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Application of metallomics to understand environmental metal exposure

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Abstract

Environmental metal exposure is rarely a single-element event and even more rarely a single-chemical-species event. Metals and metalloids circulate as dynamic mixtures whose toxicity, transport, and biological effects are governed by speciation, binding to biomolecules, subcellular localization, and interactions with endogenous metal homeostasis. Metallomics, the comprehensive study of elemental distributions, metal species, and metal–biomolecule interactions across biological systems has emerged as a powerful framework for moving exposure science beyond "total metal concentration" toward mechanistically meaningful measurements. Metallomics integrates high-sensitivity multi-element quantification (ICP-MS), elemental speciation (LC/CE–ICP-MS coupled to molecular MS), metalloproteomics, metallometabolomics, spatial metal imaging (LA-ICP-MS and complementary mass spectrometry imaging), and single-cell elemental analysis. Together, these tools enable investigators to trace environmental exposures from external sources to internal dose, then to biologically effective dose, and finally to downstream pathway disruption. This review synthesizes peer-reviewed evidence on metallomics platforms and study designs used to understand environmental exposures, with emphasis on how speciation and ligand binding control toxicity, how spatial mapping reveals tissue and cell-type vulnerability, how single-cell metallomics resolves heterogeneity masked by bulk averaging, and how integrative "metallomics + other omics" strategies illuminate causal pathways linking exposure to disease. We discuss best practices in sampling, quality assurance, contamination control, and data integration, and we highlight emerging directions such as non-targeted speciation, isotope tracing, and multiscale exposure-to-biology pipelines.

Keywords: Metallomics; exposome; ICP-MS; LC–ICP-MS; Element speciation; Metalloproteomics; Metallometabolomics; LA-ICP-MS imaging; Single-cell ICP-MS; Metal mixtures; Biomonitoring; Bioavailability; Toxic metals

1. Introduction: Why environmental metal exposure needs metallomics

Environmental health practice has long relied on measuring metals in air, water, soil, food, and biospecimens [1, 2]. Those measurements are indispensable, but they can be biologically blunt. Total lead in blood or total arsenic in urine may signal exposure, yet these totals collapse a complex reality: the body does not experience metals as totals. It experiences chemical species free ions, inorganic complexes, organometallic compounds, nanoparticles, protein-bound forms and experiences them in specific locations plasma, red blood cells, cerebrospinal fluid, mitochondria, lysosomes each with distinct toxicological meaning. Metallomics was proposed as a response to that complexity: a field focused on metals and metalloids in biological systems, their interactions with biomolecules, their transport across interfaces, and their role in physiology and toxicity [3-5]. Environmental metallomics extends this concept to exposures arising from polluted environments and mixtures, explicitly considering how toxic and essential elements interact and how exposure perturbs metabolic pathways [6-8]. This framing is important because environmental exposure is almost always a mixture problem: essential metals (Fe, Cu, Zn, Se) modulate the uptake and toxicity of toxic metals (Pb, Cd, As, Hg), and inflammatory or nutritional states reshape metal binding and distribution.

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Metallomics matters is that it connects exposure science to mechanism. Many environmentally relevant outcomes neurodevelopmental deficits, cardiometabolic disease, kidney injury are driven by redox imbalance, mitochondrial dysfunction, disrupted metalloproteins, and altered signaling networks [9, 10]. Those are metal-sensitive processes, if measurement tools can capture metal–biomolecule interactions and spatial distributions, they can convert association studies into pathway-informed causal narratives [11]. Finally, metallomics is increasingly practical. Advances in ICP-MS instrumentation, laser ablation imaging, and hyphenated separation techniques now allow measurement of dozens of elements with high sensitivity and, crucially, allow the investigator to choose the correct "resolution" for the question: total burden, species identity, tissue map, or single-cell variability.

2. Conceptual framework: From external exposure to biologically effective dose

A useful way to understand metallomics in environmental exposure research is to align it with a four-level exposure framework:

- External exposure: metals in the environment (air, water, soil, diet, consumer products).
- Internal dose: what enters the body and appears in accessible matrices (blood, urine, hair, nails).
- Biologically effective dose: the fraction that reaches target tissues in reactive or bioavailable forms (labile pools, organometallic species, protein-bound complexes that deliver metals to receptors).
- Biological response: altered pathways, stress responses, and downstream disease processes.

Traditional biomonitoring often stops at internal dose. Metallomics pushes the measurement deeper, toward biologically effective dose and response, by tracking not only "how much," but "in what form," "bound to what," and "where [12-14]." This matters because toxicity hinges on speciation. Arsenic provides the classic example: inorganic arsenic metabolites and methylated species differ sharply in toxicity and kinetics, and urine arsenic speciation is often necessary to interpret exposure sources and risk [15]. Similarly, mercury's methylated form drives neurotoxicity and biomagnification, so distinguishing methylmercury from inorganic mercury is central to meaningful exposure assessment [16, 17]. Advances in LC–ICP-MS and related hyphenated methods are frequently highlighted as enabling technologies for such distinctions [18].

It also matters because biology is spatial. A concentration in whole blood cannot reveal whether a metal is accumulating in brain regions, placenta microcompartments, or kidney proximal tubules [19, 20]. Spatial metallomics, especially LA-ICP-MS imaging, has become a cornerstone for linking exposure to tissue-level vulnerability, and it has been used in contexts ranging from neurobiology to developmental exposure assessment [21]. Finally, even within a single tissue, cell types differ in uptake, storage, and susceptibility. Bulk tissue homogenates average away that heterogeneity. Single-cell ICP-MS approaches now provide direct quantification of elemental content per cell, allowing investigators to detect resistant subpopulations, exposure gradients, and cell-state dependencies that bulk analysis misses.

3. Core metallomics platforms for environmental exposure research

Inductively coupled plasma mass spectrometry (ICP-MS) remains the backbone of metallomics because of its sensitivity, wide dynamic range, and capability for simultaneous multi-element quantification [22, 23]. In environmental exposure studies, ICP-MS enables high-throughput measurement of metal panels in blood, urine, hair, nails, and tissues crucial for mixture analyses and for studying essential–toxic metal interactions [24-27]. Reviews focused on metallomics in environmental and health research highlight ICP-MS as a core technology that supports both total metal quantification and, when paired with separations, species-resolved analysis [28-30]. However, bulk ICP-MS has an interpretive ceiling. It measures total elemental abundance after sample digestion, which destroys speciation information and eliminates knowledge of what proteins or metabolites carried the metal. In practice, total metal panels are most powerful when they serve as the first layer: they identify exposure signatures, mixture profiles, and candidate elements that warrant deeper speciation or spatial analysis. A major strength of ICP-MS in exposure science is that it supports standardized workflows and relatively robust inter-laboratory comparability when appropriate reference materials and contamination control are used. But that strength can be undermined if sample handling is not metallomics-aware. Many trace elements are sensitive to collection tube materials, anticoagulants, digestion reagents, and lab air contamination. The "metallomics mindset" treats pre-analytical steps as part of the measurement system, not as housekeeping.

3.1. Elemental speciation: LC/CE–ICP-MS and the rise of species-aware exposure assessment

Elemental speciation refers to separating and quantifying different chemical forms of an element (oxidation state, organometallic compounds, protein-bound complexes). LC–ICP-MS (and CE–ICP-MS) has become a dominant approach

because ICP-MS offers element-specific detection, while chromatography provides separation of species [31]. Feldmann and colleagues have emphasized that speciation analysis is shifting toward both targeted and non-targeted approaches as instrumentation and workflows evolve [32]. For environmental exposure research, speciation often answers questions that totals cannot. Urinary arsenic speciation distinguishes inorganic exposure from dietary organoarsenicals and supports more accurate risk interpretation [33, 34]. Mercury speciation helps attribute exposure source (fish consumption vs occupational) and, importantly, relates more directly to neurotoxic risk [35, 36]. In selenium biology, speciation can illuminate nutritional adequacy versus abnormal forms associated with metabolic disruption [37]. Even for essential metals, speciation can matter: the distribution between "labile" and protein-bound pools can signal oxidative stress, inflammation, or altered homeostasis. A challenge is species stability. Many metal species interconvert during collection and storage. Oxidation states can change; protein–metal complexes can dissociate; adsorption to containers can occur. That is why successful speciation studies treat sampling chemistry as part of method design: stabilizers, immediate freezing, minimal headspace, and validated holding times become essential.

3.2. Metalloproteomics: identifying metal-binding proteins as targets and biomarkers

Metalloproteomics aims to identify and quantify metalloproteins and metal–protein complexes, revealing which proteins bind which metals under specific conditions. Early conceptual reviews positioned metallomics and metalloproteomics as fields dedicated to understanding uptake, transport, storage, and function of trace metals in biology. More recent methodological reviews outline advances in metalloproteomics workflows, including chromatographic separation paired with ICP-MS for metal quantification and molecular MS for protein identification [38-40]. In environmental exposure contexts, metalloproteomics can clarify mechanisms of toxicity and adaptation. For example, exposure to cadmium or mercury may induce metallothioneins cysteine-rich proteins that bind metals and metalloproteomics can quantify those complexes as biomarkers of biologically effective dose [41, 42]. Similarly, shifts in iron-binding proteins (transferrin, ferritin) can reflect inflammation and iron dysregulation pathways that modulate susceptibility to toxic metals [43, 44]. In neurotoxicology, mapping metal associations with proteins involved in synaptic function or mitochondrial respiration can reveal vulnerability pathways that totals alone cannot [45, 46]. A core limitation is that metalloproteomics is technically demanding: metal–protein interactions can be labile, and proteomic workflows often use buffers and conditions that can strip metals from proteins. Therefore, metalloproteomics requires "native" or metal-preserving separations, careful choice of chelator-free reagents, and orthogonal confirmation strategies. The field's progress has been closely tied to hyphenated approaches that use ICP-MS to confirm metal presence in fractions and ESI-MS/MS to identify the corresponding proteins.

3.3. Metallometabolomics: element-tagged metabolites and metal-sensitive pathways

Metallometabolomics (sometimes framed as "metallo-metabolomics") focuses on metals associated with small molecules and how metal status shapes metabolic networks. While not always as mature as metabolomics for organics, it offers unique advantages: metals can serve as intrinsic "tags" that enable selective detection of metal-containing metabolites, and metal perturbations often cause characteristic metabolic signatures reflecting oxidative stress, mitochondrial dysfunction, and altered enzyme cofactor availability. Discussions connecting metallomics with other omics highlight metallo-metabolomics as a pathway to discover element-associated metabolites and interpret metal stress in biological systems. For environmental exposure, metallometabolomics can move the field from "exposed vs unexposed" toward "what pathway is disrupted." For example, arsenic exposure has been associated with disruptions in one-carbon metabolism and oxidative stress pathways [47]; selenium status can shift antioxidant and thyroid-relevant metabolic signatures [48]; manganese or lead exposure can perturb neurotransmitter precursor pathways [49, 50]. While many of these signatures are not specific to metals, combining metabolomics with metallomics (multi-element panels, speciation, and protein binding) improves mechanistic attribution.

4. Spatial metallomics: seeing where metals go and why that matters

4.1. LA-ICP-MS imaging: quantitative elemental maps in tissues

Laser ablation ICP-MS (LA-ICP-MS) enables spatially resolved elemental mapping in tissue sections by ablating microscopic areas and quantifying elements via ICP-MS [51]. Reviews in the *Metallomics* literature and related outlets describe LA-ICP-MS as a central technique for bioimaging and metallomics, enabling detection of metals in tissues with high sensitivity and supporting quantitative regional comparisons [52-55]. In environmental exposure research, LA-ICP-MS is valuable because tissue heterogeneity often defines toxicity [56]. The brain is regionally specialized; the placenta has distinct microanatomical zones that regulate fetal exposure; the kidney has segment-specific handling of metals. A proof-of-concept study in *Metallomics* used LA-ICP-MS to examine multi-metal distributions in placental tissue, illustrating how spatial patterns can reveal biologically meaningful exposure gradients and tissue responses that are invisible in bulk assays. LA-ICP-MS also supports mixture mapping. Environmental exposure rarely involves one

metal; LA-ICP-MS can map multiple metals simultaneously, enabling discovery of co-localization patterns (e.g., Pb with Ca-rich structures, Cd with Zn-binding regions) that suggest shared transport routes or competitive binding. This spatial approach becomes especially powerful when paired with histology or immunostaining, allowing elemental maps to be aligned with cell types and pathological features.

4.2. Complementary imaging approaches: MSI, X-ray methods, and multimodality workflows

Metallomics imaging is not limited to LA-ICP-MS. Mass spectrometry imaging (MSI) approaches and X-ray methods can offer complementary strengths: MSI can detect organic metabolites and, in some modes, metal-containing compounds; synchrotron-based X-ray fluorescence can provide speciation-relevant information for some elements. A 2025 review on mass spectrometry imaging of metals discusses how LA-ICP-MS offers high sensitivity for metals [57], while other MSI techniques can add molecular context exactly the type of multimodal fusion that environmental exposure studies increasingly need.

In ecotoxicology, imaging has become a tool for linking environmental exposure to organism-level outcomes by showing metal distribution across tissues and subcellular compartments. A 2022 review on metal bioimaging in environmental toxicological studies emphasizes the value of modern imaging technologies at nanoscale and macroscale resolution in aquatic organisms, supporting mechanistic interpretation of toxicity in real-world exposure contexts [58]. The trend is clear: spatial metallomics is moving from "pretty maps" to quantitative, hypothesis-driven measurement integrated with pathology, transcriptomics, and functional assays. That shift is essential if imaging is to meaningfully inform exposure risk assessment rather than serving as descriptive evidence.

5. Single-cell metallomics: resolving heterogeneity in exposure and response

5.1. Why single-cell matters for environmental exposure

Environmental metal exposures do not distribute evenly across cell populations. Inhaled particles deposit unevenly across lung regions; metals enter circulation and partition into plasma and cells; tissue uptake depends on transporters and cellular state. Even within a single tissue, some cells may accumulate metals strongly (due to transporter expression or phagocytic behavior), while neighboring cells remain relatively unexposed. Bulk tissue analysis averages these differences, often obscuring relationships between metal burden and biological response. Single-cell ICP-MS (scICP-MS) directly quantifies elemental content per cell, capturing distributions rather than averages. Reviews and technical papers describe scICP-MS as a fast and powerful approach for evaluating elemental composition at the single-cell level and for assessing cellular bioavailability of metal species such as arsenite. This is especially relevant for exposure science because "bioavailability" is often a cellular concept: what reaches and enters cells determines effect.

5.2. Environmental applications: from microbes to human-relevant cells

Single-cell elemental analysis has been applied broadly, including in environmental sciences and microbiology, and reviews describe expanding applications and methodological trends. In environmental contexts, single-cell approaches can quantify metal uptake in algae and microbes that form the base of food webs, offering insight into bioaccumulation and trophic transfer. In human health contexts, they can evaluate cell-type-specific uptake and response in immune cells, epithelial cells, or organoid systems exposed to environmentally relevant metal mixtures. Single-cell data can also improve mixture science. Instead of treating "metal mixture" as a single exposure vector, investigators can ask whether mixtures produce distinct uptake patterns: does cadmium co-enter the same cells as zinc? Does lead accumulate preferentially in specific immune subsets? Those patterns can reveal shared transport or competition mechanisms, guiding mechanistic hypotheses and intervention targets.

5.3. Practical challenges: throughput, interferences, and biological interpretation

Single-cell metallomics is technically demanding. Cells must remain intact, avoid aggregation, and be introduced into the instrument in a way that ensures single-cell events rather than coincident multi-cell signals. Sample preparation can alter membrane permeability and cause leaching of metals, which is why methodological papers emphasize validated preparation workflows and avoidance of fixation artifacts where possible. Biological interpretation is also nontrivial: a cell's metal burden reflects both exposure and physiological handling (efflux, sequestration), so interpreting single-cell distributions often benefits from pairing with markers of cell type and activation state. Despite these challenges, the payoff is high. Single-cell metallomics makes it possible to treat metal exposure as a distributional phenomenon—exactly what environmental inequality and differential susceptibility often look like at the cellular level.

6. Integrating metallomics with other omics: toward mechanistic exposomics

6.1. Why integration is necessary

Metals rarely act alone; they act through binding, displacement, redox chemistry, and enzyme perturbation. These mechanisms are best captured when metallomics is integrated with transcriptomics, proteomics, metabolomics, and epigenomics. Editorial and review literature on new analytical developments in metallomics highlights growth in sophisticated techniques for metal speciation and spatial distribution in cells, reflecting the field's movement toward mechanistically rich, integrative datasets. Integration also improves causal inference. If increased urinary arsenic correlates with diabetes risk, metallomics can identify which arsenic species dominate and whether those exposures align with disruptions in insulin signaling metabolites or oxidative stress markers. If prenatal cadmium exposure correlates with growth restriction, spatial placental metallomics can reveal whether cadmium co-localizes with altered distributions of essential metals and whether those patterns align with stress-response pathways in the same regions.

6.2. Best practices and quality assurance in environmental metallomics

Metallomics is uniquely vulnerable to contamination because target analytes are ubiquitous. Trace metals can leach from collection tubes, pipette tips, lab water, and even dust. Therefore, contamination control is not a minor procedural detail; it is a central methodological pillar. Good practice includes using certified metal-free materials, running field blanks and lab blanks, and documenting every material that contacts the sample. For speciation, the core QA question is: did the method measure what was present in the body, or did the method create new species? Stabilization protocols and validated holding times are essential. The increased interest in speciation trends and future directions reflects recognition that speciation is both powerful and fragile. Spatial metallomics faces its own QA challenges: quantification in LA-ICP-MS requires calibration strategies and careful control of ablation parameters. Tissue heterogeneity affects ablation yield, so matrix-matched standards or internal normalization strategies are often required. Reviews of LA-ICP-MS imaging discuss the technique's state-of-the-art and continuing development toward robust quantitative bioimaging. Single-cell ICP-MS requires verifying that measured events correspond to single cells. This involves optimizing cell concentration, flow rates, acquisition settings, and validating coincidence rates.

7. Future directions: where metallomics is headed for environmental health

Environmental exposure is evolving—industrial processes, nanoparticles, and new contamination sources introduce forms that classic panels may not capture. Non-targeted speciation and element-selective screening are therefore becoming more important. Feldmann's work on changing trends in ICP-MS speciation analysis captures this shift toward broader, discovery-oriented workflows. Species-independent quantification is another major opportunity. In some workflows, ICP-MS can quantify an element independent of its molecular identity, while molecular MS identifies the compound. This combination supports discovery without losing quantitative rigor—particularly valuable when unknown metal-binding metabolites or proteins emerge under environmental stress.

The next phase of spatial metallomics will likely involve deeper integration with spatial transcriptomics and multiplex imaging. Metals influence gene programs and cell states; conversely, cell state controls metal transporters and sequestration. Co-registration of elemental maps with cell-type markers transforms environmental exposure research into spatial systems toxicology, where investigators can ask: which cells near which metal hotspots activate which stress pathways? Single-cell approaches are expanding, with ongoing methodological development and increasing use in environmental and biological studies. As throughput increases and integration with cell typing improves, single-cell metallomics could become a standard tool for identifying susceptible cell populations and for evaluating how metal mixtures reshape immune and epithelial landscapes.

8. Conclusion

Metallomics has shifted environmental metal exposure research from a measurement paradigm focused on "how much" to a mechanistic paradigm focused on how metals exist, where they go, what they bind, and how they perturb biology. Bulk ICP-MS provides the foundation for multi-element exposure profiling and mixture science. Speciation analysis resolves the chemical forms that determine toxicity and source attribution. Metalloproteomics and metallometabolomics link exposures to molecular targets and pathway disruption. Spatial metallomics reveals organ microanatomical vulnerability and interface dynamics, while single-cell metallomics captures heterogeneity that defines real-world susceptibility. The practical implication is clear: environmental health questions increasingly require resolution-matched measurement. Not every study needs LA-ICP-MS maps or metalloproteomics, but studies that aim to explain disease mechanisms, identify causal species, or pinpoint vulnerable tissues will continue to benefit from

metallomics' multiscale toolbox. As analytical chemistry advances toward non-targeted speciation and multimodal spatial biology, metallomics will become even more central to understanding the true biology of environmental metal exposure.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed..

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