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Biochemical Mechanisms of Heavy Metal-Induced Oxidative Stress in Humans; Article Review

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Abstract

Toxic metals are still a very important biochemical and public health issue because certain metals like lead (Pb), cadmium (Cd), mercury (Hg) and arsenic (As) can be found in environmental media, and disrupt the homeostasis of cells. Oxidative stress is one of the key pathways but not exclusive pathway of toxicity caused by metals. Metals can cause an increase in the production of Reactive Oxygen Species (ROS), damage mitochondria, interact with sulfhydryl groups, disrupt the homeostasis of the essential metals, and cause changes in antioxidant signaling. These modifications can lead to the initiation of lipid peroxidation, protein oxidation, DNA damage, inflammation and cell-death signaling. This review is a summary of biochemical pathways associated with metal-induced oxidative injury, the nature of commonly used biomarkers (malondialdehyde [MDA], glutathione [GSH], superoxide dismutase [SOD], catalase [CAT], glutathione peroxidase [GPx] and 8-hydroxy-2′-deoxyguanosine [8-OHdG]), and the difficulties in using biomarkers to inform clinical or environmental-health decisions. Specificity of assays, sample handling, exposure assessment, confounding, and distinguishing between mechanistic plausible and proven clinical causation are highlighted. The available evidence reviewed shows that it is more beneficial to use a group of validated exposure measurements along with a panel of biochemical markers than on a single oxidative stress indicator. More standardization of analytical protocols, longitudinal study designs and better integration of environmental and biological measurements are needed for better comparability and clinical interpretation.

Keywords

Heavy Metals;
Oxidative Stress;
Biochemistry;
Glutathione;
Malondialdehyde;
Antioxidant Enzymes;
Biomarkers;
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1. Introduction

Exposure to toxic metals can be via contaminated drinking water, food, soil and dust, ambient air and occupational processes. Some farming practices, industrial discharges, combustion, battery recycling and production, smelting and mining may add to the environmental load of metals. Exposure can be different for various chemicals species, routes, concentrations, duration, bioavailability, and individual susceptibility. "Heavy metals" is a popular term in environmental-health literature, but not a strictly toxicological term; here it is used in the traditional usage—of toxic metals and metalloids like Pb, Cd, Hg and As. (Briffa et al., 2020; Järup, 2003; Tchounwou et al., 2012). (Järup, 2003; Tchounwou et al., 2012).

Biochemically, toxic metals have a variety of effects, such as affecting enzyme activity, mitochondrial energetics, thiol redox systems, calcium signaling, and gene regulation. Oxidative stress is a disturbance in redox signaling and control, which can lead to damage in molecules if the levels of reactive species are too high in comparison to antioxidant and repair mechanisms. It is not a single disease nor an indication of exposure. Smoking, diet, age, inflammation, medication, the environment of the sample being processed, chronic disease or other factors can affect the same biomarker; thus, there needs to be biochemical and epidemiological context in order to interpret the marker. (Ercal et al., 2001; Jan et al., 2015; Valko et al., 2005).

Recent reviews have highlighted that the multiple pathways of oxidative, inflammatory, endocrine and epigenetic mechanisms are interconnected, and not a single pathway in metal toxicity (Jomova et al., 2025; Kolawole et al., 2025). This narrative review aims to summarize the biochemical pathways of metal-induced oxidative stress, critically review the most commonly used biomarkers and establish priorities for research and monitoring (Briffa et al., 2020; Jomova et al., 2025; Kolawole et al., 2025; Tripathi et al., 2024).

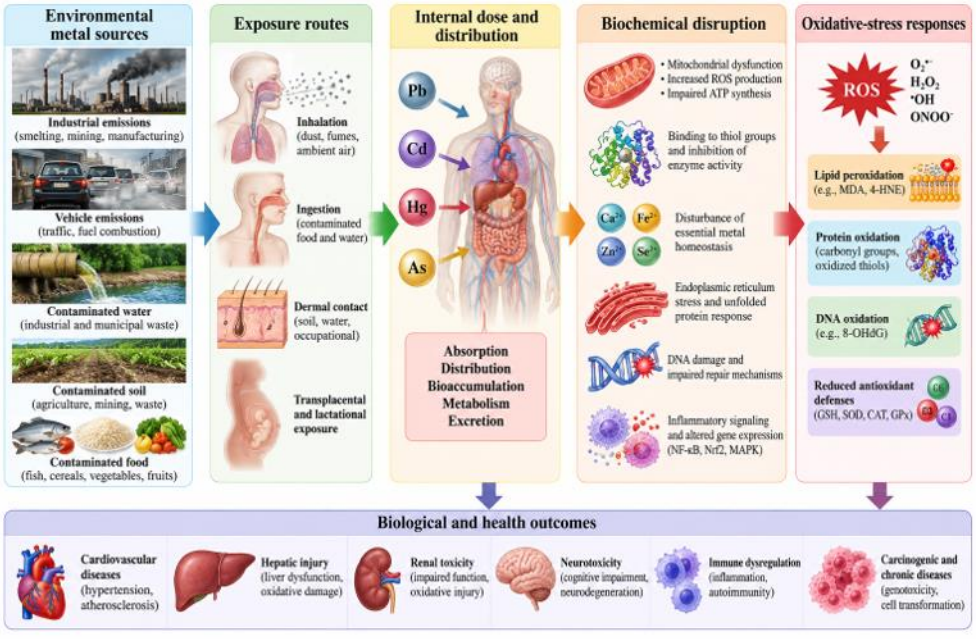


Figure 1. Conceptual pathway from environmental metal sources and exposure routes to internal dose, biochemical disruption, and oxidative-stress responses.

2. Literature Review Approach

This is no systematic review or meta-analysis, but a narrative review of the manuscript. The literature was searched by targeting specific keywords on Pubmed and publisher records such as heavy metals, lead, cadmium, mercury, arsenic, oxidative stress, reactive oxygen species, glutathione, antioxidant enzymes, MDA, 8-OHdG and biomarkers. Peer-reviewed reviews and methodological papers published in the last 6 years (2020-2026) were prioritized, and foundational papers were retained to discuss basic concepts and limitations in analytical methods. This search was meant to assist in a critical narrative synthesis and was not designed to do pooled effect estimation or provide "exhaustive" coverage. There are no new experiments or data on patients presented, nor are there pooled effect estimates or unpublished numerical results.

3. Biochemical Mechanisms of Metal-Induced Oxidative Stress

3.1. Reactive oxygen species and redox imbalance

Reactive oxygen species are superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2) and, under the right chemical circumstances, the highly reactive hydroxyl radical ($^{\bullet}OH$). Molecules also play their role in normal signaling, immune defense and adaptation. Oxidative stress occurs when their production, localization or persistence is greater than their levels of regulation and repair. Toxic metals may contribute to this imbalance by a variety of indirect mechanisms such as: by disrupting electron transport in mitochondria, by inducing oxidant generating enzymes, by reducing levels of low molecular weight antioxidants, or by affecting the function of redox sensitive proteins (Halliwell & Whiteman, 2004; Sies et al., 2017; Murphy et al., 2022). (Birben et al., 2012; Pizzino et al., 2017).

Bio-relevant redox cycling of different toxic metals is not the same. While Cd and Pb are not expected to become part of the Fenton-type chemistry, in biological environments, the metals of Fe and Cu are expected to be able to play a direct role in Fenton-type chemistry, while Cd and Pb may play an indirect role by causing abnormal ROS production due to mitochondrial dysfunction, antioxidant depletion, and displacement of essential metals from protein-binding sites. This distinction is significant since the chemical mechanism is not just related to the term “heavy metal” but also to the metal's speciation and the local biochemical environment (Jomova et al., 2025; Jomova et al., 2025; Valko et al., 2005).

3.2. Mitochondrial dysfunction

Reactive species can be produced in the mitochondria and can act on the mitochondria. Exposure to metals can lead to dysfunction of the respiratory-chain complexes, changes in membrane potential, changes in ATP production, and changes in electron leakage. This mitochondrial damage could lead to increased ROS production and trigger stress responses such as mitochondrial permeability transition and apoptosis signaling. These responses vary in intensity and direction, depending on the dose, duration, cell type and the type of exposure (acute or chronic). Results from cell and animal models are of a mechanistic nature and do not necessarily translate to the same quantitative impact in exposed populations of humans (Jomova et al., 2025; Tripathi et al., 2024).

3.3. Glutathione and thiol-dependent defenses

Reduced glutathione (GSH) plays a key role in the detoxification of peroxides, maintenance of thiol status of proteins, conjugation reactions, and redox signaling in the cell. GSH is used by glutathione peroxidases to reduce hydrogen peroxide and lipid hydroperoxides to oxidized glutathione (GSSG) which can then be regenerated by glutathione reductase with NADPH. There are toxic metals that bind sulfhydryl groups, or affect GSH synthesis and recycling. This decrease of GSH could thus suggest depletion or changes in the redox status of the organism; however GSH alone is not sufficient to define the cause or the total antioxidant capacity of a biological system (Giustarini et al., 2016; Monostori et al., 2009).

3.4. Antioxidant enzymes and Nrf2 signaling

Superoxide dismutases transform superoxide to hydrogen peroxide, and catalase and glutathione peroxidases help to remove hydrogen peroxide. Lower or earlier exposure may lead to an up-regulation of antioxidant enzymes as an adaptive response while sustained or high exposure can lead to inhibition of enzymes, depletion of co-factors, or over-whelm of defense systems. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that controls genes that are responsible for antioxidant defense and detoxification. It is important to note that the activation of the Nrf2 pathway can be a protective mechanism, but if the pathway is activated continuously it may indicate an ongoing level of cellular stress and does not necessarily imply that there is no tissue damage. (Jomova et al., 2024; Tripathi et al., 2024) (Ighodaro & Akinloye, 2018; Jomova et al., 2024).

3.5. Oxidation of lipids, proteins and DNA.

Reactive species can start the process of lipid peroxidation in polyunsaturated fatty acids which will result in lipid hydroperoxides and secondary products like MDA and 4-hydroxynonenal. Modifications to protein structure, receptor signaling and enzyme activity may result from protein oxidation. The levels of oxidative DNA lesions, such as 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-OHdG or 8-oxo-dG as appropriate) can be indicative of oxidative nucleic-acid damage and repair. The endpoints listed are all molecular targets and are not interchangeable. A coherent biomarker panel has the potential to deliver greater information than an individual biomarker, as long as the methods used for analysis and the kind of sample is suitable (Halliwell & Whiteman, 2004; Murphy et al., 2022).

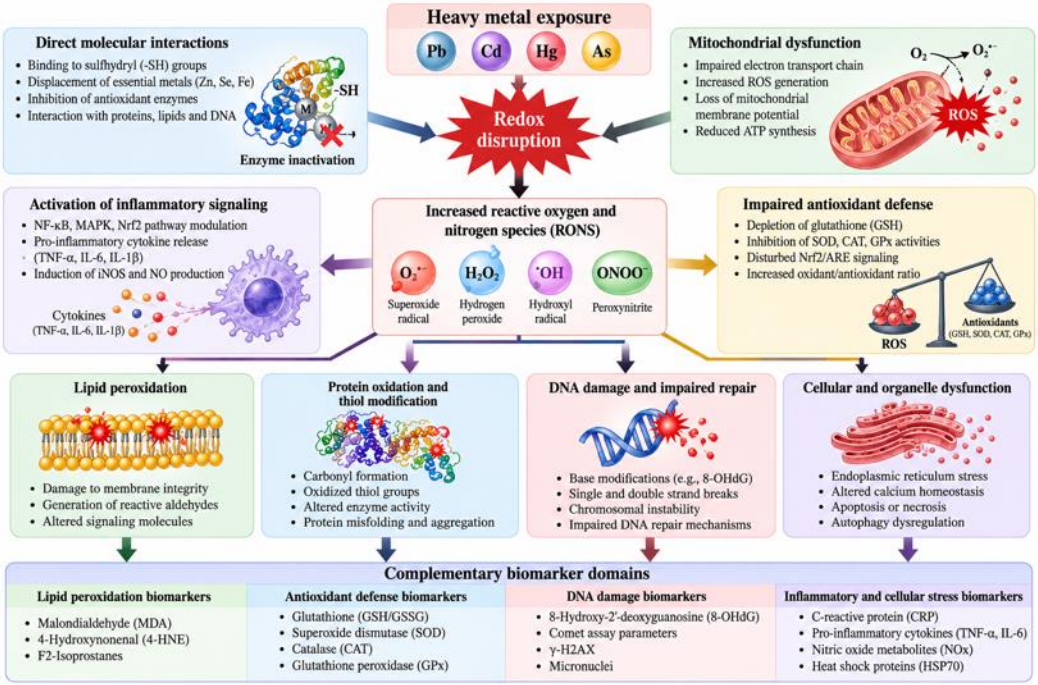


Figure 2. Mechanistic links between redox disruption and complementary biomarker domains.

4. Metal-Specific Biochemical Considerations

Table 1. Heavy Metals and Metalloids: Biochemical Mechanisms of Toxicity and Exposure Biomonitoring Considerations.

Metal/metalloid	Relevant biochemical mechanisms	Common exposure/biomonitoring considerations
Lead (Pb)	Indirect ROS generation, thiol interactions, interference with heme synthesis and essential-metal-dependent processes; possible effects on vascular and neural function. (Flora et al., 2012).	Blood lead is commonly used for recent or ongoing exposure assessment; interpretation depends on timing and exposure history.
Cadmium (Cd)	GSH depletion, mitochondrial dysfunction, altered antioxidant enzyme activity, inflammatory signaling, and interference with zinc-dependent proteins. (Genchi et al., 2020).	Blood and urine cadmium can reflect different exposure windows; smoking is an important potential confounder.
Mercury (Hg)	Strong affinity for thiol/selenol groups; altered antioxidant enzyme function and mitochondrial processes. Toxicokinetics differ by chemical species. (Bernhoft, 2012; National Research Council, 2000).	Speciation and matrix matter: blood, urine, and hair may reflect different mercury forms and exposure periods.
Arsenic (As)	Metabolism of inorganic arsenic species, thiol interactions, oxidative and nitrosative stress, and effects on signaling and DNA regulation. (Tchounwou et al., 2012).	Total arsenic may be misleading without speciation because seafood-derived organic arsenicals can contribute to measured totals.

5. Biochemical Biomarkers: Utility and Limitations

5.1. Malondialdehyde and lipid peroxidation

MDA serves as an index for lipid peroxidation, and is widely used. Can be quantified either by TBARS assays, chromatography or mass-spectrometry. There are limitations, however, including the fact that TBARS assays are not specific for MDA and may be affected by other compounds present in the sample and/or by heating or storage of samples that cause artifacts. The selectivity of the analysis can be improved by chromatographic separation or by specific methods which have been validated. The report should include the type of measurement, the material being analyzed, the calibration, the units, sample procedure, and quality control procedure(s) (Aguilar Diaz De Leon & Borges, 2020; Murphy et al., 2022). (Ayala et al., 2014; Tsikas, 2017).

5.2. GSH and GSSG

Reduced and oxidized glutathione in the cell can be measured to get information on thiol redox status. GSH however, are sensitive to oxidation once

collected. It is important to process rapidly, stabilize appropriately, control the temperature and differentiate between plasma, serum, whole blood and tissue homogenates. GSH/GSSG ratio is also a valuable redox indicator, but is very sensitive to pre analytical oxidation and should not be considered without appropriate collection and analysis procedures (Giustarini et al., 2016; Monostori et al., 2009).

5.3. SOD, CAT, and GPx

The activity of antioxidant enzymes can be indicative of adaptive responses or of the deterioration of the antioxidant enzyme defense system. Results are dependent on the biological matrix, the principle of the assay, temperature, pH, concentration of the substrate and the normalization method. Enzyme activity can vary in different tissues; vary with time after exposure, or increase or decrease. Therefore, when antioxidants were found to decrease, it must be stated what enzyme, what matrix, in what direction and by what method, in order to be specific.

5.4. 8-OHdG and other molecular damage markers

To study oxidative DNA damage and/or excretion of DNA repair intermediates, 8-OHdG/8-oxo-dG is used. ELISA methods may be useful but could have different cross reactivities and specificities; chromatographic and mass-spectrometric methods can provide more analytical specificity. Normalizing urinary concentrations may be necessary (e.g., creatinine) and care should be taken when oxidizing DNA during the extraction process in the case of DNA-based assays. The panel may be supplemented by protein carbonyls, F2-isoprostanes, and inflammatory markers, but each of these has unique biological and/or analytical limitations (Frijhoff et al., 2015; Murphy et al., 2022).

5.5. Exposure biomarkers are not effect biomarkers

MDA, GSH, antioxidant enzymes, and 8-OHdG measure biological responses or damage and thus are of primary interest for internal burden, while metal concentrations in blood, urine, hair, or nails are of primary interest for exposure or internal burden. The two classes should not be confused with each other and used jointly. A high metal level does not mean that this is the oxidative marker caused by this metal nor does an abnormal oxidative marker mean that this is the exposure that is responsible. Combination of exposure measurement, biological-effect markers, clinical endpoints and relevant covariates into stronger studies.

Table 2. Biomarkers and Evidence Domains for Assessing Metal-Induced Oxidative Stress and Their Interpretive Limitations.

Evidence domain	Examples	What it can support	Key limitation
Exposure / internal dose	Blood lead; urine cadmium; speciated arsenic; mercury in an appropriate matrix	Characterization of exposure and, where appropriate, internal burden	Matrix and sampling time reflect different exposure windows; speciation may be essential
Oxidative response	MDA or F2-isoprostanes; protein carbonyls	Evidence consistent with oxidative molecular damage	Assay specificity and pre-analytical artifacts can affect results
Antioxidant defense	GSH/GSSG; SOD; CAT; GPx	Information on thiol status and antioxidant-system response	Direction of change can reflect adaptation, inhibition, or tissue-

			specific effects
DNA oxidation / repair	Urinary 8-oxo-dG or validated DNA-based measures	Evidence relevant to oxidative nucleic-acid damage or repair	Methods are not interchangeable; normalization and extraction artifacts matter
Clinical / contextual outcomes	Renal function; blood pressure; neurological or metabolic outcomes; exposure history	Clinical relevance and contextual interpretation	Confounding and observational design limit causal inference

6. Summary of Biomarker Interpretation

Table 3. Biochemical Oxidative Stress and Exposure Biomarkers: Biological Significance, Analytical Limitations, and Recommended Reporting Practices.

Biomarker	Biochemical meaning	Main caveat	Good reporting practice
MDA/TBARS	Lipid-peroxidation-related signal	TBARS is not specific; pre-analytical artifacts possible	Name the assay and matrix; report calibration and QC
GSH/GSSG	Thiol redox status	Rapid ex vivo oxidation; matrix-dependent values	Stabilize samples promptly; report both analytes when feasible
SOD	Superoxide dismutation activity	May rise adaptively or fall after inhibition/damage	Specify isoform/matrix and activity units
CAT	Hydrogen-peroxide decomposition	Activity depends on assay conditions and tissue	Report method, temperature, substrate and normalization
GPx	Peroxide reduction using GSH	Different isoforms and substrates affect results	Specify assay principle and substrate
8-OHdG/8-oxo-dG	Oxidative nucleic-acid damage/repair marker	Method-dependent specificity and sample handling	Identify analytical platform and normalization
Blood/urine metal	Exposure or internal-dose indicator	Matrix reflects different time windows and species	Use validated methods; record exposure timing and metal speciation

7. Evidence Integration and Clinical Translation

However, recent syntheses have reported that many toxic metal exposures, oxidative-stress markers and inflammatory pathways have been associated, with the magnitude of the effects depending on the dose, duration, population and assay. Kolawole et al. (2025) for instance, reported that evidence correlated exposure to Pb with inflammatory markers like CRP, IL-6 and TNF-α in addition to evidences relating exposure to Cd with oxidative-damage markers. However, this synthesis doesn't eliminate limitations of the observational studies, such as confounding, selection bias, exposure misclassification, and heterogeneity of laboratory methods (Jomova et al., 2025; Kolawole et al., 2025; Wąsik, 2026).

To translate to the clinic, there needs to be separation between an analytically measurable biomarker and a clinically validated test. A biomarker could also be used for research surveillance, even if there is not a validated threshold to have a diagnosis of metal-induced oxidative injury for a person. A marker or panel must demonstrate analytical validity, be repeatable, be shown to have a reference interval, be correlated with meaningful outcomes and provide additional value when compared to existing exposure markers and clinical evaluation before being used clinically.

Removal/reduction of exposure, occupational controls, clean water and food, and evidence-based medical management should be emphasized in intervention studies, as appropriate. Exposing individuals to antioxidants is not a recommended method for treatment of metal exposure, and nor should it be suggested as an alternative to exposure control. Chelation is used for limited use cases and toxicities and should be administered to patients only under the supervision of a qualified clinician, otherwise it may be detrimental to the patient. (Agency for Toxic Substances and Disease Registry [ATSDR] 2020, World Health Organization [WHO] 2021).

7.1 Integrating exposure, effect, and susceptibility evidence

Best results are obtained by the combined use of external exposures, internal-dose markers, biochemical effect markers and clinical data. Blood lead provides an indication of the immediate or chronic exposure while urine, blood, and hair may provide different windows of exposure for other metals and chemical species. However, the importance of speciation is suggested by the fact that the relatively less toxic organic arsenic compounds present in seafood can affect the total urinary arsenic determination for arsenic. These differences minimize the risk of exposure misclassification, and do not use oxidative-stress markers as a metal-specific diagnostic test (World Health Organization [WHO], 2022; Chakif & Furrer, 2026).

7.2 Oxidative-stress biomarkers: an evidence-weighted approach

A practical panel should consist of a collection of markers that represent a variety of domains of biological activity and not multiple tests that measure similar downstream effects. Assay conditions may produce nonspecific signals and it is possible to get inexpensive and accessible assays, but requires caution. If resources and validated methods are available, specificity can be enhanced by using F2-isoprostanes or chromatographic or mass-spectrometric approaches. The pre-analytical stabilization of samples for GSH/GSSG measurement needs to be stringent, and the biological matrix, the principle of the assay, the units, and the normalization procedure should be reported for antioxidant-enzyme activities. The current methodological guidance strongly stresses that there is no single method that is adequate for characterizing redox biology and that it is hard to measure ROS directly (Murphy et al. 2022; Krishnamurthy et al. 2024).

Table 4. Minimum quality and reporting framework for human studies of metal-associated oxidative stress.

Quality element	Minimum reporting detail	Why it matters
Exposure characterization	Metal species where relevant, biological matrix, collection timing, occupational/environmental history	Supports correct interpretation of exposure window and source
Sample handling	Collection tubes, processing delay, storage temperature, freeze–thaw history	Reduces pre-analytical bias, especially for redox-sensitive analytes
Analytical validation	Assay principle, calibration, detection/quantification limits, precision, quality controls	Allows assessment of accuracy, reproducibility, and comparability
Biomarker reporting	Units, matrix, normalization, reference/comparison group, missing data	Prevents ambiguous or misleading comparisons
Confounding control	Age, sex, smoking, diet, medications, renal/hepatic function, co-exposures	Reduces alternative explanations for biomarker differences
Inference	Effect sizes and uncertainty; distinguish association from causation	Avoids overstating mechanistic or clinical implications

7.3 Strength of evidence and limits of translation

It is recently confirmed that the oxidative, inflammatory, mitochondrial and genomic pathways are interconnected with each other in metal toxicity. The strength of evidence varies between metal, chemical species, dose, exposure time and outcome, however. Results from experimental systems can help to elucidate mechanisms but are not necessarily a human risk estimate. Other potential factors of co-exposure, smoking, diet, socioeconomic factors, renal function and laboratory methods also affect observational studies. A 2025 systematic review of heavy-metal toxicity biomarkers called for the integration of exposure assessment with the careful selection of effect markers, along with clinically meaningful endpoints (Kolawole et al., 2025), and a 2026 integrative clinical review advocated for the same (Chakif & Furrer, 2026).

7.4 Implications for environmental and occupational biochemistry

First of all, from an applied biochemistry standpoint, it is important to identify the source of exposure and decrease it as much as possible. Biomarker testing can be used to aid surveillance and research, but should be considered along with the exposure history and the validated clinical or public health guidance specific to the metal. Antioxidant supplements should never be used to treat metal toxicity, and chelation should not be used as a blanket treatment. Metal toxicity should only be treated with chelation if it has been specifically indicated and is clinically supervised. Prevention, workplace controls, safe water/food and validated biomonitoring continue to be key elements in minimising exposure risk (WHO, 2021, 2022, 2024, 2026).

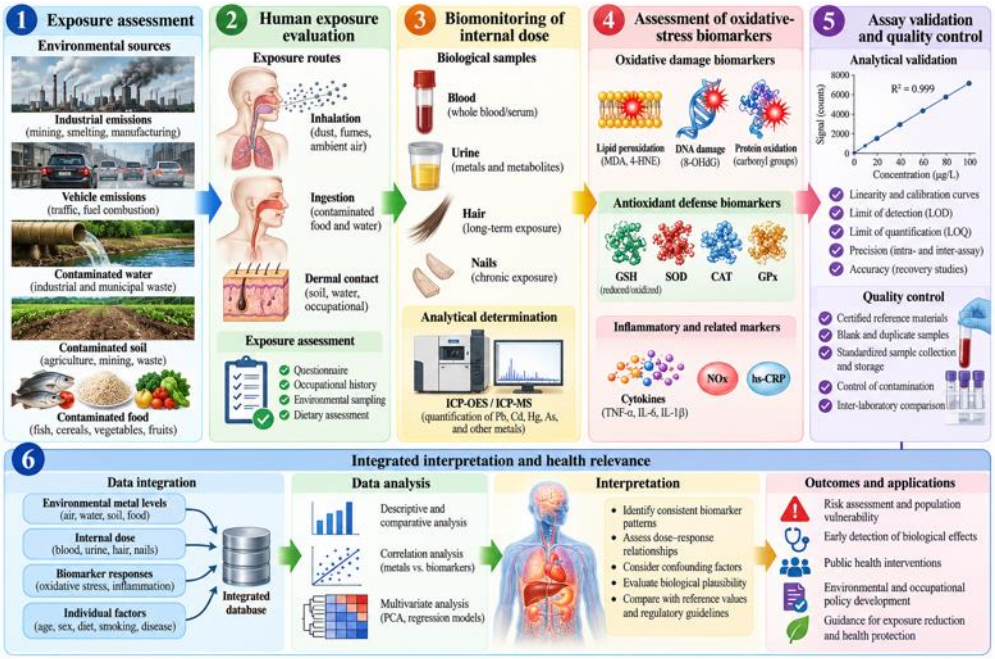


Figure 3. Recommended workflow for evaluating metal-related oxidative stress, from exposure assessment and assay validation to integrated interpretation.

8. Research Gaps and Future Directions

- Standardize the collection, storage, processing, validation of the assays for oxidative-stress biomarkers and reporting.
- Provided validated exposure measures and biochemical markers and clinically relevant outcomes in the same participants.
- Utilize prospective designs and multiple measurements to establish temporal relationships, and minimize reverse causation concerns.
- Take measurements and adjust for smoking, food, and age, sex, kidney and liver function, medications, work history and co-exposures.
- Use the correct method to distinguish between metal species and biological matrices; don't just report the total metal concentration.
- Pre-register analytical plans, provide full summary tables and provide de-identified data and code if ethically possible.
- Properly test new multi-omics and AI-generated signatures in separate patient cohorts prior to clinical use.

9. Review limitations

This is a narrative review without the use of a registered systematic review protocol, but with targeted literature searches. The list was not meant to be comprehensive and no attempt was made to determine or offer a quantitative estimate of the amount of a biochemistry present. A lack of comparability among studies is due to publication bias, differences in metal speciation and exposure assessment, and the variability in biomarker assays. The conclusions are therefore mechanistic and interpretive only and not intended to diagnose, causation or a treatment effect.

10. Conclusion

The biochemical homeostasis disruption can be mediated by multiple pathways, such as mitochondrial dysfunction, thiol depletion, alteration of antioxidant signaling, lipid peroxidation, molecular damage, and inflammation, all of which are interconnected by heavy metals. MDA, GSH/GSSG, SOD, CAT, GPx and 8-OHdG are complementary, but not redundant, measures of biological response. They are interpreted analytically, considering the sample, the exposure and the clinical situation. There is no single

oxidative stress marker that is specific for a metal exposure or has the ability to establish causation. Standardized laboratory methods, a comprehensive exposure and effect assessment, longitudinal evidence and transparent data reporting need to be relied on for future progress.

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