CHAPTER 6

REVIEW OF CURRENT RESEARCH ON THE EFFECTS OF HEAVY METALS ON TISSUE REGENERATION PROCESSES: ECOLOGICAL AND MEDICAL-BIOLOGICAL ASPECTS

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INTRODUCTION

Rapid industrialization, urbanization, and intensification of agricultural production are accompanied by unprecedented anthropogenic pressure on the environment. Among the numerous environmental pollutants, heavy metals occupy a special place due to their high toxicity, resistance to degradation, ability for long-term migration in biosphere components, and bioaccumulation in living organisms[1, 2]. Priority ecotoxicants in this group include lead (Pb), cadmium (Cd), copper (Cu), zinc (Zn), chromium (Cr), and nickel (Ni), which enter the environment primarily through the activities of metallurgical, galvanic, chemical enterprises, thermal power generation, motor transport, as well as through the use of mineral fertilizers and plant protection agents[3,4].

The problem of heavy metal contamination becomes particularly relevant for Ukraine – a country with significant industrial potential, a large share of heavy industry, and high anthropogenic pressure on water bodies. In a number of regions, particularly in Dnipropetrovsk, Donetsk, Zaporizhzhia, and Mykolaiv regions, concentrations of heavy metals in surface waters, bottom sediments, and soils exceed permissible levels many times over, posing a real threat to

[1] Environmental exposure of arsenic impairs the cardiometabolic profile, skeletal muscle health, and neurological function. *Curr Opin Biomed Eng*. 2024. № 30. P. 100529. DOI: 10.1016/j.cobme.2024.100529

[2] Войціцький В. М., Хижняк С. В., Данчук В. В., Мідик С. В., Кеппл О. Ю., Ушкалов В. О. Надходження і міграція важких металів наземними та водними екосистемами. *Біоресурси і природокористування*. 2019. Т. 11. № № 1–2. С. 59–68. DOI: 10.31548/bio2019.01.007

[3] Environmental exposure of arsenic impairs the cardiometabolic profile, skeletal muscle health, and neurological function. *Curr Opin Biomed Eng*. 2024. № 30. P.100529. DOI: 10.1016/j.cobme.2024.100529

[4] Хижняк С. В., Войціцький В. М., Данчук В. М., Мідик С. В., Лапоша О. А., Ушкалов В. О. Шляхи міграції стійких пестицидів трофічними ланцюгами наземних і водних екосистем. *Біоресурси і природокористування*. 2018. Т. 10. № № 1–2. С. 36–43.

public health. Aquatic ecosystems are particularly vulnerable to heavy metal contamination, as they serve as final reservoirs for most pollutants entering through atmospheric precipitation, industrial and domestic wastewater, and surface runoff from agricultural lands[5].

It has been established that metals can induce powerful oxidative stress, damage nucleic acids, cause mitochondrial dysfunction, disrupt epigenetic regulation of gene expression, and activate apoptotic and ferroptotic signaling cascades. Of particular concern is the effect of heavy metals on reparative tissue regeneration processes, as impaired wound healing leads to chronic wounds, reduced patient quality of life, increased frequency of postoperative complications, and economic losses for the healthcare system. Numerous experimental studies on animals and cell cultures demonstrate that chronic heavy metal exposure is accompanied by inhibition of fibroblast proliferation, impaired collagen synthesis, reduced angiogenesis, and slowed keratinocyte migration in the wound defect[6]. Clinical observations confirm these data, indicating an increased incidence of trophic ulcers, diabetic foot, and slow-healing postoperative wounds in patients living in areas of technogenic pollution[7].

Despite significant progress in studying individual aspects of the problem, comprehensive studies that combine ecological monitoring of aquatic ecosystems with in-depth investigation of molecular-cellular mechanisms and clinical manifestations of regeneration disorders in people living in areas with varying anthropogenic loads are critically insufficient. This is particularly true for the Mykolaiv region, where, due to the activities of industrial enterprises (including metallurgical plants, shipyards, and chemical industry enterprises), significant contamination of water bodies with heavy metals is observed, yet systematic medical-biological studies of the impact of this contamination on tissue regeneration are practically absent[8].

This necessitates systematic and critical generalization of available scientific data to form a holistic understanding of the impact of heavy metals on tissue regeneration processes, identify research gaps, and develop a conceptual model that integrates ecological, molecular-biological, and clinical approaches.

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[5] Repair and regeneration: ferroptosis in the process of remodeling and fibrosis in impaired organs. *Cell Death Discov*. 2024. № 10. P. 424. DOI: 10.1038/s41420-024-02181-2

[6] Peters K., Staehlke S., Rebl H., et al. Impact of Metal Ions on Cellular Functions: A Focus on Mesenchymal Stem/Stromal Cell Differentiation. *Int J Mol Sci*. 2024. № 25 (18). P. 10127. DOI: 10.3390/ijms251810127

[7] Repair and regeneration: ferroptosis in the process of remodeling and fibrosis in impaired organs. *Cell Death Discov*. 2024. № 10. P. 424. DOI: 10.1038/s41420-024-02181-2

[8] Войціцький В. М., Хижняк С. В., Данчук В. В., Мідик С. В., Кеппл О. Ю., Ушкалов В. О. Надходження і міграція важких металів наземними та водними екосистемами. *Біоресурси і природокористування*. 2019. Т. 11. № № 1–2. С. 59–68. DOI: 10.31548/bio2019.01.007

Such a model can serve as a theoretical basis for planning further empirical studies aimed at assessing public health risks associated with environmental heavy metal contamination and developing effective strategies for the prevention and correction of regeneration disorders.

The aim of this work is to systematize and generalize current scientific data on the sources, migration, and bioaccumulation of heavy metals in aquatic ecosystems, the molecular and cellular mechanisms of their toxic effects with an emphasis on disorders of reparative tissue regeneration, and the analysis of clinical consequences of metal bioaccumulation for the development of a conceptual research model.

1. Ecological aspects of heavy metal contamination of aquatic ecosystems and their bioaccumulation

1.1. Sources of input and migration of heavy metals in aquatic ecosystems

The main anthropogenic sources of heavy metal input into aquatic ecosystems are industrial discharges (enterprises of metallurgical, machine-building, galvanic, chemical, and wood-processing industries), atmospheric deposition (products of fuel combustion, motor vehicle emissions, technological emissions from industrial enterprises), agricultural runoff (washout from fields of mineral fertilizers, pesticides, ameliorants), as well as domestic wastewater (containing detergents, cosmetics, pharmaceuticals containing metals). In addition, surface runoff from urbanized areas, where metals accumulate in soils, road dust, and atmospheric emissions, is a significant source of heavy metals[9].

Once in the aquatic environment, heavy metals undergo complex physicochemical transformations that determine their migration capacity, bioavailability, and ecological hazard. Metals can be present in water in dissolved ionic form, as part of complex compounds (with carbonates, sulfates, chlorides, organic ligands), sorbed on suspended particles (clay minerals, iron and manganese hydroxides, organic matter), or precipitated in bottom sediments. The distribution of metals between these forms depends on numerous factors: pH and redox potential of the aqueous medium, temperature, salinity, presence of complexing agents (humic and fulvic acids), hydrodynamic conditions (flow velocity, mixing), and biological activity. The most bioavailable and toxic form is the free ionic form of metals, while sorbed and complexed forms are less accessible to aquatic organisms.

The migration capacity of heavy metals in aquatic ecosystems varies significantly. Thus, cadmium and zinc are characterized by high mobility and the ability for long-term transport in dissolved state, while lead and copper

[9] Амонс С. Е., Яковець Л. А. Вплив важких металів на основні фізіологічні процеси зернових та зернобобових культур. *Сільське господарство та лісівництво*. 2023. № 30. С. 211–227. DOI: 10.37128/2707-5826-2023-3-16

tend to sorb onto suspended particles and precipitate into bottom sediments. Chromium in its toxic hexavalent form (Cr^{6+}) is highly mobile, while the less toxic trivalent chromium (Cr^{3+}) rapidly hydrolyzes and precipitates. Nickel occupies an intermediate position, demonstrating moderate mobility and the ability to form complexes with organic substances[10].

1.2. Comparative characteristics of heavy metal concentrations in water bodies of Ukraine and the world

Analysis of literature data indicates significant regional differences in levels of heavy metal contamination of aquatic ecosystems. The highest concentrations of Pb, Cd, Cu, Zn, Cr, and Ni in surface waters and bottom sediments are observed in industrially developed regions of the world: Southeast Asia (China, India, Vietnam), Latin America (Mexico, Peru, Chile), Eastern Europe (Poland, Czech Republic, Ukraine), and certain areas of Africa (South Africa, Zambia). Table 1 presents summarized data on heavy metal concentrations in water bodies of various regions of the world.

Table 1

Average concentrations of heavy metals (mg/L) in surface waters of different regions of the world

Region	Pb	Cd	Cu	Zn	Cr	Ni
Western Europe	3–15	0.3–2	5–30	20–100	2–15	5–25
Eastern Europe	10–80	1–15	10–80	50–400	10–60	10–50
Southeast Asia	20–150	2–30	15–120	80–600	15–100	15–80
North America	2–10	0.2–1.5	3–25	15–80	1–10	3–20
Ukraine (overall)	15–60	1–10	10–70	40–300	8–50	8–40
Mykolaiv region	25–90	3–18	20–120	60–450	15–80	12–60
MPC Ukraine*	30	5	10	100	50	20

Summarized from data[11, 12, 13].

**MPC – maximum permissible concentration for water bodies of domestic drinking water use (according to Ukrainian regulatory documents).*

[10] Черниченко І. О., Литвиченко О. М., Бабій В. Ф., Кондратенко О. Є., Главачек Д. О. До питання фонового рівня забруднення ґрунтів важкими металами для визначення впливу воєнних дій. Довкілля та здоров'я. 2025. № 1 (114). P. 18–23. DOI: 10.32402/dovkil2025.01.018

[11] Environmental exposure of arsenic impairs the cardiometabolic profile, skeletal muscle health, and neurological function. *Curr Opin Biomed Eng*. 2024. № 30. P. 100529. DOI: 10.1016/j.cobme.2024.100529

[12] Войціцький В. М., Хижняк С. В., Данчук В. В., Мідик С. В., Кеппл О. Ю., Ушкалов В. О. Надходження і міграція важких металів наземними та водними екосистемами. *Біоресурси і природокористування*. 2019. Т. 11. № № 1–2. С. 59–68. DOI: 10.31548/bio2019.01.007

[13] Жукова О. Г., Старжинський П. С., Прокопенко І. О. Забруднення водних екосистем важкими металами внаслідок військових дій та їх вплив на здоров'я людини. *Екологічна безпека держави 2025 :* матеріали Науково-практичної конференції. Київ, 2025. С. 61–63. DOI: 10.18372/2786-8168.19.19971

As seen from Table 1, in water bodies of Ukraine, heavy metal concentrations significantly exceed levels characteristic of Western Europe and North America and approach those of Southeast Asia.

A particularly dangerous situation is observed in the Mykolaiv region, where exceedances of MPC for lead, cadmium, copper, zinc, chromium, and nickel range from 1.5 to 12 times. The high concentration of heavy metals in the water bodies of the Mykolaiv region is associated with the activities of large industrial enterprises, particularly the metallurgical plant "Naftokhimik", shipbuilding yards, machine-building enterprises, and significant anthropogenic pressure on the Southern Bug River and its tributaries[14].

1.3. Bioaccumulation and biomagnification of heavy metals in trophic chains

One of the most dangerous properties of heavy metals is their ability for bioaccumulation – selective accumulation in the tissues of living organisms at concentrations significantly exceeding their content in the environment[15]. Mechanisms of bioaccumulation include passive adsorption of metals on cell surface structures (especially algae and bacteria), active transport uptake through ion channels and transporters (for metals with physiological functions, e.g., Cu, Zn), as well as phagocytosis and pinocytosis of metal-containing particles. In aquatic organisms, metal bioaccumulation depends on a number of factors: species and physiological state of the organism, temperature, pH, salinity, metal concentration in water and food, exposure duration, presence of chelators and other competing ions[16].

Of greatest ecological and medical concern is biomagnification – the increase in heavy metal concentrations with each successive trophic level. Studies show that bioaccumulation factors (ratio of metal concentration in organism tissues to its concentration in water) for different metals and species range from tens to hundreds of thousands[17]. In particular, for cadmium, the bioaccumulation factor in algae can reach 10^4–10^5, in mollusks – 10^3–10^4, in fish – 10^2–10^3. This

[14] Войціцький В. М., Хижняк С. В., Данчук В. В., Мідик С. В., Кеппл О. Ю., Ушкалов В. О. Надходження і міграція важких металів наземними та водними екосистемами. *Біоресурси і природокористування*. 2019. Т. 11. № № 1–2. С. 59–68. DOI: 10.31548/bio2019.01.007

[15] Environmental exposure of arsenic impairs the cardiometabolic profile, skeletal muscle health, and neurological function. *Curr Opin Biomed Eng*. 2024. № 30. P. 100529. DOI: 10.1016/j.cobme.2024.100529

[16] Черниченко І. О., Литвиченко О. М., Бабій В. Ф., Кондратенко О. Є., Главачек Д. О. До питання фонового рівня забруднення ґрунтів важкими металами для визначення впливу воєнних дій. Довкілля та здоров'я. 2025. № 1 (114). P. 18–23. DOI: 10.32402/dovkil2025.01.018

[17] Хижняк С. В., Войціцький В. М., Данчук В. М., Мідик С. В., Лапоша О. А., Ушкалов В. О. Шляхи міграції стійких пестицидів трофічними ланцюгами наземних і водних екосистем. *Біоресурси і природокористування*. 2018. Т. 10. № № 1–2. С. 36–43.

means that even at relatively low metal concentrations in water, their content in fish tissues (especially predatory species at the top of the trophic pyramid) can reach toxic levels, posing a direct threat to the health of people consuming this fish[18].

In Ukraine, the problem of heavy metal bioaccumulation in aquatic ecosystems is particularly acute. Studies conducted in the basins of the Dnipro, Dniester, Southern Bug, and Siverskyi Donets rivers indicate significant accumulation of Pb, Cd, Cu, Zn, Cr, and Ni in the tissues of indigenous fish species (carp, perch, pike, zander, bream)[19]. It has been established that the content of lead in fish muscles from contaminated water bodies of the Mykolaiv region is 3–5 times higher, and cadmium – 2–8 times higher than permissible standards for food products. Consumption of such fish by the population leads to chronic intake of heavy metals into the body and their accumulation in critical organs (bones, kidneys, liver, hair, nails), which is confirmed by biomonitoring data[20].

1.4. Medical-ecological studies of heavy metal bioaccumulation in the population

Results of medical-ecological studies conducted in Ukraine and abroad convincingly demonstrate a clear correlation between the level of heavy metal bioaccumulation in the population and increased incidence of chronic diseases. Studies of populations living in areas of technogenic pollution reveal a significant increase in the content of Pb, Cd, Cu, Zn, Cr, and Ni in hair, blood, urine, and nails of residents compared to controls[21]. In Ukraine, the most indicative are studies conducted in the industrial regions of Donbas, Prydniprovia, and Pryazovia, where the content of heavy metals in biological substrates of the population is 2–10 times higher than background levels[22].

Of particular interest are studies demonstrating a link between chronic heavy metal intake and tissue regeneration disorders. Thus, in patients with chronic

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[18] Жукова О. Г., Старжинський П. С., Прокопенко І. О. Забруднення водних екосистем важкими металами внаслідок військових дій та їх вплив на здоров'я людини. *Екологічна безпека держави 2025 :* матеріали Науково-практичної конференції. Київ, 2025. С. 61–63. DOI: 10.18372/2786-8168.19.19971

[19] Мосієнко Н. М. Вплив важких металів на екологічно безпечне споживання продукції рибництва і аквакультури. *Grail of Science*. 2022. № 17. P. 204–206. DOI: 10.36074/grail-of-science.22.07.2022.036

[20] Jomova K., Valko M. Advances in metal-induced oxidative stress and human disease. *Toxicology*. 2023. № 498. P. 153645. DOI: 10.1016/j.tox.2023.153645

[21] Войціцький В. М., Хижняк С. В., Данчук В. В., Мідик С. В., Кеппл О. Ю., Ушкалов В. О. Надходження і міграція важких металів наземними та водними екосистемами. *Біоресурси і природокористування*. 2019. Т. 11. № № 1–2. С. 59–68. DOI: 10.31548/bio2019.01.007

[22] Andrusyshyna I. M., Dmytrukha N. M. Biomonitoring of heavy metals in the population of Ukraine: consequences of the impact of the Chernobyl Accident and current challenges. *Ukrainian Journal of Medical Science.* 2026. Vol. 32 (1). P. 105–119. DOI: 10.37621/ujms.32.1.2026.07

trophic ulcers of the lower extremities living in industrial areas, concentrations of Pb and Cd in blood and hair are significantly higher than in patients from favorable regions, and these indicators negatively correlate with the rate of ulcer healing[23]. Similar data were obtained in the study of postoperative wounds: in patients with high body content of heavy metals, delayed epithelialization, increased frequency of suppuration, and formation of coarse scars are observed. Furthermore, chronic heavy metal intoxication is associated with an increased risk of cardiovascular diseases (ischemic heart disease, arterial hypertension), nephropathies, osteoporosis, neurodegenerative disorders (Alzheimer's disease, Parkinson's disease), which additionally complicates the wound process and hinders regeneration[24].

2. Molecular and cellular mechanisms of heavy metal effects on tissue regeneration processes

2.1. Induction of oxidative stress and its role in regeneration impairment

The primary and most universal mechanism of heavy metal toxicity in cells is the induction of oxidative stress, which consists of excessive generation of reactive oxygen species (ROS) and disruption of the prooxidant-antioxidant balance.

Heavy metals, especially variable-valence metals (iron, copper, chromium), can catalyze Fenton and Haber-Weiss reactions, resulting in the formation of highly reactive hydroxyl radicals (OH) that damage lipids, proteins, and DNA[25]. In addition, metals (especially Pb and Cd) disrupt the functioning of the mitochondrial electron transport chain, leading to increased production of superoxide anion radical (O_2^-) and hydrogen peroxide (H_2O_2)[26].

Chronic elevation of ROS levels in regenerating tissues causes a number of negative consequences. First, oxidative modification of lipid cell membranes disrupts their permeability and receptor function, which is particularly critical for actively proliferating cells (fibroblasts, keratinocytes, endothelial cells). Second, oxidative damage to proteins leads to their denaturation and aggregation, disrupting the function of enzymes, transport proteins, and signaling molecules. Third, DNA damage (formation of 8-oxoguanine, single- and double-strand breaks, crosslinks) activates repair systems, but under chronic oxidative stress,

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[23] Черниченко І. О., Литвиченко О. М., Бабій В. Ф., Кондратенко О. Є., Главачек Д. О. До питання фонового рівня забруднення ґрунтів важкими металами для визначення впливу воєнних дій. Довкілля та здоров'я. 2025. № 1 (114). P. 18–23. DOI: 10.32402/dovkil2025.01.018

[24] Cosselman K. E., Navas-Acien A., Kaufman J. D. Environmental factors in cardiovascular disease. *Nat Rev Cardiol*. 2023. № 20 (7). P. 471–488.

[25] Stockwell B. R. Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. *Cell.* 2022. № 185 (14). P. 2401–2421.

[26] Jomova K., Valko M. Advances in metal-induced oxidative stress and human disease. *Toxicology*. 2023. № 498. P. 153645. DOI: 10.1016/j.tox.2023.153645

repair becomes inefficient, leading to accumulation of mutations and cellular senescence[27].

Particularly sensitive to oxidative stress caused by heavy metals are stem and progenitor cells, which play a key role in tissue regeneration. Studies show that mesenchymal stromal cells (MSCs), endothelial progenitor cells, and muscle satellite cells demonstrate high sensitivity to oxidative stress, manifested by decreased proliferative activity, impaired differentiation, activation of apoptosis, and premature senescence[28].

Since these cells provide continuous tissue renewal and reparative responses, their dysfunction under heavy metal exposure leads to depletion of tissue regenerative potential and chronicity of the pathological process.

2.2. DNA damage, epigenetic changes, and disruption of signaling pathways

Heavy metals cause direct and indirect (via ROS) DNA damage, activating the DNA damage response (DDR) signaling cascade, which includes phosphorylation of ATM (ataxia telangiectasia mutated) and ATR (ATM- and Rad3-related) kinases, activation of effector Chk1/Chk2 kinases, and cell cycle arrest at G1/S and G2/M phases. When repair fails, proapoptotic signaling pathways (p53, caspase cascade) are activated, leading to elimination of damaged cells. In the context of tissue regeneration, excessive activation of apoptosis in proliferating cell pools leads to a deficiency of cellular material necessary for filling the wound defect and tissue remodeling.

In addition to DNA damage, heavy metals can induce epigenetic changes, including DNA hypo- and hypermethylation, histone modifications (acetylation, methylation, phosphorylation), and changes in microRNA expression[1]. These epigenetic changes can lead to persistent alteration of gene expression regulating proliferation, differentiation, angiogenesis, and extracellular matrix synthesis, even after cessation of metal exposure. In particular, it has been established that chronic lead and cadmium exposure is accompanied by hypermethylation of promoters of tumor suppressor genes (p53, p16, p21), leading to their transcriptional repression and creating conditions for uncontrolled proliferation of fibroblasts and endothelial cells, which may contribute to fibrogenesis and disruption of normal tissue remodeling[29].

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[27] Repair and regeneration: ferroptosis in the process of remodeling and fibrosis in impaired organs. *Cell Death Discov*. 2024. № 10. P. 424. DOI: 10.1038/s41420-024-02181-2

[28] Peters K., Staehlke S., Rebl H., et al. Impact of Metal Ions on Cellular Functions: A Focus on Mesenchymal Stem/Stromal Cell Differentiation. *Int J Mol Sci*. 2024. № 25 (18). P. 10127. DOI: 10.3390/ijms251810127

[29] Environmental exposure of arsenic impairs the cardiometabolic profile, skeletal muscle health, and neurological function. *Curr Opin Biomed Eng*. 2024. № 30. P. 100529. DOI: 10.1016/j.cobme.2024.100529

An important mechanism of regeneration impairment is the effect of heavy metals on key signaling pathways that regulate cell proliferation, differentiation, and migration. Studies show that metals can inhibit the Wnt/β-catenin signaling pathway,

which plays a critical role in maintaining stemness and activating proliferation upon tissue damage[30]. In addition, the TGF-β/Smad signaling pathway, which regulates fibroblast differentiation into myofibroblasts, collagen synthesis, and extracellular matrix production, is disrupted. The effect of metals on the PI3K/Akt/mTOR signaling pathway leads to disruption of cellular metabolism, reduced protein synthesis, and inhibition of angiogenesis. Disruption of the MAPK/ERK signaling pathway, which regulates keratinocyte proliferation and differentiation, slows epithelialization of the wound defect.

2.3. Mitochondrial dysfunction, apoptosis, and ferroptosis

Mitochondria are one of the primary targets of heavy metal toxicity. Metals accumulate in mitochondria, disrupting the functioning of the electron transport chain, inhibiting Krebs cycle enzymes and oxidative phosphorylation, and causing opening of the mitochondrial permeability transition pore (mPTP). This leads to uncoupling of oxidative phosphorylation, sharp reduction of ATP synthesis, increased ROS production, and release of proapoptotic factors (cytochrome c, AIF, Smac/DIABLO) from the intermembrane space into the cytosol[31].

Mitochondrial dysfunction plays a key role in tissue regeneration impairment for several reasons. First, energy deficiency inhibits macromolecule synthesis (proteins, nucleic acids, lipids) necessary for cell proliferation and migration, as well as for extracellular matrix synthesis[32]. Second, mitochondrial ROS initiate chain reactions of oxidative damage spreading to other cellular compartments. Third, release of proapoptotic factors activates the caspase cascade, leading to massive apoptosis of cells in the wound bed, disrupting the normal course of inflammatory and proliferative phases of healing.

In recent years, particular attention has been drawn to the phenomenon of ferroptosis – an iron-dependent regulated form of cell death characterized by

[30] Peters K., Staehlke S., Rebl H., et al. Impact of Metal Ions on Cellular Functions: A Focus on Mesenchymal Stem/Stromal Cell Differentiation. *Int J Mol Sci*. 2024. № 25 (18). P. 10127. DOI: 10.3390/ijms251810127

[31] Environmental exposure of arsenic impairs the cardiometabolic profile, skeletal muscle health, and neurological function. *Curr Opin Biomed Eng*. 2024. № 30. P. 100529. DOI: 10.1016/j.cobme.2024.100529

[32] Peters K., Staehlke S., Rebl H., et al. Impact of Metal Ions on Cellular Functions: A Focus on Mesenchymal Stem/Stromal Cell Differentiation. *Int J Mol Sci*. 2024. № 25 (18). P. 10127. DOI: 10.3390/ijms251810127

accumulation of lipid peroxides, iron overload of cells, and oxidative membrane damage. Studies show that heavy metals, especially iron and copper, can actively induce ferroptosis through ROS generation, inhibition of the glutathione peroxidase 4 (GPX4) system, and accumulation of toxic lipid hydroperoxides. In the context of regeneration, ferroptosis can play a dual role. On one hand, it is necessary for elimination of damaged cells in the wound and initiation of the inflammatory response, which is critical for the onset of regeneration. On the other hand, excessive activation of ferroptosis in proliferating cells, endothelial cells, and fibroblasts leads to loss of cellular material, impaired angiogenesis, hypoxia, and chronic inflammation. Furthermore, ferroptosis is associated with fibroblast activation and excessive collagen deposition, contributing to fibrogenesis and disruption of normal tissue remodeling[33, 34].

2.4. Effect of heavy metals on key cellular processes of regeneration

The effects of heavy metals on key cellular processes of reparative regeneration have been studied in models of cell cultures (fibroblasts, keratinocytes, endothelial cells, MSCs) and experimental animals (rats, mice, guinea pigs)[35]. Summarized data from these studies are presented in Table 2.

As seen from Table 2, heavy metals cause multifactorial disruption of almost all key processes that ensure normal wound healing. Particularly critical is the inhibition of angiogenesis and fibroblast proliferation, as this leads to hypoxia, nutrient deficiency, delayed clearance of the wound from necrotic masses, and formation of weak, immature scar tissue. At the same time, activation of fibrogenesis under metal influence can create a paradoxical situation where, despite excessive collagen deposition, the mechanical properties of the scar remain low due to its immaturity and disorganization of collagen fibers[36, 37].

Experimental studies in animals confirm that chronic heavy metal intake leads to significant slowing of healing of various types of wounds (mechanical, thermal, surgical), reduced mechanical strength of the scar, increased frequency of suppuration, and formation of coarse keloid scars. In animals with experimental diabetes mellitus additionally exposed to heavy metals,

[33] Andrusyshyna I. M., Dmytrukha N. M. Biomonitoring of heavy metals in the population of Ukraine: consequences of the impact of the Chernobyl Accident and current challenges. *Ukrainian Journal of Medical Science.* 2026. Vol. 32 (1). P. 105–119. DOI: 10.37621/ujms.32.1.2026.07

[34] Stockwell B. R. Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. *Cell*. 2022. № 185 (14). P. 2401–2421.

[35] Cosselman K. E., Navas-Acien A., Kaufman J. D. Environmental factors in cardiovascular disease. *Nat Rev Cardiol*. 2023. № 20 (7). P. 471–488.

[36] Cosselman K. E., Navas-Acien A., Kaufman J. D. Environmental factors in cardiovascular disease. *Nat Rev Cardiol*. 2023. № 20 (7). P. 471–488.

[37] Stockwell B. R. Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. *Cell*. 2022. № 185 (14). P. 2401–2421.

regeneration disorders were even more pronounced, indicating a synergistic negative effect of metals and metabolic disorders[38].

Table 2

Effects of heavy metals on key processes of tissue regeneration

Regeneration process	Effect of heavy metals	Mechanisms	Consequences
Fibroblast proliferation	Inhibition (up to 40–70% depending on concentration)	Oxidative stress, DNA damage, inhibition of signaling pathways (PI3K/Akt, MAPK/ERK)	Deficiency of extracellular matrix synthesis
Collagen synthesis	Reduction (up to 50–80%)	Oxidative modification of enzymes (prolyl hydroxylase, lysyl hydroxylase), disruption of collagen gene expression	Reduced mechanical strength of scar
Angiogenesis	Inhibition (up to 60–90%)	Oxidative stress, ferroptosis of endothelial cells, inhibition of VEGF/VEGFR signaling, reduced MMP-2, MMP-9 activity	Hypoxia, nutrient deficiency in wound
Keratinocyte migration	Slowing (up to 50–70%)	Disruption of cytoskeleton reorganization, decreased integrin and cadherin expression	Delayed wound epithelialization
MSC differentiation	Disruption	Altered expression of transcription factors (Runx2, PPARγ, Sox9)	Deficiency of tissue regenerative potential
Fibrogenesis	Enhancement	TGF-β/Smad activation, excessive collagen deposition, activation of fibroblast ferroptosis	Formation of hypertrophic and keloid scars

Summarized from data[39].

3. Clinical consequences of heavy metal bioaccumulation and conceptual research model

3.1. Clinical observations and epidemiological data

Clinical observations in humans convincingly confirm the results of experimental studies, demonstrating a clear correlation between the level of heavy metal bioaccumulation and tissue regeneration impairment.

[38] Peters K., Staehlke S., Rebl H., et al. Impact of Metal Ions on Cellular Functions: A Focus on Mesenchymal Stem/Stromal Cell Differentiation. *Int J Mol Sci*. 2024. № 25 (18). P. 10127. DOI: 10.3390/ijms251810127

[39] Peters K., Staehlke S., Rebl H., et al. Impact of Metal Ions on Cellular Functions: A Focus on Mesenchymal Stem/Stromal Cell Differentiation. *Int J Mol Sci*. 2024. № 25 (18). P. 10127. DOI: 10.3390/ijms251810127

Epidemiological studies conducted in different countries (USA, China, Poland, Italy, Ukraine) demonstrate that populations living in areas of technogenic heavy metal contamination have significantly higher rates of chronic trophic ulcers, diabetic foot, slow-healing postoperative wounds, and postoperative complications (suppuration, wound dehiscence, formation of coarse scars).

In Ukraine, the most indicative are studies conducted in the Mykolaiv, Dnipropetrovsk, and Zaporizhzhia regions. Thus, in surgical patients in the city of Mykolaiv with high levels of Pb, Cd, Cu, Zn, Cr, and Ni in hair and blood, significant slowing of postoperative wound healing was observed (average healing time increased by 5–12 days), increased frequency of suppuration (by 2–4 times), and formation of hypertrophic scars (by 3–5 times) compared to the control group. Similar data were obtained in the study of patients with chronic trophic ulcers of the lower extremities: high concentration of heavy metals in the body was an independent risk factor for prolonged non-healing of ulcers, ineffectiveness of conservative therapy, and recurrence[40].

Clinical studies also confirm the link between heavy metal bioaccumulation and microcirculation disorders, which are important factors in regeneration. In patients with high blood levels of Pb, Cd, and Cr, decreased capillary blood flow, slowed venous outflow, increased blood viscosity, and endothelial dysfunction are observed, manifested by reduced vasodilation, increased endothelin-1 levels, and decreased nitric oxide (NO) levels[41]. These microcirculatory disorders create additional obstacles to the delivery of oxygen, nutrients, and immune system cells to the wound area, slowing healing and increasing the risk of infectious complications[42].

3.2. Research gaps and justification for the need for a comprehensive approach

Despite a significant body of scientific data confirming the negative impact of heavy metals on tissue regeneration, there are substantial gaps that hinder the formation of a holistic picture and the development of effective prevention and treatment strategies. First, most studies focus on individual metals in isolated experimental systems, while in real conditions the body is exposed to a mixture of metals that can interact (synergistically, antagonistically, or additively).

[40] Хижняк С. В., Войціцький В. М., Данчук В. М., Мідик С. В., Лапоша О. А., Ушкалов В. О. Шляхи міграції стійких пестицидів трофічними ланцюгами наземних і водних екосистем *Біоресурси і природокористування*. 2018. Т. 10. № № 1–2. С. 36–43.

[41] Cosselman K. E., Navas-Acien A., Kaufman J. D. Environmental factors in cardiovascular disease. *Nat Rev Cardiol*. 2023. № 20 (7). P. 471–488.

[42] Peters K., Staehlke S., Rebl H., et al. Impact of Metal Ions on Cellular Functions: A Focus on Mesenchymal Stem/Stromal Cell Differentiation. *Int J Mol Sci*. 2024. № 25 (18). P. 10127. DOI: 10.3390/ijms251810127

Second, the vast majority of work has been performed on cell cultures and experimental animals, while extrapolation of these results to humans requires caution due to species differences in metabolism, distribution, and sensitivity to metals[43].

Third, practically absent are comprehensive studies that combine ecological monitoring of aquatic ecosystems (metal concentrations in water, bottom sediments, soils) with biomonitoring of the population (metal content in hair, blood, nails, urine), in-depth study of molecular-cellular mechanisms of regeneration impairment (oxidative stress, mitochondrial dysfunction, ferroptosis, disruption of signaling pathways), and clinical observations (wound healing dynamics, complication rates, scar quality). This is particularly true for Ukraine, where despite high levels of environmental heavy metal contamination, systematic medical-ecological studies of the impact of this contamination on tissue regeneration are practically absent[44].

Fourth, insufficient attention has been paid to the study of populations living in areas with varying anthropogenic loads, particularly in the Mykolaiv region. The absence of such studies does not allow assessment of regional features of heavy metal impact on public health, identification of vulnerable risk groups, or development of targeted prevention and correction measures for regeneration disorders. Furthermore, there is a lack of studies evaluating the effectiveness of various strategies for correcting regeneration disorders (antioxidant therapy, chelation therapy, use of regenerative technologies) in patients chronically exposed to heavy metals[45].

3.3. Conceptual research model

Based on the generalization of analyzed scientific data and identified gaps, we have formulated a conceptual research model that describes the cascade of events from ecological load to clinical consequences of tissue regeneration impairment. The model includes four sequential levels that are logically interconnected (Fig. 1).

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[43] Environmental exposure of arsenic impairs the cardiometabolic profile, skeletal muscle health, and neurological function. *Curr Opin Biomed Eng*. 2024. № 30. P. 100529. DOI: 10.1016/j.cobme.2024.100529

[44] Хижняк С. В., Войціцький В. М., Данчук В. М., Мідик С. В., Лапоша О. А., Ушкалов В. О. Шляхи міграції стійких пестицидів трофічними ланцюгами наземних і водних екосистем. *Біоресурси і природокористування*. 2018. Т. 10. № № 1–2. С. 36–43.

[45] Peters K., Staehlke S., Rebl H., et al. Impact of Metal Ions on Cellular Functions: A Focus on Mesenchymal Stem/Stromal Cell Differentiation. *Int J Mol Sci*. 2024. № 25 (18). P. 10127. DOI: 10.3390/ijms251810127

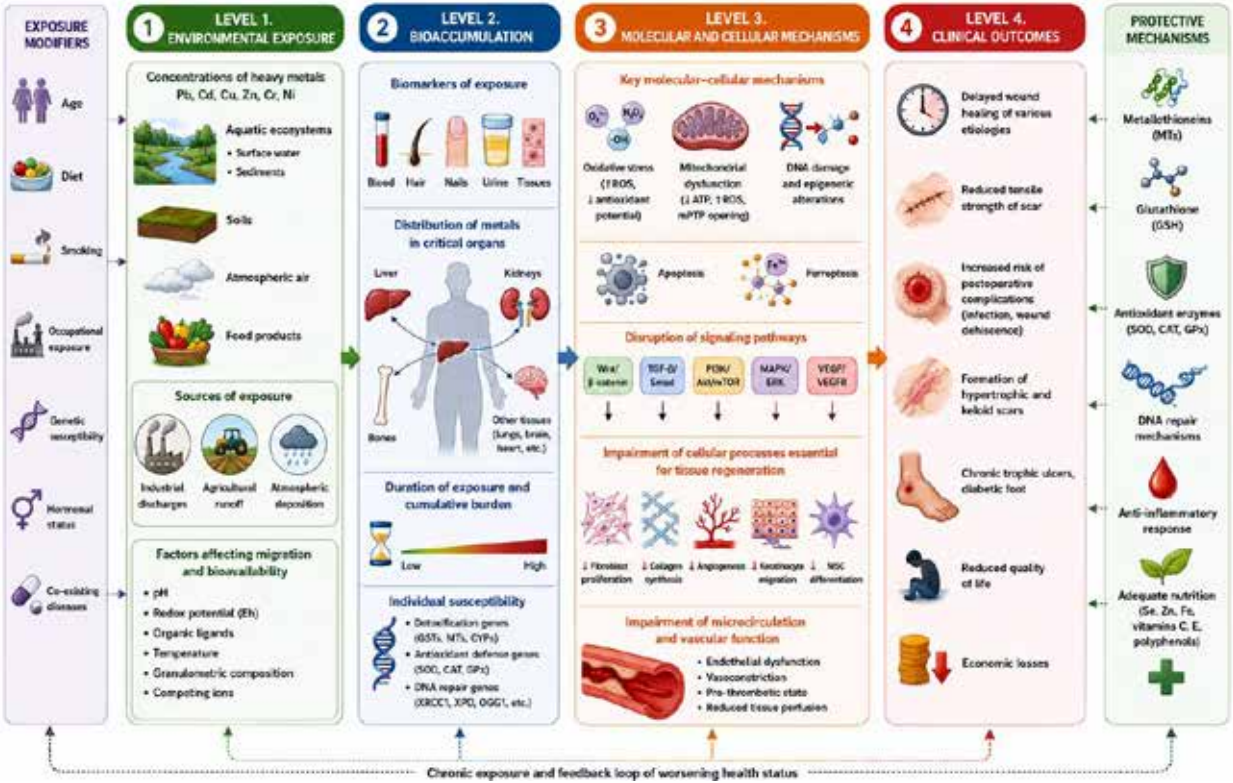

Fig. 1. Conceptual model of research on the effects of heavy metals on tissue regeneration

Level 1: Ecological load:

– concentrations of Pb, Cd, Cu, Zn, Cr, Ni in aquatic ecosystems (surface waters, bottom sediments);

– concentrations of metals in soils, atmospheric air, food products;

– sources of input (industrial discharges, agricultural runoff, atmospheric deposition);

– factors affecting migration and bioavailability (pH, redox potential, organic ligands).

↓

Level 2: Bioaccumulation:

– metal content in hair, blood, nails, urine, tissues of the population;

– distribution of metals between critical organs (bones, kidneys, liver);

– duration of exposure, cumulative load;

– individual sensitivity (polymorphism of detoxification, antioxidant defense, DNA repair genes).

↓

Level 3: Physiological effects at the molecular-cellular level:

– oxidative stress (ROS, decreased antioxidant potential);

– mitochondrial dysfunction (reduced ATP, ↑ROS, mPTP opening);

– DNA damage and epigenetic changes;

– apoptosis and ferroptosis of cells;

– disruption of signaling pathways (Wnt/β-catenin, TGF-β/Smad, PI3K/Akt/mTOR, MAPK/ERK, VEGF/VEGFR);

– inhibition of fibroblast proliferation, reduced collagen synthesis;

– impaired angiogenesis, keratinocyte migration, MSC differentiation;

– microcirculation disorders, endothelial dysfunction.

↓

Level 4: Clinical consequences:

– delayed wound healing of various etiologies;

– reduced mechanical strength of the scar;

– increased frequency of postoperative complications (suppuration, wound dehiscence);

– formation of hypertrophic and keloid scars;

– chronicity of trophic ulcers, diabetic foot;

– reduced quality of life, economic losses.

The proposed model allows: a) logical linking of different research levels (ecological, biomonitoring, molecular-cellular, clinical); b) identification of critical links requiring priority investigation; c) justification of marker selection for each level; d) planning of empirical studies aimed at assessing the impact of specific environmental factors on tissue regeneration in specific

regions (particularly in the Mykolaiv region); e) development and evaluation of the effectiveness of strategies for prevention and correction of regeneration disorders caused by heavy metals.

The model has particular value for planning studies in the Mykolaiv region, where high levels of heavy metal contamination of aquatic ecosystems are observed, yet systematic medical-ecological works integrating all four levels are absent. Implementation of such studies will allow: 1) assessment of the real ecological load on the region's population; 2) determination of levels of metal bioaccumulation in different age and professional groups; 3) identification of molecular-cellular markers of regeneration impairment; 4) establishment of clinical correlates of these disorders; 5) development of scientifically grounded recommendations for the prevention and treatment of regeneration disorders under conditions of technogenic contamination.

CONCLUSIONS

1. The generalization of current scientific data indicates that aquatic ecosystems of Ukraine, particularly in the Mykolaiv region, are subject to significant anthropogenic pressure from heavy metals (Pb, Cd, Cu, Zn, Cr, Ni), the concentrations of which in surface waters and bottom sediments exceed maximum permissible levels many times over. Due to their ability for bioaccumulation and biomagnification, these metals enter the human body through drinking water and food products (fish, seafood), posing a threat of chronic intoxication.

2. The molecular and cellular mechanisms of heavy metal toxicity leading to impairment of reparative tissue regeneration include induction of oxidative stress, DNA damage, mitochondrial dysfunction, activation of apoptosis and ferroptosis, disruption of signaling pathways regulating cell proliferation, differentiation and migration, as well as epigenetic changes. These mechanisms manifest as inhibition of fibroblast proliferation, reduced collagen synthesis, impaired angiogenesis, slowed keratinocyte migration, as confirmed by the results of experimental studies on animals and cell cultures.

3. Clinical observations and epidemiological studies confirm the correlation between the level of heavy metal bioaccumulation in the population and increased incidence of chronic diseases, delayed wound healing, increased frequency of postoperative complications, and formation of coarse scars. Particularly indicative are data from industrial regions of Ukraine, especially the Mykolaiv region, where high levels of environmental heavy metal contamination are associated with unsatisfactory tissue regeneration indicators in surgical patients.

4. Significant research gaps have been identified: the absence of comprehensive studies that combine ecological monitoring of aquatic

ecosystems with biomonitoring of the population, in-depth study of molecular-cellular mechanisms of regeneration impairment, and clinical observations, particularly in the Mykolaiv region. Insufficient attention has been paid to individual sensitivity to metals related to genetic polymorphism, as well as the effectiveness of strategies for correcting regeneration disorders.

5. A conceptual research model has been developed that integrates four levels – ecological load → bioaccumulation → physiological effects (molecular-cellular disorders) → clinical consequences – which can serve as a theoretical basis for planning empirical studies aimed at assessing public health risks associated with environmental heavy metal contamination and developing scientifically grounded recommendations for the prevention and correction of regeneration disorders under conditions of anthropogenic pressure.

SUMMARY

This article systematizes and summarizes current scientific data on the sources of heavy metal (Pb, Cd, Cu, Zn, Cr, Ni) input into aquatic ecosystems, their migration, transformation, and bioaccumulation in trophic chains. A comparative characterization of metal concentrations in various water bodies of Ukraine and the world is presented, and regional features of contamination are identified. The molecular mechanisms of heavy metal toxicity are analyzed, including the induction of oxidative stress, DNA damage, mitochondrial dysfunction, apoptosis, ferroptosis, and disruption of signaling pathways that regulate cell proliferation, differentiation, and migration. Special attention is paid to the effects of metals on reparative tissue regeneration – fibroblast proliferation, collagen synthesis, angiogenesis, keratinocyte migration, and scar tissue formation. A comparative analysis of the results of experimental studies on animals (rats, mice, guinea pigs) and cell cultures, as well as clinical observations in humans, is presented. The results of medical-ecological studies conducted in Ukraine and abroad are summarized, demonstrating a correlation between the level of heavy metal bioaccumulation in the population and an increased incidence of chronic diseases, delayed wound healing, and increased frequency of postoperative complications. Significant research gaps are identified, particularly the absence of comprehensive studies that combine ecological monitoring of aquatic ecosystems with clinical observations of tissue regeneration in people living in areas with varying anthropogenic loads (particularly in the Mykolaiv region). A conceptual research model is formulated that integrates ecological load, bioaccumulation, physiological effects, and clinical consequences, which can serve as a basis for designing empirical studies.

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