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From Environment to Human Disease: An Integrated Review of Heavy Metal Exposure Pathways and Toxicity

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A B S T R A C T

Heavy metals such as chromium (Cr), mercury (Hg), lead (Pb), cadmium (Cd), nickel (Ni), and arsenic (As) enter the environment mainly through anthropogenic activities, including industrial effluents, agricultural inputs, and domestic wastewater, and subsequently accumulate in water, soil, and biota. These elements can bioaccumulate and biomagnify along aquatic and terrestrial food chains, leading to chronic exposure in humans via drinking water and contaminated food commodities. Heavy metals disrupt cellular homeostasis by inducing oxidative stress, impairing membrane function, altering signalling pathways, and interfering with essential metal-dependent enzymes, which contributes to neurotoxicity, nephrotoxicity, reproductive dysfunction, and carcinogenesis. This review summarizes sources and pathways of heavy metal contamination in aquatic environments, dietary and groundwater exposure routes in humans, and the major molecular mechanisms underlying toxicity, highlighting the need for integrated monitoring, regulatory control, and remediation strategies to reduce the global health burden associated with heavy metal pollution.

Introduction

Metals are commonly present in the environment, but some are considered contaminants because they can disturb ecological balance even at low concentrations. "Heavy metals" are generally defined as metallic elements with high densities that are highly toxic even at lower levels. While some metals are essential for biological function, the accumulation of non essential heavy metals specifically lead, nickel, cadmium, mercury, and arsenic may cause significant adverse health effects. International bodies, including the World Health Organization (WHO), have regularly reviewed the effects of heavy metals on human health due to their persistence and toxicity. According to the National Priorities List of the Agency for Toxic Substances and Disease Registry (ATSDR), arsenic ranks first based on a combination of its frequency, toxicity, and potential for human exposure.

The primary routes of heavy metal entry into the biosphere include food, air, and drinking water (1). Anthropogenic activities have significantly accelerated this contamination. The main sources of pollution include

industrial waste, household sewage, and municipal garbage, which are directly dumped into natural water bodies (2). For example, cadmium emissions increased dramatically during the 20th century because cadmium-containing compounds such as those used in rechargeable nickel-cadmium batteries are rarely reused. Similarly, arsenic contamination mainly occurs in food and water, where long-term exposure increases the risk of skin cancer, pigmentation changes, and hyperkeratosis (3). Once ingested, these metals disrupt major metabolic processes. Carcinogenic metals like arsenic and nickel lead to redox reactions in biological systems. The accumulation of these heavy metals triggers the production of reactive oxygen species (ROS), which cause oxidative stress and lead to various diseases (4).

The bioaccumulative nature of these toxins is particularly concerning for vulnerable populations, such as nursing infants. Research indicates that heavy metals can be transferred from mother to child. For instance, (5) stated that forty five healthy lactating women living in coastal urban areas of mid-Taiwan were monitored for metal transfer. The study analyzed 180 human milk samples classified into four lactation stages and found that lead, cadmium, aluminium, and arsenic concentrations were the highest in colostrum (e.g., Al 56.45 ± 22.77 ng/mL) and demonstrated a declining trend with advancing stages of lactation. Furthermore, maternal lifestyle factors influence this transfer; it was found that infants of smoking mothers were exposed to more Cd than those of nonsmoking mothers(4), (6). This review aims to summarize the anthropogenic sources and pathways of heavy metal contamination, their bioaccumulation in aquatic and terrestrial food chains, and the molecular mechanisms that underlie their toxicity in humans.

Heavy Metals in Aquatic Systems and Human Exposure

Sources, Transport, and Bioaccumulation in Surface Waters

Heavy metal pollution in aquatic environments poses serious threats to ecosystem integrity, aquaculture, and public health. Surface waters receive metals from multiple anthropogenic inputs, including industrial effluents, mining discharge, urban runoff, agricultural drainage, and improper disposal of domestic and municipal wastes (7), (8), (9). Toxic elements such as lead (Pb), cadmium (Cd), arsenic (As), and mercury (Hg) are of particular concern because they are persistent, non-biodegradable, and capable of accumulating in sediments and biota.

Once released into aquatic systems, heavy metals partition between water, suspended particles, and bottom sediments. Sediments act as both a sink and a potential secondary source: under changing redox conditions or physical disturbance, sediment-bound metals can be remobilized into the water column and re-enter the food web (10). Aquatic organisms absorb metals across gills, skin, and gastrointestinal tracts, leading to bioaccumulation when uptake exceeds excretion (8), (11). With trophic transfer, metal concentrations often increase at higher trophic levels (biomagnification), which is particularly relevant for predatory fish consumed by humans (7), (12), (13).

Ecological, Health, and Economic Consequences in Aquatic Systems

Metal-contaminated waters and sediments adversely affect fish physiology, behavior, and reproduction. Documented impacts include stunted growth, impaired reproductive performance, developmental abnormalities, and elevated mortality (9), (14), (15), (16). Early life stages are especially sensitive: exposure of embryos and larvae to metals such as Cu and Pb reduces hatching success and disrupts normal development. Methylmercury, in particular, markedly suppresses sperm motility, compromising fertilization and recruitment in fish populations (15), (17).

The degradation of aquatic habitats due to inputs from household effluents, industrial waste streams, airborne deposition, and agricultural runoffs has led to declining biodiversity and increased prevalence of disease in aquatic organisms (18).Some metals (e.g., Cr, Zn, Cu) are required only in trace quantities for normal metabolic function and enzyme activity but become toxic when concentrations exceed physiological thresholds, whereas others (As, Pb, Hg, Cd, Tl) have no known biological function and are toxic even at low concentrations (19). Continuous discharge of untreated or partially treated wastes into rivers, lakes, and coastal waters reduces the availability of safe, reusable water, increases treatment costs, and disrupts aquatic food webs (20), (21).

The ecological damage translates directly into socioeconomic burdens. Heavy metal contamination of

aquaculture sites and wild fisheries lowers fish quality and marketability, reduces yields, and undermines consumer confidence in seafood safety (7), (9), (22). Communities that depend on capture fisheries or aquaculture for income and nutrition experience declining catches, loss of livelihood options, and increased health risks from consumption of contaminated products. These pressures intensify food insecurity and income inequality in already vulnerable populations (23).

Agricultural pollution further exacerbates aquatic metal burdens. Runoff and direct dumping of agricultural residues and agrochemicals into water bodies introduce metals and other toxicants that are rapidly accumulated by aquatic organisms, then transferred through the food chain (24). In parallel, contamination-driven losses in aquatic biodiversity and and increased vulnerability to microbial contamination and waterborne diseases such as diarrhoea and cholera illustrate the broader public health implications of degraded aquatic systems (20), (21).

Human Health Risks from Metal-Contaminated Drinking Water

Inorganic arsenic and other toxic heavy metals in drinking water are recognized by the International Agency for Research on Cancer (IARC) and the U.S. Environmental Protection Agency (EPA) as major contributors to both carcinogenic and non-carcinogenic health outcomes. Elevated concentrations of Cd, As, and Cr in potable water are now documented public health threats in more than 30 countries. Daily consumption of water containing Cr at 8.3μg/L – 51μg/L and As at approximately 50μg/L has been associated with increased risks of liver, lung, kidney, and bladder cancers. Even lower chronic doses, such as 0.0012 mg/kg/day of arsenic in drinking water, have been linked to skin lesions and respiratory dysfunction (25).

Lsong-term exposure to Cd in drinking water and food can result in anosmia, chronic renal failure, hypertension, cardiovascular disease, osteoporosis, and other systemic disorders (26). Elevated Pb levels contribute to anemia, neurological deficits, and hematological abnormalities, whereas Hg exposure is associated with renal and hepatic damage and altered lipid metabolism, including increased blood cholesterol and heightened risk of heart disease (14). Antimony (Sb) has additionally been implicated in dyslipidemia and cardiovascular pathology when present at high concentrations.

Heavy metals enter sewage and industrial wastewater through multiple processes, including electroplating, electrolysis, metal smelting, and chemical manufacturing (27). Recognizing the value of these metals, some industries now integrate metal removal with recovery, simultaneously reducing environmental burdens and generating economic returns from process and bleed streams (28). The choice of treatment technology such as membrane filtration, ion exchange, or chemical precipitation depends on target metals and required removal efficiencies. Among these, chemical precipitation is widely adopted because of its relative simplicity, cost effectiveness, and operational robustness, particularly for Cd, As, Hg, Cu, and Pb.

Dietary Exposure to Heavy Metals via the Food Chain

Metal Contamination of Food Commodities

Dietary intake represents a major route of chronic exposure to heavy metals. Persistent elements such as Pb, Cd, As, Hg, and Cr can accumulate in soils, waters, and sediments, from which they are taken up by crops, livestock, and aquatic organisms (29), (30), (31). Bioaccumulation occurs when organisms absorb metals at a rate that exceeds their capacity for detoxification and excretion, resulting in progressively higher internal concentrations over time (12), (32). Through trophic transfer, these metals ultimately reach humans at the top of terrestrial and aquatic food chains.

Several food crops are known to accumulate metals from contaminated soils and irrigation water. Musa paradisiaca (banana), Zea mays (maize), and Cucumeropsis manii (melon) have been reported to contain elevated metal levels when grown in polluted environments, posing direct health risks to consumers (31). In aquatic systems, fish and other higher trophic organisms are particularly vulnerable to metal bioaccumulation from water and sediments and often serve as key vectors for human exposure (12), (13).

Heavy metals also enter the human body through the consumption of vegetables irrigated with wastewater or treated effluents. Species such as Colocasia esculenta, Raphanus sativus, and Brassica nigra can accumulate substantial metal burdens under these conditions, leading to altered plant biochemistry and reduced nutritional quality. Intake of such contaminated vegetables has been

associated with immune suppression, malnutrition, gastrointestinal cancers, and impaired cognitive development (33).

Health and Socioeconomic Impacts of Dietary Exposure

The toxicological profiles of heavy metals are well characterized. Chronic dietary exposure can cause neurological impairment, renal dysfunction, hematological disorders, reproductive and endocrine disruption, and multiple forms of cancer. Lead, for instance, is strongly associated with cognitive deficits and developmental delays in children, even at relatively low exposure levels (14), (29), (30). Cadmium is linked to kidney damage, disturbances in calcium homeostasis, and decreased bone mineral density, leading to bone fragility and fractures. Many of these metals also induce oxidative stress, triggering reactive oxygen species (ROS) formation, lipid peroxidation, and DNA damage (34), (35).

Accumulation of heavy metals in human tissues has been associated with complex chronic diseases, including Alzheimer's disease, diabetes, various cancers, and allergic disorders (19), (36). Lead, in particular, readily accumulates in bones and soft tissues and can cause irreversible damage to the brain, central nervous system, and excretory organs when body burdens rise above critical thresholds (37). Arsenic exposure contributes to neuromuscular dysfunction, protein coagulation, and injury to reproductive, hepatic, and endocrine systems, as well as characteristic skin lesions (hyperpigmentation and keratosis) (38), (39).

Heavy metals such as Cd, Pb, Al, and Mn can cross the placental barrier, and intrauterine exposure has been associated with fetal growth restriction and developmental abnormalities (40). Nickel, while functioning as a component of urease and other metalloenzymes, becomes toxic at elevated levels and may contribute to dermatological, respiratory, and systemic effects (41). Although essential trace elements such as Fe, Cu, Zn, and Cr(III) are integral to cytochromes and enzyme systems, their narrow margin between essentiality and toxicity underscores the importance of maintaining tightly regulated intake (19). The socioeconomic ramifications of metal-contaminated food systems are substantial. Agricultural communities that depend on contaminated soils and water supplies may experience reduced yields, rejection of produce in local and international markets, and increased healthcare expenditures related to metal-associated diseases (12), (29). Populations with limited access to diverse diets are particularly vulnerable, as they rely heavily on a small number of staple crops and aquatic products that may be contaminated (30), (32), (42). These conditions exacerbate existing health inequities and fuel cycles of poverty and malnutrition.

Cadmium, Chromium, and Rice and Water Based Exposure

In many regions, contaminated drinking water remains the primary route of exposure to metals such as As, Pb, Ni, and Cd, prompting growing concern among regulatory authorities (43). Cadmium ions (Cd^{2+}) disrupt mitochondrial integrity, increasing the passive permeability of the inner mitochondrial membrane to cations such as Na^{+}, K^{+}, H^{+}, and Li^{+}, which impairs energy metabolism and cellular homeostasis. Cd that enters the food chain is particularly hazardous because it accumulates in human organs and tissues, with slow elimination rates and cumulative toxicity (26).

Hexavalent chromium Cr(VI) and divalent cadmium Cd(II) represent the most soluble and bioavailable oxidation states of these metals in many contaminated environments (27). Industrial use of Cr and Cd in plating, pigments, and alloys leads to soil and water contamination around industrial hubs, and recycling/recovery remains limited due to technological and economic constraints. Rice paddies irrigated with polluted water or cultivated on contaminated soils can accumulate substantial Cd concentrations in grains, which then enter the human diet and pose chronic health risks. Consumption of Cd-contaminated rice has been linked to nephrotoxicity, skeletal demineralization, and increased risk of carcinogenesis, complicating food safety assurance in rice-dependent populations (27), (44).

Groundwater Metal Contamination and Human Health

Sources, Distribution, and Health Risk Assessment

Groundwater is a critical source of drinking and irrigation water worldwide, and its contamination with heavy metals has emerged as a major environmental and public health challenge. Metals such as Pb, Cd, As, and

Cr enter groundwater through leaching from industrial waste dumps, mine tailings, smelting sites, landfills, and poorly managed municipal and hazardous waste facilities (45), (46). Agricultural activities, including the use of metal-containing fertilizers, pesticides, and irrigation with contaminated surface water, further contribute to subsurface metal loads (46), (47).

Health risk assessments consistently show that chronic ingestion of metal-contaminated groundwater can lead to a spectrum of adverse outcomes, including neurotoxicity, nephrotoxicity, hepatotoxicity, and elevated cancer risks (46), (48), (49). Contaminated water contributes to global cancer burden, with heavy metals like arsenic and chromium posing significant carcinogenic risks (50). Lead exposure from drinking water disproportionately affects children, resulting in cognitive impairment, behavioral changes, and developmental delays (51). Arsenic and cadmium exposures are linked respectively to skin lesions and renal dysfunction, further underscoring the need for proactive monitoring and remediation (49), (52).

Groundwater quality often exhibits spatial and seasonal variability. During wet seasons, enhanced infiltration and leaching from contaminated soils, mine wastes, and industrial zones can elevate metal concentrations in aquifers (47), (48).

This seasonal fluctuation necessitates continuous, rather than sporadic, water quality monitoring, especially in regions susceptible to heavy rainfall, flooding, or high agricultural intensity (46), (53). Spatial heterogeneity in hydrogeology, land use, and pollution sources means that localized studies are essential to characterize exposure scenarios and refine health risk assessments (48), (52), (53).

Socioeconomic Burden and Regulatory Responses

Beyond direct biomedical impacts, groundwater contamination imposes heavy socioeconomic costs. Communities reliant on polluted aquifers for drinking and irrigation face increased medical expenses, reduced work productivity, and lower agricultural output (46), (51). Crop yields and quality may decline when metal-laden groundwater is used for irrigation, perpetuating malnutrition and economic instability in agrarian regions. Rapid population growth, urban expansion, unregulated groundwater abstraction, and widespread discharge of untreated domestic and industrial sewage further degrade groundwater quality across many parts of the world (54). Nitrate pollution of groundwater and surface water, often co-occurring with metal contamination, has been associated with elevated risks of malignant digestive system cancers (55). These intertwined chemical hazards illustrate the need for integrated water quality management and health protection strategies.

Effective responses require strengthening regulatory frameworks for waste disposal, industrial effluent standards, and groundwater protection zones, alongside investments in infrastructure for wastewater treatment and safe drinking water supply (51), (53). Public health education and risk communication are equally important to enable communities to adopt safer water use practices and demand regulatory enforcement (56).

Toxic Mechanisms of Heavy Metals in Humans

Heavy metals such as Pb, Cd, As, Hg, and Cr exert toxicity through diverse and often overlapping molecular pathways. Their ability to accumulate in critical organs, generate oxidative stress, disrupt enzyme activity, and interfere with cellular signalling underlies a wide spectrum of clinical outcomes, ranging from neurodevelopmental deficits to carcinogenesis (30), (31), (34), (57), (58). To compare environmental accumulation behaviour with human exposure risk across metals, the key bioaccumulation indices (BCF, BMF, Kd) along with international regulatory limits were compiled and summarized in Table 1.

Oxidative Stress and Disruption of Signalling Pathways

A central mechanism of heavy metal toxicity is the induction of oxidative stress. Many metals catalyze or promote the formation of reactive oxygen species, which damage lipids, proteins, and nucleic acids, leading to loss of membrane integrity, enzyme inactivation, and genotoxicity (34), (59). Persistent oxidative damage has been linked to neurodegenerative conditions, including Alzheimer's and Parkinson's diseases (34), (58). For example, $HgCl_2$ exposure triggers ROS generation and apoptosis in human lung fibroblasts, resulting in cell cycle arrest and cell death (60). Cd and Pb interfere with mitochondrial electron transport, aggravating ROS production and further compromising cellular energy metabolism (30), (34).

Heavy metals also perturb intracellular signalling pathways. They can activate or inhibit redox-sensitive transcription factors such as NF-κB and p53, which regulate cell cycle progression, DNA repair, and apoptosis (60), (61). Dysregulation of these pathways can support uncontrolled proliferation, resistance to apoptosis, and tumor promotion (62). Furthermore, metals may mimic or compete with essential trace elements at binding sites in enzymes and receptors, thereby deranging endocrine and metabolic homeostasis (29), (58).

Exposure Routes, Bioaccumulation, and Organ-Specific Toxicity

Humans encounter heavy metals through ingestion of contaminated food and water, inhalation of polluted air, and dermal contact with contaminated soil or dust (63), (64). Repeated exposure, even at low doses, can lead to bioaccumulation in organs such as the liver, kidneys, bones, and brain, where metals may persist for years (30), (42). Consumption of metal-laden fish and shellfish is a well-recognized route for bioaccumulation of Hg, Cd, Pb, and As in human tissues (58), (65).

The clinical manifestations of heavy metal exposure are broad. Chronic intoxication is associated with developmental disorders, cardiovascular disease, renal impairment, reproductive dysfunction, and various cancers (30), (42), (58). Lead is especially damaging in children, causing lasting cognitive and behavioural deficits (57), (66). Cumulative exposure necessitates regular biomonitoring and early intervention to prevent progression to irreversible organ damage.

Emerging evidence also links low-level chronic exposure to certain metals with reproductive and metabolic disorders. Polycystic ovarian syndrome (PCOS), affecting approximately 6-13% of women of reproductive age globally(67), has been associated with altered body burdens of Cd, As, Hg, and Pb, even when concentrations fall within conventional "low-level" ranges. Consensus reports from the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) highlight that women with PCOS frequently exhibit perturbed levels of heavy metals and critical trace elements, suggesting a possible role for environmental exposures in disease pathophysiology (68). PCOS is characterized by polycystic ovarian morphology, anovulation, and menstrual irregularities, alongside metabolic and hormonal disturbances that may be influenced by metal-induced oxidative stress and endocrine disruption.

Molecular Events Underlying Specific Metal Toxicities

Heavy metals commonly interact with sulfhydryl (-SH) groups in proteins and non-enzymatic antioxidants. Binding to reduced glutathione (GSH) and other thiol-containing molecules leads to the formation of organometallic complexes that deplete antioxidant defenses and inhibit critical biochemical reactions (69), (70). In endocrine-metabolic disorders such as PCOS, persistent hyperandrogenemia, visceral obesity, and chronic low-grade inflammation are frequently observed. Women with PCOS show elevated circulating levels of pro-inflammatory markers, including interleukin-18 (IL-18), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), white blood cell count, and ferritin, coupled with decreased adiponectin, an anti-inflammatory adipokine (71). Environmental metals may exacerbate this inflammatory milieu by promoting oxidative stress and cytokine dysregulation. Mercury preferentially accumulates in the kidneys, where it damages proximal tubular cells and impairs renal function (72). Epidemiological analyses have demonstrated associations between blood Hg levels (median approximately 0.73 μg/L ± 0.91 μg/L) and mild elevations in alanine aminotransferase (ALT) among adolescents aged 12–17 years, as well as significant correlations between Hg concentrations and liver enzyme activities (ALT, aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT)) in individuals older than 60 years (72). In persons with chronic alcohol consumption, higher blood Hg levels are linked to amplified oxidative stress, impaired cellular metabolism, hepatocellular injury, and pronounced elevation of GGT (73).

Lead-Induced Oxidative and Haematological Toxicity

Lead exerts classical toxicity through interference with heme biosynthesis. It inhibits ferrochelatase and δ-aminolevulinic acid dehydratase (ALAD), key enzymes in the heme pathway, resulting in impaired hemoglobin production and anemia (74).

Table.1 Bioaccumulation Metrics and Regulatory Limits for Priority Heavy Metals Across Major Human Exposure Pathways

Metal	Exposure Route	Log_{10} BCF	Log_{10} BMF	Kd (L/kg)	Regulatory Limit	Typical Exceedance	Major Sources
Mercury (Hg)	Fish consumption	5.0–6.5	0.3–0.8	10^4–10^6	0.5–1 mg/kg (Codex)	5–20× in tuna, shark, swordfish	Biomagnification; atmospheric deposition; mining
Cadmium (Cd)	Rice / paddy	2.5–4.0	0.1–0.4	10^3–10^5	0.2 mg/kg (rice)	2–5× in contaminated regions	Phosphate fertilizers; wastewater irrigation; mining runoff
Cadmium (Cd)	Leafy vegetables	2.5–4.0	0.1–0.4	10^3–10^5	0.3 mg/kg (vegetables)	1.5–3× urban/agricultural soils	Soil deposition; fertilizers; irrigation water
Lead (Pb)	Leafy vegetables	2.0–3.5	0.0–0.3	10^4–10^5	0.3 mg/kg	1.5–5× near traffic/industrial belts	Atmospheric deposition; contaminated soils
Arsenic (As)	Drinking water	3.0–4.5	0.2–0.5	10^2–10^4	10 µg/L (WHO)	10–50× in South Asian groundwater	Geogenic leaching; mining; poor filtration
Chromium (Cr VI)	Groundwater	1.5–3.0	0.1–0.3	10^2–10^3	50 µg/L (WHO total Cr)	2–10× in industrial regions	Tannery effluents; electroplating; industrial discharge

BCF = Bioconcentration factor (organism water partition coefficient, L/kg)
BMF = Biomagnification factor (higher trophic level concentration ratio)
Kd = Sediment-water partition coefficient (L/kg)
µg/L = Micrograms per liter mg/kg = Milligrams per kilogram (wet weight)
Codex = Codex Alimentarius Commission standards (FAO/WHO)

Pb exposure also alters activities of antioxidant enzymes, including catalase (CAT), superoxide dismutase (SOD), glutathione reductase (GR), and glutathione oxidase (Gox), and perturbs levels of GSH and oxidized glutathione (GSSG), thereby compromising redox balance (75).

By enhancing membrane lipid peroxidation and suppressing antioxidant defences, Pb promotes extensive oxidative damage.

At low exposure levels, Pb may transiently stimulate certain immune responses, whereas higher exposures are typically immunosuppressive. Elevated interferon-γ (IFN-γ) concentrations have been observed in Pb-exposed individuals, with positive correlations between blood Pb and IFN-γ levels, indicating immune modulation (76).

Pb exposure has also been associated with altered pulmonary function test (PFT) values and increased systolic and diastolic blood pressure, along with raised total blood cell counts, reflecting its systemic impact on cardiovascular and haematological systems (77).

Chromium, particularly in the hexavalent state Cr(VI), is another potent toxicant. Epidemiological data link Cr(VI) exposure with increased mortality and elevated incidence of cancers of the lung, larynx, kidney, bladder, bone, thyroid, and testis (78).

Mechanistically, Cr(VI) and Cr(III) generate ROS, cause DNA damage, and induce genomic instability (79). Chromium-induced genotoxic lesions include DNA inter- and intra-strand crosslinks, DNA–chromium–protein crosslinks, single- and double-strand breaks, and characteristic p53 mutations, as well as perturbation of transcriptional regulation (80), (81).

Cadmium can substitute for essential metals such as Zn, Ca, and Fe at critical binding sites, thereby disrupting metal-dependent enzymes and Signalling pathways (82). Cd bound to metallothionein (MT) is efficiently reabsorbed in renal proximal tubules, leading to accumulation in the kidney and chronic nephrotoxicity. Disturbances in calcium homeostasis also contribute to hepatic injury, in part through upregulation of dynamin-related protein 1 (Drp1) and mitochondrial dysfunction (83). Cd exposure is thus associated with osteoporosis, bone fractures, and multi-organ damage.

Cadmium-Mediated Renal, Skeletal, and Carcinogenic Effects

Cadmium toxicity extends beyond renal and skeletal systems to affect the prostate, gastrointestinal tract, breast, and lungs (84), (85). Proposed mechanisms include sustained ROS production, suppression of protective gene expression, dysregulated cellular proliferation, and promotion of apoptosis in some cell types and survival in others. Workers in Cd-processing industries exhibit increased risk of nephron carcinogenicity (84). One mechanistic hypothesis implicates aberrant activation of the β-catenin Signalling pathway in Cd-driven renal carcinogenesis. Cd–metallothionein (MT) complexes accumulate because MT has a slow turnover rate. Cd exposure leads to cytoplasmic accumulation and overexpression of β-catenin, a transcriptional co-regulator involved in Wnt Signalling, thereby facilitating evasion of normal growth controls and promoting tumor development through ROS-dependent mechanisms (85).

Arsenic exposure is also associated with genotoxic and immunomodulatory effects. In rural women chronically exposed to low As levels, significantly elevated concentrations of pro-inflammatory cytokines, including IL-6, TNF-α, and IL-12, have been reported alongside increased DNA damage markers such as 8-hydroxy-2'-deoxyguanosine (8-OHdG) (86). Arsenite (As^{3+}) may damage the male reproductive system via dysregulation of NF-κB Signalling, a pathway critical for spermatogenesis. Prenatal exposure is particularly dangerous: As readily crosses the placenta and has been associated with spontaneous abortion, preterm birth, stillbirth, and low birth weight (39).

In the skin, As accumulates and induces hyperpigmentation and keratosis. Reduced expression of integrins in keratinocytes is thought to contribute to cutaneous manifestations and altered apoptosis (38). Carcinogenicity of As involves chromosomal abnormalities, oxidative stress, and deregulated growth factor signalling, collectively promoting malignant transformation (87).

In conclusion, heavy metal contamination of aquatic systems, agricultural soils, and groundwater forms a connected exposure continuum in which bioaccumulation and biomagnification drive significant

human health risks through drinking water and the food chain.

Evidence from experimental and epidemiological studies shows that metals such as Pb, Cd, As, Hg, and Cr exert toxicity primarily via oxidative stress, disruption of signalling pathways, and organ-specific accumulation, leading to developmental, metabolic, and carcinogenic outcomes.

Reducing this burden requires coordinated actions that couple stricter control of industrial and agricultural emissions with routine monitoring of water and food, as well as deployment of effective treatment and remediation technologies at community and industrial scales.

Future work should prioritize mechanistic studies that link environmental concentrations to molecular and clinical endpoints, and develop risk assessment frameworks that integrate ecological, health, and socioeconomic impacts to guide evidence-based regulation.

Author Contributions

Uday Sankar Allam: Investigation, formal analysis, writing—original draft. Benson Wesley Buraga: Validation, methodology, writing—reviewing. Vidya Prabhakar Kodali:—Formal analysis, writing—review and editing. Vijay A.K.B. Gundi: Investigation, writing—reviewing. Mary Sandeepa Gujjula: Resources, investigation writing—reviewing.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

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Conflict of Interest The authors declare no competing interests.

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