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Heavy Metal Exposure and Immune Dysfunction: Mechanistic Pathways in Humans and Animals

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REVIEW ARTICLE

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ABSTRACT

In the past few years, contamination of the environment by heavy metals has emerged as a significant global issue. Heavy metals comprise a category of metals and metalloids with an atomic density above 4,000 kg m^{-3}. Heavy metals, including Nickel (Ni), Cobalt (Co), Copper (Cu), Zinc (Zn), and Lead (Pb), are found in the biota. These metals, referred to as traces, are crucial for numerous metabolic activities in organisms such as animals, plants, and microbes. Heavy metals can enter the human body through the use of contaminated drinking water or the ingestion of soil or crops cultivated on polluted land. Heavy metals, including lead, mercury, cadmium, and copper, are cumulative toxins that pose environmental risks and are known to be very harmful. These metals are significant contributors to oxidative stress within cells and play a crucial role in the etiology of various human illnesses, including carcinogenesis. Exposure to heavy metal toxicity results in neurological impairment, intellectual disability, cerebral palsy, lung carcinoma, gastrointestinal disorders, dermatitis, and fetal demise. Numerous metals have been demonstrated to directly alter and/or impair DNA by creating DNA adducts that provoke chromosomal breakage. The unregulated access to the dumpsite allows scavengers to forage for raw materials daily, most of which ultimately reenters neighborhoods as animal feed and even human sustenance. Feral chickens, pigs, goats, dogs, and cats traverse the dumpsite, consuming hazardous waste and becoming carriers of bugs and parasites, which are subsequently transmitted to nearby residences, so inducing diseases in both animals and humans.

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In the last few decades, the advancement of human civilization, the swift evolution of the manufacturing sector, and the utilization of various chemical-based goods have resulted in significant pollution from domestic trash, chemicals used in agriculture, and mineral extraction activities that release waste into the environment. A diverse array of industrial waste and environmental contaminants perpetually disrupts the equilibrium of toxic remnants and poses hazards of heavy metal contamination to human beings [1][2]. Heavy metals and metalloids possess atomic numbers above 20 and densities greater than 4 g/cm^3 [3]. Major heavy metals such as manganese, cobalt, zinc, copper, selenium, iron, molybdenum and chromium have crucial chemical and physical functions in plants as well as animals at low concentrations [4]. These trace metals are essential components of certain vital enzymes that participate in redox reactions, biosynthesis, transport, and various metabolic processes [5]. Non-essential heavy metals and metalloids like nickel, cadmium, vanadium, mercury and arsenic lack any recognized biological function; instead, they produce detrimental health effects. Both essential and non-essential heavy metals can become harmful if their concentrations beyond specific thresholds [6].

The legacy of contaminated soil globally has been attributed to manufacturing, warfare, mining, amplification, vehicular traffic, and fuel transportation [7]. The soil served as an enclosure for the disposal of both solid and liquid garbage at the period of urban expansion and associated manufacturing operations. It is posited that once entombed and concealed, the contaminants do not present a threat to humans or to the ecosystem that may ultimately disappear [8]. Manay et al. determined that the primary sources of soil contamination are human-caused, leading to the buildup of contaminants in the soil that may attain a concerning level [9]. Pollution from agriculture has been recognized as the third most significant danger to soil functioning across Europe and the Asian continent, fourth in Africa's north, fifth in Asia, seventh in the Northwest Pacific, eighth in North America, and ninth in sub-Saharan Africa and Latin America. Food and Agriculture Organization and Intergovernmental Technical Panel on Soils. In numerous regions globally, plant growth is hindered by soil pollutants, which can induce nutritional imbalances and soil acidification [10]. In total, there are five million sites of environmental contamination where heavy metals and metalloids exceed the geological baseline levels in the soil [11]. Soil heavy metal emissions exceed ten billion dollars monthly in worldwide economic impact [12].

Toxic metals distributed into ecosystems through various natural and human-induced processes, leading to ecosystem destruction [13]. The primary contributors of toxic metals in agricultural activities are organic waste manure, the use of fertilizers, and wastewater from industrial drainage [14]. Modern agriculture has been compromised by heavy metal contamination resulting from various socio-economic, technological, and developmental challenges, constituting a significant crisis in both developed and developing nations. This scenario presents an enormous obstacle in identifying environmentally friendly and economically viable methods to address heavy metal contamination. This review paper seeks to investigate a long-term research by analyzing the principal studies conducted in the field of heavy metal contamination in contemporary agriculture [15].

Origins and pathways of heavy metal exposure

A significant proportion of soils may accumulate heavy metals beyond the established background levels, posing potential health concerns to people, vegetation, farm animals, ecological systems, or other environments in both rural and urban contexts [16]. Numerous investigations indicate that the sources of contamination include: (i) heavy metals as soil pollutants due to accelerated human cycling rates compared to natural processes; (ii) the transfer of contaminants from mining sites to various sustainable spots, increasing the immediate exposure risk; (iii) elevated levels of metals in superficial goods relative to their reception environments; and (iv) heavy metals exhibit greater mobility in soil compared to pedogenic or powdered metallic soils, rendering them easier to absorb [17].

Toxic metals distribution in both water and food

Metals that are toxic can infiltrate surroundings and crops through various pathways. The heavy metal contamination of food arises from the erosion of rock base, direct contamination of the air, and crop irrigation contaminated water and polluted aquifers. Environmental contamination, chiefly Because of industrial and human activity, pertains to soil or groundwater, which are the predominant pathways for heavy metals. Studies indicate that elevated levels of heavy alloys in the human food are associated with geographical location, available food sources, and industrial activities. At times, a metallic substance is not emitted in the surrounding until the manufacturing events of humans lead to contact with naturally present metals. Soil contamination near a mine can lead to the accumulation of heavy metals in nearby crops [18]. Specific geographies and associated sectors are recognized for the proliferation of heavy metals in elevated absorptions; for instance, in China, locales adjacent to coal-fired power plants exhibit mercury pollution levels up to tenfold higher than the normal sample taken from soil 55km distant from these sites [19].

Heavy metals are introduced into the environment via processes that are natural and human activities. Bryliński et al. demonstrated that igneous steel constitutes 94% Earth's crust and approximately 6% of sedimentary rock [20]. Rolka et al. proposed that the basalt pillar contains substantial amounts of Mn, Pb, Cd, Cu, and Zn along with an abundance of heavy metals such as Cd, Co, Ni, and Cu. Naturally occuring processes, including climatic and geological activities, such as weathering and ground breeze are necessary for the dissolution of heavy metals into soil systems [21]. Kumar et al. demonstrated that organic sources of heavy metals are less significant than human based activities [22]. Numerous industrial processes, including the mining and smelting of metalliferous ores, metal processing, burning fossil fuels, sewage sludge, and other agricultural practices, are the main causes of excessive accretion of metals in the environment [23].

Heavy metals in fertilizers

He et al. asserts that agriculture constitutes the primary human impact on soil. Plants can acquire macronutrients such as nitrogen, phosphorus, potassium, sulfur, calcium, and magnesium, as well as accumulate micronutrients, to facilitate rapid growth and synchronize the completion of their life cycle [24]. If the soil lacks essential heavy metals such as Mn, Cu, Mo, Zn, Ni, Fe and Co, which are vital for plant growth, these may be administered to plants via foliar spray [25]. Farmers routinely utilize substantial chemical manures in contemporary agricultural systems, supplying nitrogen, phosphorus, and potassium as essential nutrients for crop development. Trace amounts of heavy metals are present as contaminants in these fertilizers, which can substantially elevate the heavy metal concentration in the soil [26].

Heavy metals in wastewater

Maurya et al. demonstrated that urbanized and industrial waste water, along with the corresponding effluents, has been a prevalent practice in numerous regions globally for up to 400 years [27]. It is projected that 20 million hectares of arable land worldwide have been irrigated using wastewater [28]. Research demonstrates that 50 percent of vegetation in urban regions of various Asian and African cities is sourced from agriculture reliant on irrigation systems. In the National Capital Territory (NCT) of Delhi, vegetables are grown on 1,700 hectares of land watered with sewer water in the regions surrounding Najafgarh and Okhla [29]. The farmers typically do not concern themselves with environmental advantages or risks, focusing instead on optimizing their yields and profits [30]. Accumulation of heavy metal and their movement in the soils are enhanced by manure irrigation. Numerous studies indicated that the concentrations of zinc, magnesium, iron, copper, lead, nickel, and Cadmium in soils irrigated with well water contaminated by sewage exhibited an inverse tendency [31].

Air-borne sources of heavy metals

Aerial sources It include emissions from stacks or ducted air, gas, and vapor streams, as well as fugitive discharges such as dirt from storing zones or waste materials. The particles in the gas stream are metallic shapes emitted by aerial sources. Sądej et al. found that heavy metals transform into oxides and aggregate as fine particles unless a reducing environment is sustained. Stack emissions are frequently dispersed over a vast area by natural air currents until they are eliminated from the gas stream by dry and/or wet precipitation mechanisms. As emissions occur near the ground, fugitive emissions are often dispersed over a smaller region. The concentration of metals originating from both types of emissions is contingent upon site-specific factors. Solid particles are concealed within the fire and smoke emitted from the chimneys of factories and power plants, gradually settling on land [32]. The aerial release of Pb from the burning of fuel containing tetraethyl lead is an additional source of heavy metal contamination, as it significantly adds to Pb accumulation in urban soils and those near important thoroughfares. The main sources of heavy metals in transference corridors, aside from deplete emissions, include the degradation of clutch brake and tyres linings, the erosion of road surfaces, and other infrastructural components [21]. Figure 1 illustrates the potential pathways of exposure and the effects of heavy metals on human health.

The toxicity of these elements is widely recognized, their many applications in technology, medicine, and agriculture continue to pose a significant threat to human health. Notwithstanding the extensive endeavors of organizations like the World Health Organization, and European Environment Agency (EEA), industrial advancement results in escalating concentrations of dangerous metals in the environment, posing a direct and/or indirect risk to human health [33]. This study synthesizes current information regarding the sources of heavy metals hazardous to people, including Cd, Ni, Pb, Hg, and As as well as their effects on human's health, particularly focusing on the chemical reactions of these harmful metals with proteins. Microbial purification methods are also succinctly outlined [34].

The influence of toxic substances on enzymatic pathways of human

The contention among metallic ions for protein-binding sites might hinder the transit of specific substances and the breakdown of chemical events within human bodies. The configuration of the proximal surroundings of the binding site associated with metal selection. Nevertheless, the degree of selection varies for each protein, necessitating investigation at the level of single-protein [35].

The significant part of metal ions' effects on the human body is metallic-mediated interactions between proteins. Comprehending this relationship is essential for grasping the molecular specifics of heavy metal effects on human health [36].

Metallothioneins, identified in 1957 as proteins that bind cadmium, possess a high cysteine content that enables them to bind and sequester heavy metals. They also demonstrate significant importance for other metals, rendering them suitable candidates for protein-based metal biosensors [37]. Furthermore, many proteins and multiple lysosome-like organelles contribute to homeostasis by serving as storage locations and regulating cytosolic metal concentrations in eukaryotes [38]. Metallothioneins appear to be defensive proteins synthesized in response to many forms of stress [39].

Lead continues to be the most widely researched hazardous element due to historical human exposure and the neurotoxic effects of Pb(II). Lead has been demonstrated to inhibit voltage-activated and receptor-operated calcium channels in both invertebrate and mammalian neurons. Lead ions have been demonstrated to inhibit N-, L-, and T-type voltage-gated calcium channels in mammals [40]. Exposure to Pb(II) disrupts synapse formation, potentially resulting in enduring effects on subsequent signaling. Arsenite reacts with thiol-containing molecules, such as glutathione, resulting in the creation of the final metabolite dimethylarsinic acid (DMA), which is subsequently eliminated. Conversely, certain data indicate that metabolically produced methylated forms of arsenic may exhibit more toxicity than their parent compounds. Methylation is proposed to serve as activation routes that augment arsenic toxicities, rather than functioning as detoxifying mechanisms. The toxicities of metabolically produced methylated compounds differ based on their degree of methylation [41].

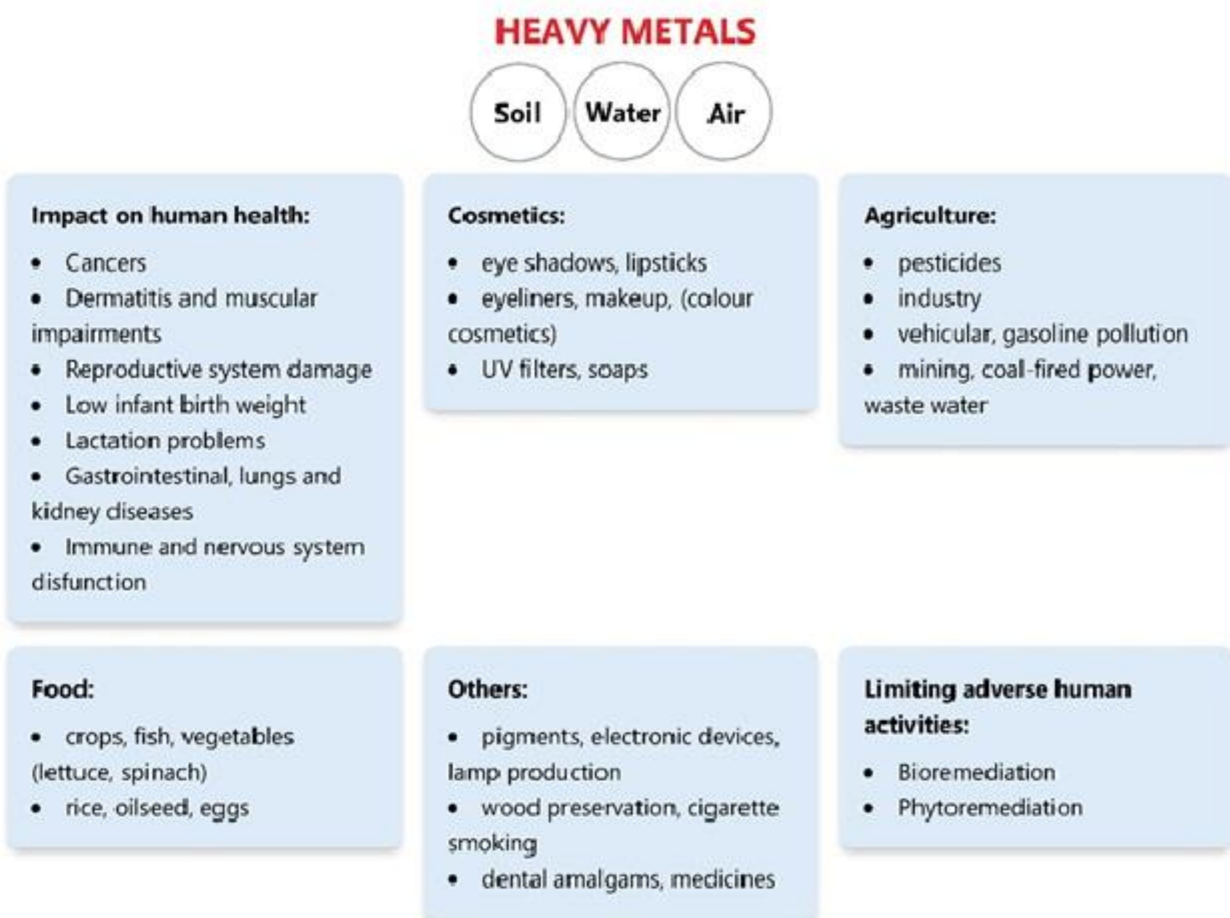

Figure 1. Pathways of exposure and the effects of these hazardous metals on human health.

In animal models, toxicity of brain was linked to disruptions in the expression of the receptor and changes in the cellular manifestation of subsequent protein signaling [42]. Arsenic may replacement phosphate in the negative ion exchange transport mechanism and replace phosphate in enzymatic reactions, hence reducing ATP production in vitro. As previously stated, certain heavy metals are essential in trace levels for the optimal functioning of human enzymes or required by other organisms but not by vertebrates (e.g., Ni). While nickel is a vital element for certain plants, bacteria, fungi, and invertebrates it can induce allergies, bronchitis, and malignancies of the nose and lungs in people, as evidenced by reports from nickel refinery workers [43].

Nickel can indirectly contribute to stomach ulcers and malignancies by serving as a crucial cofactor in the enzymes of H. pylori bacteria and urease [44]. In these enzymes, nickel is coordinated with histidine, cysteine, and aspartic acid residues. Nickel exhibits a strong affinity for proteins and peptides that contain thiol groups [45]. Following coordination of nickel by specific endogenous ligands, nickel ions can induce the generation of reactive oxygen species, resulting in a redox imbalance potentially associated with carcinogenic stimulation. Furthermore, the presence of Ni(II) can impede the repair and replication of DNA [46]. The predominant health effect of nickel in humans is contact dermatitis. A recent investigation on adult human epidermal keratinocytes shown that exposure to nickel nanoparticles results in the release and the production of a nickel-binding molecule associated with the p63-regulated gene 1 protein. Typically, proteins containing histidine-rich motifs function as Ni-accessory proteins, facilitating the binding and sequestration of Ni(II) ions within cells, contingent upon the environmental conditions [47].

Comparative Analysis: Humans vs. Other Animals in Heavy Metal Exposure and Immune Dysfunction

Exposure to heavy metals creates substantial health threats which primarily damage immune system functions through inflammation and immune system suppression and oxidative stress processes.

Case Study 1: Lead (Pb) Exposure in Humans vs. Cattle

Research indicates that immune dysfunction emerges as a health consequence from lead exposure in humans who work in industries and children who dwell near polluted environments. The prolonged contact with lead reduces lymphocyte multiplication and modifies cytokine synthesis mechanisms and disrupts phagocyte functions thus making the body more vulnerable to infections [48]. Cattle exposed to lead from industrial sites accumulate this substance which suppresses their immune system thus increasing their vulnerability to bacterial and viral infections. Laboratory research shows immunoglobulin IgG and IgM become reduced while leukocytes submit to oxidative stress-induced cellular dea. Research indicates that cows present stronger humoral immune suppression than humans do but human beings show signs of cellular as well as humoral immunity suppression [49].

Case Study 2: Mercury (Hg) Exposure in Humans vs. Fish

Methylmercury in fish constitutes the main source of Pb exposure which has been associated with the immune system deregulation. Mercury exposure creates autoimmunity in human bodies by suppressing T-cell multiplication and boosting inflammatory cytokines that results in systemic lupus erythematosus development [50]. The immunological response of fish living in polluted water causes severe suppression of their immune system. The scientific study of zebrafish (Danio rerio) demonstrates that mercury exposure results in modifications to macrophage cells and higher oxidative stress levels alongside diminished infection protection. The immune responses between humans and fish differ significantly since humans develop autoimmunity while fish primarily suffer from reduced innate immunity together with higher infection susceptibility [51].

Case Study 3: Cadmium (Cd) Exposure in Humans vs. Rodents

The immune system faces damage through exposure to cadmium in smoking and food contamination because it reduces natural killer cell abilities and antigen-presenting cell performance which results in both higher vulnerability to diseases and persistent inflammation. The exposure of mice to cadmium results in thymus atrophy together with T-cell population reduction and enhanced inflammatory responses. Results from immune dysfunction run more intensely in mice because these animals have elevated metabolic levels and shorter lifespans [52].

Implications for Public Health and Risk Assessment

The human body receives heavy metals through the ingestion of contaminated drinking water coupled with contaminated soil and crops from contaminated land sources [53]. The four heavy metals lead, mercury, cadmium together with copper function as collective poisons that generate environmental risks as well as showing exceptional toxicity according to research. The metals generate oxidative stress within cells while maintaining critical roles in developing various human pathologies such as carcinogenesis [54]. Heavy metal toxicity exposure results in brain damage alongside mental retardation and cerebral palsy together with lung cancer and gastrointestinal abnormalities and dermatitis causing death of unborn fetuses according to [55]. Scientific evidence demonstrates how various metals create DNA adducts that result in chromosomal breaks after affecting DNA directly or indirectly. Scavengers working at the dumpsite enjoy unrestricted entry daily to search for materials which often ends up in local food markets as animal feed and human food products. Animals such as stray chickens and pigs and dogs and cats consume toxic substances at the dumpsite before spreading parasites through the area which causes diseases in all species living there [56].

Potential Mitigation Strategies and Future Directions

Multiple measures should be used to remedy heavy metal exposure impacts on immune function including preventative measures and therapeutic interventions and regulatory activities. Three of the most powerful environmental strategies for remediation include soil washing combined with phytoremediation and bioremediation. The phytoremediation process using Brassica juncea (Indian mustard) and Helianthus annuus (sunflower) has proved effective in extracting heavy metals from contaminated areas including soils and water [57]. Pseudomonas putida along with Bacillus subtilis microorganisms demonstrate metal detoxification and bioaccumulation capability through bioremediation which lowers metal bioavailability and human health risks [58].

When treating heavy metals the medical community employs ethylenediaminetetraacetic acid (EDTA), dimercaptosuccinic acid (DMSA) and meso-2,3-dimercaptosuccinic acid (DMPS) as safe chemical chelating agents for detox. These chemicals attach to heavy metals to help urine-driven removal which lowers toxic materials that affect the immune system [59]. Antioxidative dietary components containing vitamin C and vitamin E and selenium possess protective properties which defend against heavy metal-induced immune dysfunction and oxidative stress. The antioxidant protection from Selenium stands vital in cadmium and mercury toxicity mitigation because it strengthens enzymes while decreasing inflammation levels [60].

Mitigating heavy metal toxicity necessitates the implementation of laws and stringent regulations governing industrial emissions, mining waste disposal, and agricultural heavy metal application. States must strengthen their regulatory framework for the Minamata Convention on Mercury and the Basel Convention on hazardous waste management, as per the United Nations Environment Programm. Nanotechnology has generated designed nanoparticles that efficiently eliminate metals from aquatic environments, resulting in significant reductions in environmental contamination [61].

Conclusions

Complete mitigation of heavy metal-induced immune dysfunction needs interdisciplinary solutions using environmental cleaning efforts and dietary treatment perspectives with regulatory standards improved by innovative medical studies. Sustained implementation of these methods enables us to minimize heavy metal exposure hazards which protect both human immune health and animal immunity. Research in the future should pursue environmentally-friendly approaches that are economically feasible to resolve this worldwide environmental and health problem.

Authors' contributions

ICMJE criteria	Details	Author(s)
1. Substantial contributions	Conception, OR	1
	Design of the work, OR	2,5,6
	Data acquisition, analysis, or interpretation	3,4
2. Drafting or reviewing	Draft the work, OR	1,2,5
	Review critically for important intellectual content	3,4,6
3. Final approval	Approve the version to be published	1,2,3,4,5,6
4. Accountable	Agree to be accountable for all aspects of the work	1,2,3,4,5,6

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

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Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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