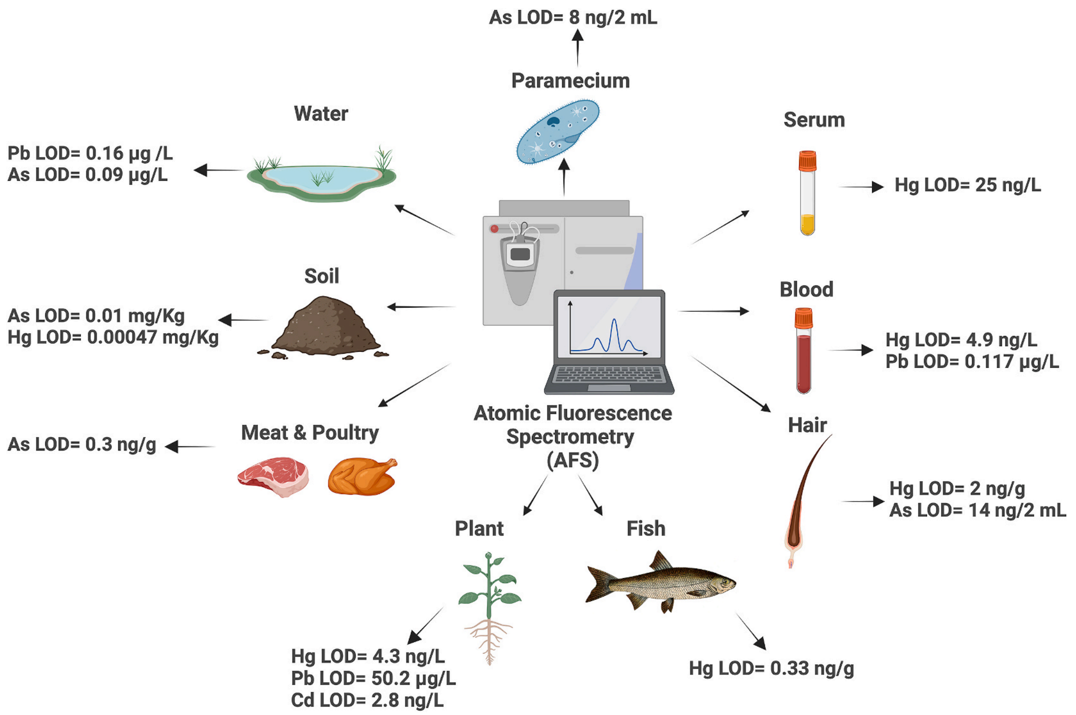

Fig. 5. Application of atomic fluorescence spectrometry in the detection of lead, mercury, cadmium, and arsenic in biological and environmental samples. A summary of the lowest reported limit of detection (LOD) of atomic fluorescence spectrometry (AFS) for lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (As) in various biological samples (blood, serum, hair, plant, fish, meat, poultry, paramecium, and diatom) and environmental samples (water and soil).

detecting trace amounts of Hg and Cd in Chinese medicines. In this technique, Ascorbic acid, cobalt ion, and thiourea were used as masking agents to enhance the generation of volatile species of Cd and Hg. The LOD for Cd and Hg were found to be 0.010 mg/L and 0.019 mg/L, respectively [93,94].

In a previous study, the CV-AFS method was used to detect Hg and Cd in tobacco leaves in which an updated atomizer was implemented to improve signal stability. The samples were chemically treated with HNO_3 for microwave-assisted digestion followed by the addition of thiourea and nickel(II) to enhance sensitivity. Concentrations of Hg and Cd in tobacco leaves were successfully identified using this approach with LODs of 2.8 ng/L and 4.3 ng/L for Cd and Hg, respectively [95].

A series of steps must be followed to accurately quantify Hg using CV-AFS. First, samples must be digested to convert all Hg species to Hg^{+2} in solution, then adding a reducing agent to produce Hg^0, followed by utilizing a gas-liquid separator to separate the Hg^0 from the solution, drying the carrier gas and concentrating the Hg on gold cartridges, quick heating to release the Hg from the gold trap, and finally detecting the Hg^0 through CV-AFS as it passes through the fluorescence cell within the inert gas. Automated sample combustion is recommended to eliminate the first three steps and reduce both analysis time and contamination risk. However, commercially available combustion-AFS systems are currently not available [96]. In a previous study, a combination of two commercially available instruments, a CV-AFS system, and a combustion-AAS instrument, was used to quantify Hg in biological samples including hair, nails, and blood in addition to environmental samples including raisins, coal, carrots, tea, tobacco, and tomato leaves in their fresh state. The combustion-amalgamation technique measured Hg in these samples in a range of 2–1000 ng/g. Blood samples of 0.5–1 mL were deposited onto filter paper cards, allowing for the measurement of an AFS signal. Hg was successfully detected in the blood-spotted filter paper in 4.9 ± 1.5 ng/g which falls within the range reported by the CDC for adult females aged 16–49, suggesting that quantitative analysis is achievable in samples with low concentrations or limited volumes [96,97]. Unlike acid digestion methods, the combined system effectively isolates Hg from the sample matrix and eliminates potential contamination, systematic bias of results, and loss of analyte during sample preparation [96].

The precision of Hg measurements can be affected by extensive and time-consuming sample preparation methods such as dry-ashing, block digestion, or microwave-assisted acid digestion. Slurry sampling is a practical solution in this context. Slurries enable the direct measurement of Hg using AFS, as they consist of solid dispersions in a liquid phase that can be easily delivered as solutions. This method reduces Hg loss caused by volatilization by eliminating the need for sample breakdown using wet or dry treatment processes, thus reducing analysis time, and minimizing contamination risks [98,99]. The use of slurries also allows for improved LODs and simplifies sample pre-treatment for both organic and inorganic materials. A novel slurry-based method utilizing CV-AFS has been developed for the precise and sensitive measurement of Hg in human serum blood samples. LOD for this method was determined to be 25 ng/L [99].

Chemical Vapor Generation Atomic Fluorescence Spectrometry (CVG-AFS) is also used for heavy metal measurement in samples for its sensitivity, specificity, safety, cost-effectiveness, and minimal consumption of argon gas [100]. When employing a spectro-analytic technique to analyze the components in food samples, such as fish, it is essential to undergo a sample preparation phase [101]. The acid digestion method utilizing a digester block is a simple, cost-effective, and versatile approach that can be applied to a variety of samples. Moreover, it allows simultaneous digestion of many samples. However, these methods are not suitable for the identification of volatile components. The “cold finger” reflux mechanism can be used to address this issue to make the sample preparation technique more suitable by enabling the condensation and reflux of the acid used for digestion and volatile species [102]. This modification allowed effective and efficient measurement of Hg in fish samples (canned sardines) using CVG-AFS. It demonstrates high levels of precision and accuracy, with quantification limits suitable for the low concentrations of Hg found in the samples (LOD = 0.33 ng/g). Using the acidic digestion method in the digester block with a cold finger reflux system is considered a cost-effective procedure that prevents analyte loss through volatilization. This method has the potential to be applied to the analysis of larger sample quantities [102]. Another study developed a novel one-time digestion method for analyzing As and Hg in the presence of other elements in soil samples after being ingested using a complex open system of aqua regia, hydrofluoric acid (HF), and H_3BO_3. The concentration of As and Hg was measured using CVG-AFS with LOD = 0.53 and 0.00047 mg/kg; respectively. This digestion method simplifies the process by avoiding the need for individual element processing, saving time, and increasing efficiency. It offers broad applicability, high sensitivity, and low LOD, making it a valuable tool for monitoring and controlling heavy metal pollution in large-scale geological samples [103].

Solid sampling electrothermal vaporization atomic fluorescence spectrometry (SS-ETV-AFS) is a reliable method for measuring Pb due to its minimal spectrum interferences. In this technique, solid samples are introduced into an ashing furnace and heated till ashing at 850 °C for 160 s to eliminate their content of organic components. Then, the samples are dried at 100 °C for 10 s to remove any remaining moisture. The remaining residue containing Pb is then vaporized through electrical heating at 1050 °C for 80 s in the vaporizer. Subsequently, the vaporized Pb is removed and trapped to separate any remaining matrix components [104]. In a previous study, this technique, compared to ICP-MS, was used to measure Pb content in grains and vegetables. Both techniques detected Pb levels within the range of 50.2–223.8 μg/kg. SS-ETV-AFS was found to be a more efficient method for Pb determination in food compared to microwave digestion ICP-MS. The analysis took almost 6 min and eliminated the need for chemical reagents and digestive pretreatment. So, SS-ETV-AFS reduces environmental pollution, lowers analytical costs, and is safer for operators. Therefore, SS-ETV-AFS is recommended as the preferred method for quick and on-site food detection [104].

Flow injection-hydride generation-atomic fluorescence spectrometry (FI-HG-AFS) utilizes potassium ferricyanide as an oxidant reagent to accurately measure trace amounts of Pb in different environmental and biological samples. This method is optimum for routine Pb analysis due to its simplicity, cost-effectiveness, wide linear range, excellent reproducibility, low detection limit, and elimination of pre-concentration steps [105]. In a previous study, FI-HG-AFS was applied to measure Pb content in various biological (blood, serum, and human plasma) and water (rain, tap, ground, spring, and drinking water) matrices. Spike/recovery experiments were performed at different levels of Pb content to determine matrix interferences in real samples. Pb recovery percentages in water samples ranged from 94 % to 108 %, with LODs between 0.16 and 2.5 μg/L. In biological samples, Pb recoveries ranged from 95 % to 110 %, with LODs between 0.117 and 10.25 μg/L. Overall, the technique has shown high accuracy and reliability in detecting trace levels of Pb [105].

In a previous study, the HG-AFS method was utilized to determine total As levels in poultry and calf meat samples after being digested using a mixture of concentrated H_2SO_4, HNO_3, and $HClO_4$. The method showed As LOD of 0.3 ng/g 31 samples of chicken, turkey, and calf from local markets were analyzed. It was observed that the average As concentration in calf meat (12.1 ± 3.9 ng/g) was higher than in poultry samples, while the concentrations in turkey and chicken were almost similar 3.1 ± 1.2 and 2.8 ± 1.1 ng/g, respectively [106]. In another study, the HG-AFS method was used to analyze total As in China's wastewater and sewage sludge samples. The samples underwent complete digestion with a mixture of HNO_3 and $HClO_4$ and a pre-reduction of As forms to As(III) was achieved with a solution of 1 % thiourea and 1 % ascorbic acid. Total As content was determined with LOD of 0.09 μg/L in wastewater and 0.01 mg/kg in sewage sludge with recovery rates falling within 91.0–102.0 % [107].

In a study conducted in China, biological samples that includes microbiological (real paramecium and micro diatom) and hair samples were analyzed for As content using a slurry sampling hydride generation (SLS-HG) system conjugated with in situ dielectric barrier discharge atomic fluorescence spectrometry (DBD-AFS). Sample preparation included a simple dilution of the slurry with 5 % HCl (v/v). Then, KBH_4 in KOH was used to generate arsenite from the diluted slurry in the SLS-HG unit. The in situ DBD apparatus was utilized to pre-concentrate As, enhancing the sensitivity of the HG-AFS and reducing interferences from dilution effects and matrix separation. The method achieved LOD of 8 pg and 14 pg (2 mL sampling) for microbiological and hair samples, respectively, under optimal conditions without extra pre-concentration required in some other techniques like HG-AFS. The spiked recoveries for paramecium and micro diatom samples were between 93 and 102 %. In comparison to commonly utilized analytical methods requiring digestion pretreatment, This SLS-HG-in situ DBD-AFS method demonstrated elevated analytical sensitivity, did not require digestion, was rapid, and was easily operated for the analysis of As in biological samples [108].

4. Rehabilitation of heavy metals

Due to the significant environmental threats posed by heavy metal pollution on living organisms in different ecosystems, researchers and scientific communities are under pressure to develop innovative technologies for treating wastewater and soil sources, promoting sustainable practices for anthropogenic activities including industry and agriculture. In this section, we review methodologies and techniques for removing heavy metals from contaminated soil and wastewater. Regarding rehabilitation of heavy metals from wastewater resources, there are various mechanisms such as adsorption (including electrosorption, electrochemical adsorption, and activated carbon), bio adsorbents, precipitation, filtration, ion exchange, and nanotechnology [2].

Adsorption techniques rely on the availability of active sites for the removal of heavy metals which is directly proportional and specific to the surface area of the adsorbents. For electrosorption methods, heavy metal ions are attracted towards the oppositely charged surface of the carbon electrode. The activated carbon/biochar has also been recognized as one of the efficient removal methods from wastewater, where biochar, such as rice husk can be modified with synthesized hydrogel-biochar complex to enhance its efficiency, stability and sorption capacity. Bioadsorbents such as microorganisms, though, are more eco-friendly and relatively cost-effective, for example, the removal of As can be achieved via specific types of fungi as well as *Bacillus Asus* complexes with $MnFe_2O_4$ that form a biofilm on Neem leaves which further scavenges trivalent and pentavalent As ions [20]. Other types of absorbents involve the use of minerals such as silica, zeolite, and clay. These are well recognized adsorbents, which are used in the purification of water with economical advantage. It is widely reported that clay has an exceptional capacity and selectivity for separation by cation exchange, hydrophilicity, and surface electronegativity. Moreover, its absorption power was found to be greatly enhanced with increasing the pore size, volume and surface area through heat treatment, washing with acids and pillar bearing. Also there are magnetic adsorbents, which are made of iron nanoparticles, for example iron oxides (hematite (α-Fe_2O_3), maghemite (γ-Fe_2O_3), magnetite (Fe_3O_4), embedded on a matrix base material such as carbon, CS, polymers, starch, or biomass. They are known for their high efficiency in metal ion removal from wastewater sources with multiple advantages such as low-cost, simple synthesis, high surface charge, and ability to be reutilized. Nevertheless, some environmental conditions can affect the absorption process such as pH, irradiation time, adsorbent concentration, wastewater temperature, and the initial dosage of pollutants [109]. Precipitation can be also employed to remove heavy metal ions from wastewater through the formation of stable compounds after chemical treatment, such as the removal of As from smelting water where crystalline scorodite is formed after the addition of iron salts and Ca (ClO_z) achieving 99.4 % removal efficiency [110]. The chemical treatment for metals precipitation can be also achieved using hydroxides such as lime or sodium hydroxide, which are alkaline reagents that decrease the solubility of the metal ion by elevating the pH of the solution, and therefore, a precipitate is formed. The advantages of this technique are widely described as being of low costs, easy and robust procedures due to the good control over pH in the reaction environment. Another example for efficient metal precipitation processes involve the use of sulfides such as sodium sulfide (Na_2S), sodium hydrosulfide (NaHS), calcium sulfide (CaS), barium sulfide (BaS), iron sulfide (FeS), ammonium sulfide ($(NH_4)_2S$), and sodium thiosulfate ($Na_2S_2O_3$). The use of sulfides is sometimes preferred over hydroxides because of the lower solubility of the sulphide metal compounds than hydroxide precipitates. Moreover, unlike hydroxides, they are not amphoteric and can efficiently remove metals in a shorter time over an extended pH range [111].

Finally, one of the most promising rehabilitation techniques involves the utilization of nanofiltration technology, where a polyamide core-shell surrounded with bio-functionalized matrix membrane developed with different quantities of C–S BF nanoparticles that can remove both As and Selenium (Se) ions, with an efficiency of 99 % and 98 % respectively [112]. Phytoremediation is one of the crucial techniques to overcome heavy metal-contaminated soil. This technique is environmentally friendly and can be implemented at a relatively low cost. The technique of phytoremediation relies on using certain types of plants that are capable of removing heavy metal pollutants from the soil and consequently overcoming their hazardous effects on the environment. Phytoremediation techniques can be employed via phytoextraction, phyto-filtration, phytostabilization, phytovolatilization or phytodegradation. The first type is phytoextraction, which refers to the absorption and accumulation of pollutants in the different plant organs such as roots, stems, and leaves. Secondly, phyto-filtration utilizes plant roots to remove heavy metals from wastewater through absorption, precipitation, and accumulation [113]. Thirdly, phytostabilization refers to the reduction of heavy metals bioavailability in soil, where the metals become stabilized in the rhizosphere through plant root adsorption and physical immobility of the soil. Recent research suggests the use of commercially available, metal-tolerant plants for phytostabilization such as *Lolium perenne* L. These species are capable of the efficient removal of Zn, Pb, and Cd, which leads to the reduction of heavy metals toxicity on plants, and therefore the fertility of polluted soil could be recovered [114]. Fourthly, phytovolatilization occurs upon the absorption of the heavy metals by the plant and then it gets released through the leaves into the air and occasionally degrades before being released through the leaves. Finally, phytodegradation utilizes metabolic pathways for the heavy metals degradation in the plant tissue via enzymes such as oxygenase, reductase, and dehalogenase [113].

Moreover, there are emerging innovative technologies such as nano-remediation which refers to the application of engineered or biogenic, nano-sized materials to enhance the efficiency of removal of heavy metal contaminants from soil and water. The advantages of these developed materials are correlated to some interesting characteristics, such as high surface-to-volume ratio, high efficiency, and reduced cost which further enhance their versatility and selectivity. The optimized performance of the nanomaterials can be achieved by customizing the surface area as well as the physicochemical properties via applying biopolymers as coating materials such as ethylene glycol or starch. Furthermore, the biogenically generated nanomaterials (e.g. by plants, bacteria, algae, or fungi) are widely evaluated [115,116]. In practice, the distribution of nanomaterials is performed by applying them directly onto the contaminated area or indirectly by generating the optimum conditions needed for their formation or activation, for example using spray irrigation, infiltration galleries, or injection wells for the inoculation of selected microbes through adsorption/redox reactions or enhancing the efficacy of other mechanisms such as phytoremediation. There is ongoing evaluation for various types of nanomaterials, mainly nanoparticles for their performance in heavy metals remediation purposes, for example, TiO_2-Nanoparticles and nano-scale zero-valent iron (nZVI) [117]. If we look into the TiO_2-Nanoparticles, they are proven to be successful for Pb adsorption from soil, as well as for enhancing the accumulation of Cd in soybean plants in a phenomenon called Glycine max. It is explained by the extremely enhanced absorption and accumulation of Cd in soybean shoots and roots by approximately 2–3 folds (in comparison to normal accumulation conditions) after 60 days of contact with TiO_2-Nanoparticles. A similar effect was reported for nZVI, an electron donor with a negative reduction potential, which was found to improve the potential phytoextraction of Cd and Pb phytoextraction in the roots, stems, and leaves of *Boehmeria nivea* and *Lolium perenne*, respectively. More types of nanomaterials have been assessed for similar scope such as the magnetic nanoparticles, due to their characteristic nature that provides various benefits in the remediation processes of metal-polluted soil. Several studies addressed the use of biogenic magnetite (Fe_3O_4) Nanoparticles in the remediation of common heavy metal pollutants [118–121]. Also, salicylic acid nanoparticles enhanced the phyoremediation of *Isatis cappadocica* in lands polluted with As, while MgO-Nanoparticles supported the Pb accumulation of *Raphanus sativs* [122]. Conclusively, nanotechnology-based strategies can offer several advantages compared to conventional remediation techniques being less time-consuming, with low economic costs, and customizable to each pollutant type and the targeted management scenario. Nevertheless, the real application of nano-materials on an industrial scale should be carefully evaluated from an environmental perspective [115,116,122].

5. Policy responses and Regulations on heavy metals exposure

According to the United Nations Environment Programme (UNEP 2002a), Several international and regional conventions are established to protect the environment against persistent pollutants which include heavy metals. They represent the legal framework for governments to establish the required programs for the assessment and monitoring of heavy metals in addition to evaluating the impacts on different ecosystems while following a risk-based approach. Moreover, these programs should involve information systems, promote social awareness, and educate about control strategies for pollution. In practice, there are several international conventions framed to regulate the hazards of heavy metals, such as the: Rotterdam Convention on the Prior Informed Consent (PIC) Procedure for Certain Hazardous Chemicals and Pesticides in International Trade (2004). This convention aims to regulate the shared contributions and responsibilities related to the importation of hazardous substances and their use.

There is also another convention on Long-Range Transboundary Air Pollutants (LRTAP) Protocol on Heavy Metals (2003), which aims to prevent and reduce potential sources of air pollution; it is particularly targeting contamination by Hg, Pb, and Cd. In addition to other legal protocols that intend to generally regulate and prevent the hazardous health impacts due to waste disposal, for example: the Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal (1992) [123].

Furthermore, in line with the UN agenda for adopting the SDGs (sustainable development goals), besides other international legislations and policies, the European region has already achieved a reasonable decline in industrial emissions between 2010 and 2021, with a significant decrease in heavy metals pollution where levels of Pb emissions declined by 42 %, Hg emissions by 47 % and Cd emissions by 37 % across the twenty-seven EU countries. Interestingly, the EU region was still capable of supporting industrial growth and achieved an increase in economic value by 16 % during the same period [124].

In parallel to enforcing global standards and laws for heavy metals control by regulatory authorities, it is worth noting that research experts have supported the regulatory objective and focused in the same direction. An interesting case study was reported in Bangladesh, where an insightful strategy was designed by its research community to unify the efforts of all stakeholders towards combating specific hazards of heavy metals. According to the collected data, the country suffers from several challenges regarding enforcing legal policies related to heavy metal control, particularly in foodstuffs. Despite the encouraging approaches that act towards reducing contamination levels by heavy metals, the existing local laws and policies were found to be poorly followed due to the lack of knowledge among different stakeholders, and the absence of coherent and unified protocols for the assessment and monitoring of heavy metals in foodstuffs and ecosystems. Therefore, the researchers have worked on addressing these bottlenecks and creating holistic solutions through a conceptual regulatory framework which represents an innovative approach towards covering research gaps and enforcing a unified regulatory framework with an agile nature to accommodate future amendments to enhance the safety of their local food [125].

Finally, the development of global legislation, protocols and sharing information through specialized departments in international organizations, such as the World Health Organization (WHO) and the United Nations (UN), about monitoring and controlling pollution by heavy metals, will provide immense support for developing countries towards achieving environmental sustainability goals according to Fig. 6, following the global principle of 'One Health': the health of humans, animals, and environment.

6. Conclusion and future recommendations

Heavy metals pose a significant threat to human health and the environment. Their persistence, toxicity, and bioaccumulation in ecosystems make them particularly dangerous as they contaminate the food chain and lead to health risks for both animals and humans. Heavy metals like arsenic, lead, mercury, and cadmium can cause a range of health problems, from organ damage to systemic diseases. Plants can also absorb heavy metals, affecting their growth and posing risks to consumers. Monitoring heavy metal levels is crucial for pollution control. Various analytical techniques are used to assess contamination and spatial distribution. Bioindicators like crayfish can provide valuable insights into environmental health. Understanding the migration and accumulation of heavy metals in soil is critical for minimizing risks to food crops and medicinal plants. Widespread soil contamination in regions like China highlights the urgent need for comprehensive pollution management strategies. Exposure to heavy metals can lead to nervous and cardiovascular health hazards. These metals enter the food chain through various pathways and can accumulate in the body, disrupting normal physiological processes. Different analytical techniques, including AAS, ICP-MS, ICP-AES, and AFS, can be used to detect and quantify heavy metals. AAS is a simple and low-cost technique, but it has limitations in terms of sensitivity and precision compared to ICP-MS. ICP-MS is highly sensitive but can be expensive. ICP-AES and AFS are also powerful tools for heavy metal analysis. Mitigating heavy metal pollution in soil and water is essential for safeguarding the environment and public health. Recent advancements in remediation technologies, including traditional methods and nanotechnology, offer promising solutions. International policymakers have established protocols to protect the environment and human health from heavy metal pollution. Legal frameworks and public awareness campaigns are crucial for implementing pollution control strategies.

CRediT authorship contribution statement

Basma Hossam Abdelmonem: Writing – original draft. **Lereen T. Kamal:** Writing – original draft. **Rana M. Elbaz:** Writing – original draft. **Mohamed R. Khalifa:** Writing – original draft. **Anwar Abdelnaser:** Conceptualization, Funding acquisition, Writing – review & editing.

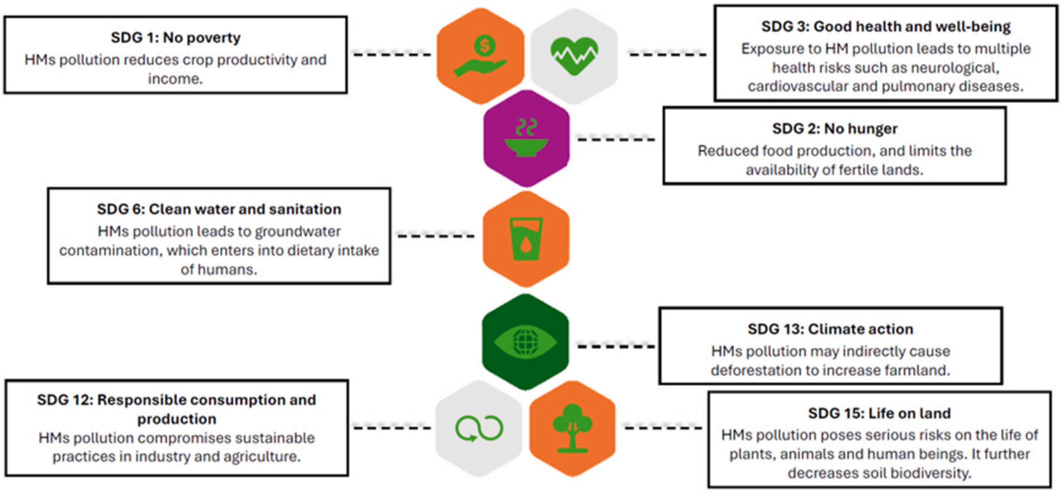

Fig. 6. A summary of the sustainable development goals (SDGs) influencing policymakers to control heavy metal pollution in ecosystems.

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Declaration of competing interest

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Glossary

Heavy Metals	Elements with a density greater than 4.5 g/cm^3, including arsenic (As), lead (Pb), mercury (Hg), and cadmium (Cd). These metals are toxic and accumulate in ecosystems, posing health risks to both wildlife and humans.
Bioaccumulation	The process by which organisms accumulate heavy metals in their bodies, often leading to toxic effects. This occurs through direct absorption or the food chain.
Oxidative Stress	A harmful process resulting from the accumulation of reactive oxygen species (ROS) that leads to cell and tissue damage. It is often induced by heavy metal exposure.
Bioindicators	Organisms such as crayfish and plants used to monitor environmental contamination by heavy metals. They provide insight into pollution levels and ecological health.
Phytoremediation	The use of plants to absorb, accumulate, and detoxify heavy metals from contaminated soils and water, aiding in environmental rehabilitation.
Rehabilitation Strategies	Scientific and regulatory efforts to mitigate the health risks of heavy metals and promote environmental sustainability, often through policies and remediation techniques.

Abbreviations

Lead	Pb
Mercury	Hg
Cadmium	Cd
Arsenic	As
AAS	Atomic Absorption Spectroscopy
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
ICP-AES	Inductively Coupled Plasma Atomic Emission Spectrometry
AFS	Atomic Fluorescence Spectrometry
CNS	Central Nervous System
ROS	Reactive Oxygen Species
MT	Metallothioneins
MMA	Monomethylarsonous Acid
DMA	Dimethylarsinous Acid
LOD	Limit of Detection
BP	Blood Pressure
HTN	Hypertension
ER	Endoplasmic Reticulum
BBB	Blood-Brain Barrier
NMDAr	N-methyl-D-aspartate Receptor
AMPAr	α-Amino-3-hydroxy-5-methyl-4-isoxazolpropionic Acid Receptor
NOS	Nitric Oxide Synthase
CV-AFS	Cold Vapor Atomic Fluorescence Spectrometry
HG-AFS	Hydride Generation Atomic Fluorescence Spectrometry
VG-AFS	Vapor Generation Non-dispersive Atomic Fluorescence Spectrometry
SS-ETV-AFS	Solid Sampling Electrothermal Vaporization Atomic Fluorescence Spectrometry
FI-HG-AFS	Flow Injection-Hydride Generation-Atomic Fluorescence Spectrometry
PHWE	Pressurized Hot Water Extraction
nZVI	Nano-scale Zero-Valent Iron
UNEP	United Nations Environment Programme

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