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Bioinorganic Chemistry of Trace Elements: Biological Functions and Toxicological Implications (a review)

[*]Madhulika Dutta[1], Hari Prasad Nath[1]
[1]Department of Chemistry, C N B College, Bokakhat, Assam, India
*Corresponding author
Email: duttamadhulika@gmail.com

Abstract
Bioinorganic chemistry looks at how metal ions and other inorganic substances work within living organisms. Trace elements, which are inorganic nutrients needed in very small amounts (less than 0.01% of body weight), serve as structural supports, help enzymes work, and send signals in all forms of life. Important transition metals like iron (Fe), copper (Cu), zinc (Zn), and manganese (Mn) have developed special ways to bind with other molecules, which helps them transfer electrons, carry out chemical reactions, keep structures stable, and control gene expression. However, the same chemical properties that make these metals useful in the body—like their ability to change oxidation states, attract sulfur, and act as Lewis acids—can also make them harmful if their levels are not balanced. Non-essential heavy metals such as cadmium (Cd), lead (Pb), and mercury (Hg) use similar binding strategies to take the place of essential metal helpers, cause damage through reactions that produce harmful free radicals, and mess up how proteins fold. This review brings together information on the chemical ways these metals bind, how the body keeps their levels in check, their useful roles in biology, and the ways they can become harmful, focusing on the delicate chemical and reaction balances that control these processes in living systems.

Keywords: Bioinorganic Chemistry, Metalloproteins, Trace Elements, Oxidative Stress, Toxicological Chemistry, Coordination Complexes.

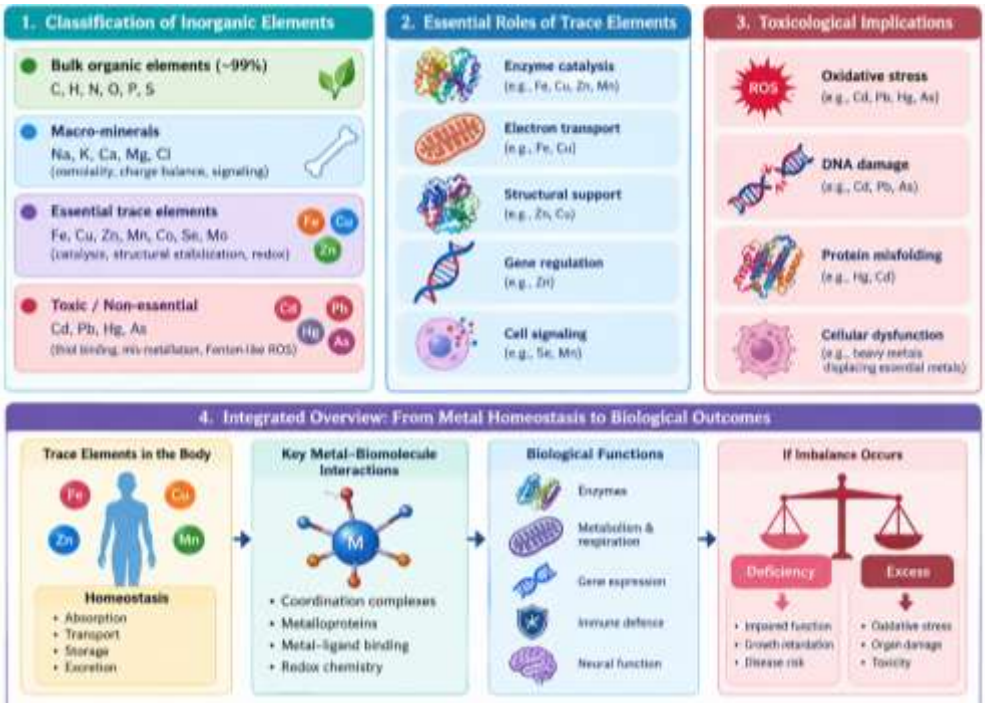


Fig. 1: Graphical representation of biological functions and taxological implications of trace elements

1. Introduction

Bioinorganic chemistry is a key area where inorganic coordination chemistry meets biological macromolecules, cellular processes, and the study of toxins [Bertini et al., 2007; Jomova et al., 2024]. Even though most living things are made up of lighter, non-metal elements like carbon (C), hydrogen (H), nitrogen (N), oxygen (O), phosphorus (P), and sulfur (S)—which make up about 99% of biological mass—life on Earth depends on transition metals, main-group metals, and metalloids that are only present in small amounts [Lippard & Berg, 1994; Mehri, 2020]. These trace elements, which are

inorganic nutrients found in less than 0.01% of body weight or needed in very small daily amounts, have essential roles as catalysts, structural supports, and signaling molecules across all forms of life [Li, 2025; Mehri, 2020].

Biological spectrum of inorganic elements:

- Bulk Organic Elements ⟶ C, H, N, O, P, S (~99% of biological mass)
- Macro-Minerals ⟶ Na, K, Ca, Mg, Cl (Osmolality, charge balance, signaling)
- Essential Trace ⟶ Fe, Cu, Zn, Mn, Co, Se, Mo (Catalysis, structural stabilization, redox)
- Toxic / Non-Essential ⟶ Cd, Pb, Hg, As (Thiol binding, mis-metallation, Fenton-like ROS)

From an evolutionary perspective, the use of transition metals in biology closely follows the history of Earth's atmospheric and oceanic oxygenation [Crichton, 2012].

In the early Archean eon, when the environment was highly reducing and rich in hydrogen sulfide (H_2S), metal availability was limited by the insolubility of metal sulfides. Iron (Fe^{2+}) and manganese (Mn^{2+}) were soluble and available, while copper (Cu^{+}) formed insoluble copper sulfide (Cu_2S). After the Great Oxidation Event, which occurred around 2.4 billion years ago due to oxygen-producing photosynthesis by cyanobacteria, the oceans changed from a reducing to an oxidizing environment. Soluble Fe^{2+} turned into insoluble ferric hydroxides (Fe^{3+}), which precipitated out of the water, while copper sulfides oxidized into soluble cupric ions (Cu^{2+}). This change allowed bioinorganic systems to use copper in new redox processes, such as terminal respiration and the catalytic activity of multi-copper oxidases [Bertini et al., 2007; Crichton,2012].

Modern biological systems classify trace elements into two main categories based on their function and potential toxicity:

1.1 Essential Trace Elements

Essential trace elements (e.g., Fe, Cu, Zn, Mn, Co, Se, Mo) are required for physiological development, metabolic homeostasis, and enzymatic turnover [Li, 2025; Mehri, 2020]. Rather than relying on simple organic functional groups (such as carboxylates or amines) which possess limited Lewis acidity and narrow redox windows, enzymes exploit the unique physical properties of metal ions to accomplish demanding chemical transformations (Holm et al., 1996; Kim et al., 2025):

i) **Multielectron Redox Catalysis:** Metals like iron and copper access multiple adjacent oxidation states (Fe^{2+}/Fe^{3+}, Cu^{+}/Cu^{2+}) to facilitate electron relays and multi-electron reductions (e.g., $O_2 \rightarrow 2H_2O$) without generating uncoupled free radical intermediates [Bertini et al., 2007; Holm et al., 1996].

(ii) Potent Lewis Acidity: Metal ions such as Zn^{2+} act as powerful Lewis acids at physiological pH, polarizing substrate bonds, activating coordinated water molecules to form nucleophilic hydroxides, or stabilizing negative charges generated in transition states [Lippard & Berg, 1994].

(iii) Structural Stabilization: Ions with flexible coordination geometries organize protein folds, facilitating tertiary and quaternary structure assemblies (e.g., zinc finger motifs in transcription factors) or bridging protein subunits [Kim et al., 2025].

1.2 Non-Essential and Toxic Metalloids/Heavy Metals

In contrast, non-essential trace elements like lead, cadmium, mercury, and arsenic have no known beneficial role in higher organisms. Even at extremely low levels, they can cause serious health problems. This is because their harmful effects come from using the same chemical rules that are used by essential metals.

(i) High Thiophilicity and Soft-Soft Interaction: Certain soft metal ions, such as mercury (Hg^{2+}), cadmium (Cd^{2+}), and methylmercury (CH_3Hg^{+}), strongly bind to soft Lewis bases, especially the thiol (-SH) groups in cysteine and the selenol (-SeH) groups in selenocysteine [Jomova et al., 2024; Valko et al., 2005].This binding can change the shape of proteins, block enzyme active sites, and lower levels of natural antioxidants like reduced glutathione (GSH).Isomorphous Substitution (Mis-Metallation): Toxic ions mimic the ionic radii and coordination geometry of essential metals (e.g., Pb^{2+} replacing Ca^{2+} or Zn^{2+}; Cd^{2+} replacing Zn^{2+}), displacing native cofactors and rendering enzymes biologically inactive [Jomova et al., 2024].

(ii) **Aberrant Redox Activation:** Some heavy metals can speed up reactions similar to the Fenton reaction, which causes widespread oxidative stress in the body.This can result in damage to fats in cell membranes, breakage of DNA strands, and cell death through apoptosis [Jomova & Valko, 2011; Valko et al., 2005].

1.3 The Homeostatic Balance

Because of this natural duality—where essential elements can become harmful in large amounts and toxic elements can act like essential ones—cells need strict control systems to stay alive [Crichton, 2012]. Living organisms use special transport systems (like P-type ATPases and solute carriers), metal-carrying proteins that stop free metal ions from spreading, and storage structures (such as ferritin and metallothioneins) to keep metal levels in the cell very low. Understanding how trace elements work in biology requires looking at many factors, including how metals form bonds, how fast they switch between different molecules, how they move through the body, and how they cause harm. This review looks at how basic chemistry rules affect how trace metals are used, how the body keeps them balanced, and how heavy metals can cause disease.

2. Coordination Chemistry Principles in Biological Systems

The functionality and toxicity of metal ions in biological systems are governed by fundamental coordination chemistry concepts:

2.1 Hard-Soft Acid-Base (HSAB) Theory

Pearson's HSAB principle classifies metal cations (Lewis acids) and cellular ligands (Lewis bases) based on charge density, polarizability, and ionic radius:

- **Hard Acids ($Fe^{3+}, Mn^{2+}, Cr^{3+}$):** Prefer hard, non-polarizable bases containing oxygen or nitrogen donors (e.g., carboxylates from aspartate/glutamate, phosphate backbones, water).
- **Soft Acids ($Cu^{+}, Hg^{2+}, Cd^{2+}, MeHg^{+}$):** Prefer soft, highly polarizable donor atoms, particularly sulfur from cysteine residues or methionine thioethers.
- **Intermediate Acids ($Fe^{2+}, Cu^{2+}, Zn^{2+}, Co^{2+}$):** Exhibit adaptable binding preferences, frequently coordinating with imidazole nitrogens of histidine.

2.2 The Irving-Williams Series

The thermodynamic stability of high-spin divalent transition metal complexes follows a predictable trend regardless of the ligand choice:

$$Mn^{2+} < Fe^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$$

Because Cu^{2+} forms the most thermodynamically stable complexes (partially driven by Jahn-Teller distortion), uncoordinated Cu^{2+} easily displaces other divalent metals like Fe^{2+} or Zn^{2+} from their native binding sites. Consequently, cells must maintain virtually zero free copper ions in the cytosol ($< 10^{-18}$ M) using specialized protein chaperones.

2.3 Ligand Field Stabilization and Geometry

The arrangement of d-electrons determines the preferred shapes in which a metal ion can coordinate with other molecules. For example, Zn^{2+} has a d^{10} configuration, meaning it has no ligand field stabilization energy (LFSE) regardless of the geometry. This allows it to form bonds with different numbers of ligands–4, 5, or 6–with quick exchange of ligands. Because of this adaptability, Zn^{2+} is very good at building structures and acting quickly as a Lewis acid catalyst. On the other hand, Fe^{3+} (d^5) and Cu^{2+}(d^9) change their shapes during electron transfer reactions, which helps drive important chemical cycles in enzymes involved in breathing and metabolism.

3. Bioinorganic Chemistry of Essential Trace Elements

Essential Trace Elements:

- Iron (Fe) ⟶ Oxygen Transport (Hemoglobin), Redox (Cytochromes, Fe-S Clusters)
- Copper (Cu) ⟶ Electron Transfer (Plastocyanin), Oxidases (Cytochrome-c Oxidase)
- Zinc (Zn) ⟶ Catalysis (Carbonic Anhydrase), Structure (Zinc Fingers)
- Manganese (Mn) ⟶ Oxygen-Evolving Complex (Photosystem II), Antioxidant (Mn-SOD)
- Cobalt (Co) ⟶ Alkyl Transfer & Radical Chemistry (Cobalamin / Vitamin B12)
- Selenium (Se) ⟶ Hydroperoxide Reduction (Glutathione Peroxidase via Selenocysteine)

3.1 Iron (Fe)

Iron is the most common trace transition metal found in living organisms. It can easily switch between the Fe^{2+} (ferrous) and Fe^{3+} (ferric) forms, which allows it to take part in processes like oxygen binding, electron transport, and chemical reactions that require catalysis.

(i) Metalloproteins: Hemoglobin and myoglobin employ iron-protoporphyrin IX (heme) centres for reversible O_2 coordination. Cytochromes utilize the Fe^{2+}/Fe^{3+} redox couple for mitochondrial electron transport.

(ii) Iron-Sulfur ($[Fe-S]$) Clusters: $[2Fe-2S]$, $[4Fe-4S]$, and $[3Fe-4S]$ centers act as low-potential electron relays (e.g., ferredoxins) and metabolic sensors (e.g., aconitase).

3.2 Copper (Cu)

Copper is an essential transition-metal ion that plays important roles in biological electron transfer, oxygen metabolism, antioxidant defense, and enzymatic catalysis. Its biological redox activity arises primarily from the reversible interconversion between Cu(I) (cuprous) and Cu(II) (cupric) states. The coordination environment of copper within proteins precisely regulates its redox potential and reactivity. Copper acts as an essential redox cofactor, transitioning between Cu^{+} (cuprous) and Cu^{2+} (cupric) [Zhang et al. 2026; Szarszone et al. 2024**].**

(i) Type 1 (Blue Copper) Centers: Present in plastocyanin and azurin; exhibit intense ligand-to-metal charge transfer (LMCT) bands around 600 nm and fast outer-sphere electron transfer.

(ii) Multicopper Oxidases: Cytochrome c oxidase reduces diatomic oxygen to water at the terminal step of the respiratory chain without releasing harmful reactive oxygen species (ROS).

3.3 Zinc (Zn)

Zinc is a redox-inert metal ion (Zn^{2+}) that functions primarily as a catalytic Lewis acid or a structural stabilizer.

(i) Catalytic Role: In carbonic anhydrase, a Zn^{2+} ion coordinated by three histidine residues and a water molecule lowers the pK_a of water from 15.7 to $\sim$ 7.0, generating a nucleophilic hydroxide ion at physiological pH.

(ii) Structural Role: In "zinc finger" motifs (Cys_2His_2 or Cys_4), Zn^{2+} organizes small protein domains to interact site-specifically with DNA/RNA sequences.

3.4 Other Essential Trace Metals

(i) **Manganese (Mn):** Forms the Mn_4CaO_5 cluster in the Oxygen-Evolving Complex (OEC) of Photosystem II, driving the photo-oxidation of water to molecular oxygen through sequential oxidation states (S_0 through S_4 states).

(ii) **Cobalt (Co):** Constitutes the core metal of cobalamin (Vitamin B_{12}), featuring a unique organometallic carbon-metal bond (Co-C) that undergoes homolytic cleavage to generate organic radicals.

(iii) **Selenium (Se):** Incorporated co-translationally as selenocysteine (Sec). The low pK_a ($\sim$ 5.2) and high nucleophilicity of the selenol group give selenoproteins (e.g., glutathione peroxidase) exceptional catalytic activity against oxidative peroxides.

4. Mechanisms of Toxicity and Pathophysiology

Trace elements operate within a strict thermodynamic and physiological boundary governed by **Bertrand's Rule of Essentiality (Fig.1)**, which dictates that both sub-physiological deficiency and supra-physiological excess lead to functional impairment, metabolic collapse,
or cellular death [Ang et al., 2023; Huang et.al., 2024).

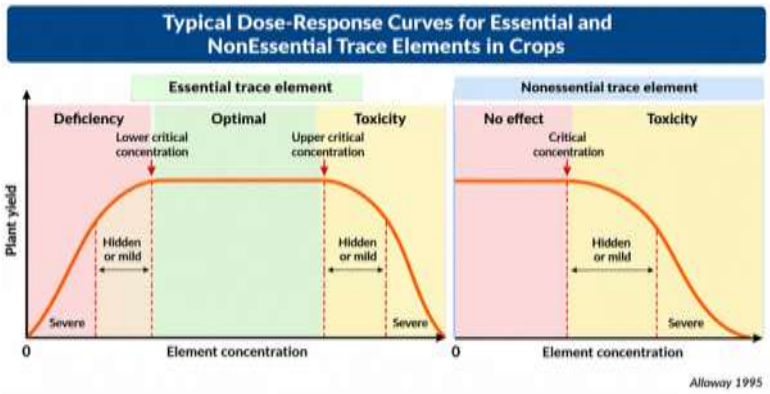


Fig.1. Dose-response relationship under Bertrand's Rule of Essentiality.
Source: [Alloway, 1995]

While essential metals are encapsulated within specialized protein microenvironments to control their reactivity, homeostatic breakdown allows free or misbound metal ions to initiate pathobiochemical cascades. The toxicity of trace elements—whether essential metals present in excess or non-essential xenobiotic heavy metals—manifests through three primary bioinorganic mechanisms: catalytic generation of reactive oxygen species (ROS), high-affinity binding to biological thiols, and structural active-site displacement (mis-metallation) [Witkowska et al. 2024].

4.1 Fenton Chemistry and Metal-Mediated Oxidative Stress

Redox-active transition metals—primarily labile, uncoordinated iron (Fe^{2+}) and copper (Cu^{+})—possess accessible one-electron reduction potentials that allow them to catalyze the

uncoupled homolytic cleavage of cellular peroxides [Dlouhy et al., 2023; Pérez de la Lastra et al., 2026]. Under physiological conditions, intracellular hydrogen peroxide (H_2O_2) is maintained at nanomolar concentrations by catalase, glutathione peroxidase (GPx), and peroxiredoxins. However, when homeostatic storage capacities are exceeded, labile Fe^{2+} and Cu^{+} react directly with H_2O_2 via classical **Fenton-type reactions (Fig.2)** to generate the hydroxyl radical (· OH), the most cytotoxic reactive oxygen species (ROS) known in biological systems [Forman & Davies, 2024]:

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + \cdot OH + OH^{-}$$
$$Cu^{+} + H_2O_2 \longrightarrow Cu^{2+} + \cdot OH + OH^{-}$$

The resulting oxidized metal species (Fe^{3+} or Cu^{2+}) are continuously re-reduced by intracellular reductants such as superoxide radical anions ($O_2^{\cdot -}$), ascorbic acid, or cellular thiols. This establishes a self-sustaining **Haber-Weiss catalytic cycle**, driving continuous, steady-state · OH production without net metal consumption [Jomova & Valko, 2011]:

$$Fe^{3+} + O_2^{\cdot -} \longrightarrow Fe^{2+} + O_2$$

$$\text{Net Haber-Weiss Reaction: } O_2^{\cdot -} + H_2O_2 \xrightarrow{Fe/Cu} \cdot OH + OH^{-} + O_2$$

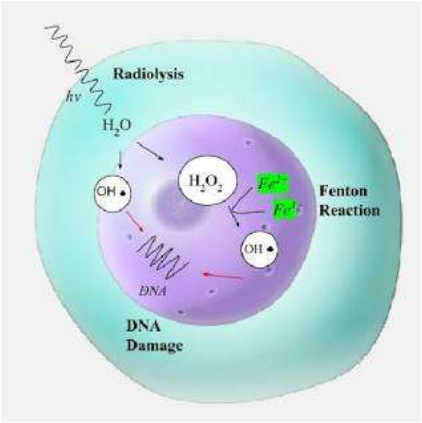


Fig.2. Metal-catalyzed Fenton reaction and downstream oxidative injury. Source: [Maken, 2023].

Because the hydroxyl radical has an exceptionally short biological half-life (~ 10^{-9} s) and a diffusion radius under 2 nm, it reacts indiscriminately with all major classes of biological macromolecules immediately at its site of formation [Valko et al., 2005]:

1. **Lipid Peroxidation of Polyunsaturated Fatty Acids (PUFAs):** Hydroxyl radicals abstract a hydrogen atom from the weak bis-allylic methylene carbon of membrane PUFAs, creating a carbon-centered lipid radical (L ·). This radical rapidly binds molecular oxygen to form a lipid peroxyl radical (LOO ·), propagating a chain reaction across lipid bilayers:

$$L \cdot + O_2 \longrightarrow LOO \cdot$$

$$LOO \cdot + L\text{-}H \longrightarrow LOOH + L \cdot$$

The decay of lipid hydroperoxides (LOOH) yields toxic aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which form covalent crosslinks with proteins and DNA, causing loss of membrane fluidity, loss of organelle integrity, and cell lysis [Jomova et al., 2024; Valko et al., 2005].

2. **Protein Carbonylation and Oxidative Modifications:** Direct attack by $\cdot OH$ on amino acid side chains—specifically proline, arginine, lysine, and threonine—introduces reactive carbonyl derivative groups (C=O). Oxidation of cysteine residues leads to aberrant disulfides (-S-S-) or irreversible sulfinic/sulfonic acids ($-SO_2H, -SO_3H$), causing protein misfolding, crosslinking, active-site inactivation, and targeted proteasomal degradation [Jomova et al., 2024].
3. **DNA Strand Cleavage and Base Modification:** Because transition metals bind directly to the negatively charged phosphate backbone of DNA, localized Fenton chemistry generates $\cdot OH$ in immediate proximity to nuclear and mitochondrial genomes. Hydroxyl radicals attack the C4′ position of the deoxyribose ring, leading to sugar breakdown, single- and double-strand DNA cleavage, and base modifications—most notably 8-hydroxy-2′-deoxyguanosine (8-OHdG), a key biomarker of mutagenic metal toxicity [Jomova & Valko, 2011; Valko et al., 2005].
4. **Ferroptosis Induction:** Accumulation of labile iron coupled with unmitigated lipid hydroperoxide buildup triggers **ferroptosis**, a distinct form of non-apoptotic, iron-dependent regulated cell death characterized by mitochondrial cristae loss and membrane rupture [Jomova et al., 2024].

4.2. Non-Essential Toxic Heavy Metals

Heavy metals without physiological roles exert toxicity through specific coordination mechanisms:

Metal	Primary Soft/Hard Affinity	Key Mechanism of Toxicity	Toxicological Manifestation
Cadmium (Cd^{2+})	Soft (-SH)	Displaces Zn^{2+} in metallothioneins and enzymes; inhibits DNA repair enzymes	Nephrotoxicity, Osteomalacia (Itai-Itai disease), Carcinogenesis
Lead (Pb^{2+})	Intermediate / Soft	Mimics Ca^{2+} and Zn^{2+}; inhibits δ-aminolevulinic acid dehydratase (ALAD)	Neurological impairment, Anemia, Encephalopathy
Mercury (Hg^{2+}, CH_3Hg^{+})	Very Soft (-SH,-SeH)	High-affinity binding to selenocysteine and cysteine; depletes glutathione	Severe neurotoxicity (Minamata disease), Teratogenicity
Arsenic (As^{III}, As^{V})	Soft (As^{III}), Hard (As^{V})	As^{III} crosslinks vicinal dithiols; As^{V} acts as a structural mimic of phosphate (PO_4^{3-})	Uncoupling of oxidative phosphorylation, Carcinogenesis

4.3 Toxic Metal Ion Substitution (Mis-Metallation)

Isomorphous substitution, or **mis-metallation**, occurs when non-essential heavy metals or excess trace elements replace essential metal cofactors within enzyme active sites or structural binding pockets [Forman & Davies, 2024]. Driven by similarities in ionic radii, coordination preferences, and oxidation states, xenobiotic metal cations exploit the flexible binding microenvironments of host proteins to gain entry. Once coordinated, the toxic ion alters active-site geometry, disrupts electron distribution, and alters catalytic kinetics [Maret, 2023].

A. Lead (Pb^{2+}) Inhibition of δ-Aminolevulinic Acid Dehydratase (ALAD)

A classic example of catalytic mis-metallation occurs in the heme biosynthetic pathway. Lead (Pb^{2+}) exhibits high thiophilicity and selectively targets the enzyme δ-aminolevulinic acid dehydratase **(**ALAD**)** (also designated as porphobilinogen synthase) [Diawara, 2025]

Under physiological conditions, native ALAD coordinates a catalytic zinc ion (Zn^{2+}) through a triad of cysteine residues ($Cys_{119}, Cys_{122}, Cys_{132}$) and a water molecule in a trigonal bipyramidal geometry:

- **Mechanism of Displacement:** Pb^{2+} (ionic radius ~ 1.19 AA) directly displaces native Zn^{2+} (ionic radius ~ 0.74 AA) from the catalytic site due to its higher thiophilic affinity (K_d for Pb^{2+} is several orders of magnitude lower than for Zn^{2+}) [Balali-Mood et al., 2021].
- **Structural Deformation:** Because of its larger ionic volume and preference for irregular coordination numbers, Pb^{2+} structurally distorts the catalytic pocket, expanding the metal-ligand bond distances and disrupting the spatial arrangement required to condense two molecules of δ-aminolevulinic acid (ALA) into porphobilinogen.
- **Pathophysiological Consequence:** Inhibition of ALAD halts heme biosynthesis, leading to severe microcytic hypochromic anaemia and accumulation of upstream neurotoxic ALA in blood and cerebrospinal fluid [Pachauri et al., 2023].

B. Cadmium (Cd^{2+}) Substitution in Zinc Finger Proteins and Transcription Factors

Cadmium (Cd^{2+}) shares identical outer-shell electronic properties (d^{10}) and divalent charge state with essential zinc (Zn^{2+}), making it an effective structural mimic [Jomova et al., 2024].

- **Zinc-Finger Disruption:** In regulatory DNA-binding proteins—such as Cys_2His_2 or Cys_4 zinc-finger transcription factors and DNA repair enzymes (XPA, MutS homologs)—a central Zn^{2+} ion acts as a structural pin to stabilize the α-helical motif that inserts into the major groove of target DNA [Blindauer, 2024; Maret, 2023; Witkowska et al., 2024].
- **Mechanism of Substitution:** Cd^{2+} replaces Zn^{2+} within these cysteine-rich tetrahedral motifs:

$$[Zn(Cys)_4]^{2-} + Cd^{2+} \longrightarrow [Cd(Cys)_4]^{2-} + Zn^{2+}$$

- **Structural and Functional Collapse:** Because Cd^{2+} possesses a significantly larger ionic radius (~ 0.95 AA) compared to Zn^{2+} (~ 0.74 AA), the metal-sulfur (Cd-S) bond lengths increase from ~ 2.3 AA to ~ 2.5 AA. This bond expansion forces steric unfolding of the peptide loop, preventing the motif from inserting into DNA. This impairs base excision repair (BER) and nucleotide excision repair (NER), promoting genomic instability and oncogenesis [Engwa et al., 2023, chwerdtle & Hartwig, 2023].

5. Homeostatic Control and Detoxification Strategies

Organisms use sophisticated molecular machinery to control trace metal concentrations:

1. **Metallothioneins (MTs):** Small, cysteine-rich proteins (approx. 30% cysteine content) that bind essential (Zn^{2+}, Cu^{+}) and non-essential (Cd^{2+}, Hg^{2+}) metal ions via metal-thiolate clusters, serving as metal buffers and radical scavengers [Blindauer, 2024]
2. **Efflux Pumps and Transporters:** The P-type ATPase family (e.g., ATP7A/ATP7B for copper, ZNT transporters for zinc) actively transport ions across lipid membranes to maintain organelle-specific concentrations or excrete excesses [Dlouhy et al., 2023; Nevitt et al., 2021].
3. **Storage Proteins:** Ferritin encapsulates up to 4,500 ferric iron atoms inside a hollow 24-subunit protein nanocage, keeping iron soluble and non-toxic as a hydrated ferric oxide/phosphate mineral core [Theil, 2023].
4. **Chelation Therapy:** Clinical intervention for toxic heavy metal poisoning uses synthetic polydentate ligands (e.g.,EDTA, dimercaprol/BAL, D-penicillamine, deferoxamine) to form thermodynamically stable, water-soluble complexes that can be safely excreted by the kidneys [Flora et al., 2023].

6. Conclusions

Bioinorganic chemistry illuminates the remarkable thermodynamic and kinetic precision with which chemical evolution has harnessed the periodic table. Over geological timescales, biological systems have adapted to the physical properties of inorganic ions—tuning coordination geometries, oxidation potentials, and Lewis acidities—to drive fundamental life

processes. Essential trace elements serve as irreplaceable catalytic engines, redox shuttles, and structural anchors that empower metabolic networks far beyond the scope of organic functional groups alone. Yet, this essentiality exists on a strict chemical knife-edge. The very intrinsic properties that endow trace transition metals with catalytic utility—such as flexible coordination environments and facile electron transfer—render them potent cellular toxins when uncoordinated, unregulated, or present in excess. Unshielded redox-active metals trigger destructive Fenton chemistry, generating hydroxyl radicals that compromise membrane fluidity, protein stability, and genomic integrity. Concurrently, non-essential heavy metals exploit these same coordination principles, infiltrating cellular pathways through high-affinity thiophilic interactions, isomorphous substitution (mis-metallation), and the disruption of structural metalloprotein folds. Deciphering the delicate interplay between trace element coordination chemistry, homeostatic transport, and molecular toxicity pathways is essential for modern biomedical science. Advancing our mechanistic insight into these bioinorganic systems underpins the development of high-selectivity clinical chelation agents, targeted metallodrug therapies, and robust risk-assessment frameworks in environmental toxicology.

7. Future Scope

Future research in bioinorganic chemistry should focus on understanding the molecular mechanisms that control the beneficial and harmful effects of trace elements. Using advanced spectroscopic, structural, and computational techniques can help gain deeper insights into how metals interact with proteins, move within the body, their coordination environments, and how they can cause incorrect metal binding. Developing chelating agents that are both effective and less toxic is an important future direction for treating heavy-metal poisoning. A better understanding of how metals cause oxidative stress, ferroptosis, DNA damage, and protein dysfunction could also lead to new treatment strategies. Artificial intelligence and computational models can further assist in predicting the structures of metalloproteins, metal-binding sites, toxicity mechanisms, and how metals interact with ligands. Future studies should combine bioinorganic chemistry with environmental toxicology and human health to better understand how metals are transported, accumulate, transform, and are detoxified in the body. More attention should also be given to the combined effects of multiple metals and other environmental stressors.

Finally, integrating bioinorganic chemistry with biotechnology, nanotechnology, green chemistry, and advanced analytical methods could lead to safer and more efficient ways to detect, remove, recover, and clean up metals. Such interdisciplinary research can enhance the use of bioinorganic chemistry in biomedical science, environmental protection, and toxicology.

Conflict of interest:

The authors declare that there is no conflict of interest associated with this work. The author has no financial, personal, or professional relationships that could have influenced the research or its interpretation.

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