Environmental Research 292 (2026) 123703

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Review article

Developmental toxicity of metals: Three decades of insights into mechanisms, epigenetics, and transgenerational inheritance

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ARTICLE INFO

Keywords:
Developmental toxicity
Metals
Chelation therapy
Oxidative stress
Epigenetics

ABSTRACT

Since the early 1990s, considerable progress has been made in understanding the teratogenic and embryotoxic effects of metals in mammalian systems. The present updated review synthesizes over three decades of research findings, examining the developmental toxicity of metals across four categories: (a) metals of greatest toxicological significance (arsenic, cadmium, lead, mercury, and uranium), (b) essential trace metals (chromium, cobalt, manganese, selenium, and zinc), (c) other metals with evident biological interest (nickel and vanadium), and (d) metals of pharmacological interest (aluminum and lithium). Recent advances in understanding molecular mechanisms, epigenetic effects, transgenerational impacts, and improved chelation therapies are comprehensively reviewed. The emergence of new analytical techniques has revealed previously unrecognized low-dose effects and complex metal-metal interactions that affect developmental outcomes. Current evidence shows that environmental exposures to multiple metals at concentrations previously considered safe can produce significant developmental toxicity through oxidative stress, epigenetic modifications, and disruption of essential metabolic pathways. Chelating agents, including improved formulations of DMSA and DMPS, continue to show promise in preventing and treating metal-induced developmental toxicity, although their own potential developmental effects require careful consideration.

1. Introduction

Metal-induced developmental toxicity remains a critical public health concern, with environmental exposures continuing to pose significant risks to embryonic and fetal development in mammalian species (Briffa et al., 2020; Hou et al., 2020). Since the publication of my original review on the topic (Domingo, 1994), the scientific understanding of metal toxicity mechanisms has dramatically evolved, with notable advances in molecular biology, epigenetics, and analytical chemistry. It has been shown that metals can induce developmental abnormalities through multiple interconnected pathways, including oxidative stress generation, epigenetic modifications, endocrine disruption, and interference with essential cellular processes (Balali-Mood et al., 2021; Liu et al., 2023; Tchounwou et al., 2012).

The global burden of metal contamination has intensified owing to expanded industrial activity, mining, and the ubiquitous use of metal-containing products (Das et al., 2023; Hou et al., 2025; Moulatlet et al., 2023; Ondrasek et al., 2025; Schumacher et al., 1991). Simultaneously, analytical capabilities have improved, allowing detection of metal effects at previously unrecognizable concentrations and revealing complex interactions between multiple metals (Yokel et al., 2006). These advances have fundamentally altered the understanding of safe exposure levels and highlighted the importance of considering mixture effects rather than individual metal toxicities (Domingo, 2025; Nordberg et al., 2022).

Among the metals of greatest concern, lead, arsenic, cadmium, and mercury pose the most significant risks to developmental health based on their prevalence, toxicity, and well-known effects. Lead has been particularly problematic due to its continued environmental persistence from historical use and its profound effects on neurodevelopment at even very low exposure levels. In turn, arsenic and cadmium have substantial risks through contaminated water and food sources, with arsenic showing particularly strong evidence for developmental neurotoxicity and carcinogenicity, while cadmium demonstrates significant reproductive and kidney toxicity. Mercury, especially in its methylated form, exhibits selective neurotoxicity with the developing nervous system being exquisitely sensitive. In contrast, essential elements such as zinc, selenium, and manganese pose risks primarily at excessive exposure levels, although deficiency states can also impair development. The comparative toxicity rankings are influenced by exposure routes,

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https://doi.org/10.1016/j.envres.2026.123703
Received 27 October 2025; Received in revised form 7 December 2025; Accepted 5 January 2026
Available online 6 January 2026
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Table 1
Developmental toxicity by metal category.

Metal Category	Metals	Primary Developmental Effects	Key Target Organs/Systems
Metals of Greatest Toxicological Significance	Arsenic, cadmium, lead, mercury, uranium	• Neurodevelopmental deficits • Cognitive impairment • Behavioral alterations • Growth restriction • Organ malformations	• Central nervous system • Kidney • Liver • Reproductive system • Cardiovascular system
Essential Trace Metals	Chromium, cobalt, manganese, selenium, zinc	• Toxicity when in excess or inappropriate form • Deficiency effects when depleted • Neural tube defects • Growth retardation • Immune dysfunction	• Brain (dopaminergic neurons) • Reproductive organs • Immune system • Skeletal system
Other Metals with Biological Interest	Nickel, vanadium	• Reproductive dysfunction • Embryotoxicity • Gamete damage • Oxidative injury	• Ovaries/testes • Sperm/oocytes • Placenta • Energy metabolism pathways
Metals of Pharmacological Interest	Aluminum, lithium	• Neurological impairment • Cardiac malformations (Li) • Reproductive toxicity • Developmental delays	• Nervous system • Heart (Ebstein's anomaly) • Reproductive system • Bone/skeletal system

bioavailability, target organ specificity, and the existence of sensitive developmental windows for each metal.

Epidemiological studies have provided compelling evidence that prenatal metal exposures, even at relatively low levels, can result in measurable developmental consequences that may not manifest until later in life (Skogheim et al., 2021; Vaiserman and Lushchak, 2021). The concept of developmental programming has emerged as a critical framework for understanding how early-life metal exposures can influence disease susceptibility throughout the lifespan. Furthermore, emerging evidence of transgenerational effects suggests that metal exposures in one generation can affect the health of subsequent generations through epigenetic mechanisms (Morgan et al., 2024; Nava-Rivera et al., 2021). Biomonitoring studies have quantified metal concentrations in developmentally relevant human tissues such as placenta, cord blood, and fetal organs, providing critical data for exposure assessment (Ortega-Romero et al., 2024; Skogheim et al., 2021).

This comprehensive review updates the understanding of metal-induced developmental toxicity by examining research published from 1994 to 2025, with particular emphasis on mechanistic insights, low-dose effects, mixture toxicity, and advances in prevention and treatment strategies.

2. Methods (search strategy)

This comprehensive review of the scientific literature was conducted by systematically searching the databases PubMed, Scopus, Web of Science and Google Scholar, for articles published between 1994 and September 30, 2025. Search terms included combinations of controlled vocabulary (MeSH/Keywords) such as “metal toxicity”, “metal teratogenicity”, “developmental exposure”, “embryotoxicity”, “chelating agents”, and specific metal names (arsenic, cadmium, lead, mercury, uranium, chromium, nickel, manganese, etc.). Boolean operators were used as follows: ("metal” OR “heavy metal” OR “trace element”) AND ("developmental toxicity” OR “teratogenicity” OR “fetal exposure").

Publications were considered if they met the following inclusion criteria: a) original research articles, systematic reviews, or authoritative reports addressing developmental or reproductive toxicity of metals in humans or mammalian models, b) studies evaluating mechanisms of action, toxicokinetics, or preventive and therapeutic strategies, and c) articles published in English and peer-reviewed. On the other hand, exclusion criteria comprised: a) non-peer-reviewed sources (e.g., conference abstracts, non-scientific reports), b) studies focusing exclusively on inorganic compounds without metal content, and c) publications focused only on plant or invertebrate models. Over 200 references were screened, with priority given to peer-reviewed original research, reviews, and meta-analyses. No formal meta-analysis was performed due to the heterogeneous nature of the studies.

3. Developmental toxicity

The developmental toxicity of metals varies considerably based on their biological roles, exposure levels, and chemical forms. For this review, metals are categorized into four groups based on their toxicological significance and biological function (Table 1). The following sections provide detailed discussions of each metal within these categories.

3.1. *Elements of greatest toxicological significance*

3.1.1. *Arsenic*

Arsenic exposure remains a global health concern, with millions of people worldwide chronically exposed mainly through contaminated drinking water (Podgorski and Berg, 2020; Rahaman et al., 2021; Tian et al., 2025). Major sources include naturally contaminated aquifers, mining, and industrial processes. Since 1994, extensive research has been focused on arsenic's developmental neurotoxicity, revealing that prenatal and early postnatal exposures can result in cognitive deficits, behavioral alterations, and increased mortality in young adults (Farzan et al., 2013; Tolins et al., 2014; Tyler and Allan, 2014). The developmental neurotoxicity of arsenic has emerged as one of the most concerning aspects of early-life exposure, with various epidemiological studies demonstrating associations between early life arsenic exposure and deficits in intelligence and memory (Tolins et al., 2014). Moreover, developmental arsenic exposure is implicated in cardiovascular toxicity, affecting both maternal and fetal systems through mechanisms involving oxidative stress and endothelial dysfunction. In the developing fetus, arsenic disrupts cardiac morphogenesis, leading to structural abnormalities including septal defects and altered chamber development. Arsenic also interferes with vascular development, affecting endothelial cell differentiation and angiogenesis. Long-term epidemiological studies have demonstrated that prenatal arsenic exposure is associated with increased cardiovascular disease risk in adulthood, including hypertension, ischemic heart disease, and peripheral vascular disease (States et al., 2009). Maternal arsenic exposure can induce cardiovascular stress, including increased blood pressure and altered cardiac output, which may further compromise placental perfusion and fetal development. These cardiovascular effects appear to involve both direct toxic mechanisms and developmental programming through epigenetic modifications of genes regulating cardiovascular function (Mahadik et al., 2024).

Animal studies, using exposure paradigms more representative of human environmental conditions, have also revealed that prolonged

oral arsenic exposure can cause developmental toxicity at maternally non-toxic levels (Wang et al., 2006). Particularly significant was the finding in rats that maternal exposure to inorganic arsenic in drinking water affects fetal brain development and postnatal behaviors, even when administered at concentrations that did not produce maternal toxicity (Chattopadhyay et al., 2002; Rodríguez et al., 2003). This contrasts with earlier studies that required high, acutely toxic doses administered parenterally to produce malformations (DeSesso et al., 1998; Wang et al., 2006).

Regarding the molecular mechanisms underlying arsenic developmental toxicity, arsenic exposure disrupts multiple cellular processes including DNA methylation patterns, mitogen-activated protein kinase (MAPK) signaling pathways, and antioxidant defense systems (Ganie et al., 2023; Garza-Lombó et al., 2019; Medda et al., 2021). The trivalent form of inorganic arsenic generates reactive oxygen and nitrogen species (ROS/RNS), leading to oxidative stress, which can directly damage cellular components and disrupt normal developmental processes (Chandravanshi et al., 2018; Prakash et al., 2015). Additionally, arsenic metabolism directly interferes with S-adenosylmethionine (SAM) production, the universal methyl donor substrate required for DNA methylation reactions. This depletion of available SAM further compounds the methylation disruptions caused by direct effects on DNA methyltransferases, creating a two-pronged mechanism for arsenic-induced epigenetic alterations.

Transgenerational effects of arsenic exposure have also emerged as a particularly concerning finding. Recent studies demonstrate that chronic arsenic exposure can produce heritable effects that persist across multiple generations (Nava-Rivera et al., 2021). DNA methylation changes, genotoxicity markers, and reproductive phenotype alterations have been documented in F1, F2, and F3 generations of arsenic-exposed animals, indicating that the effects of arsenic exposure may extend far beyond the directly exposed generation (Guo et al., 2018; Nava-Rivera et al., 2021).

The protective effects of nutritional factors against arsenic developmental toxicity have been extensively studied. Findings on protective nutrients are complex and context-dependent. For example, in a rodent model, selenium, but not zinc or folate, supplementation was protective against arsenic-induced reproductive and developmental toxicity (Wang et al., 2006), while other studies suggest potential benefits of folate in mitigating arsenic epigenetic toxicity in humans. Anyhow, inorganic arsenic readily crosses the human placenta, leading to direct fetal exposure.

3.1.2. Cadmium

Cadmium exposure during critical developmental windows affects multiple organ systems, with particularly severe consequences for reproductive development, kidney function, and neural development (Hudson et al., 2025a). Major sources of cadmium include tobacco smoke, contaminated food (e.g., rice, leafy vegetables), and industrial emissions. This metal accumulates preferentially in the kidney and liver, where it can persist for decades due to its extremely long biological half-life. Recent studies have shown that cadmium exposure during embryonic development suppresses normal ovarian growth and development, while in adults it disrupts ovarian and uterine morphology and function (Qu et al., 2022). The distribution of follicles and corpus luteum in ovarian tissues is significantly altered by cadmium exposure, with increased numbers of atretic follicles and decreased numbers of developing follicles at various maturation stages (Bhardwaj et al., 2024). These effects occur through multiple mechanisms including oxidative stress generation, interference with hormone signaling pathways, and direct cytotoxic effects on reproductive tissues. In addition to its renal and reproductive toxicity, developmental cadmium exposure is implicated in programming for hypertension and cardiovascular dysfunction later in life, potentially through oxidative stress and epigenetic disruption of vascular development pathways (Hudson et al., 2025a).

The molecular mechanisms of cadmium developmental toxicity involve extensive disruption of cellular homeostasis (Lee et al., 2025; Wang et al., 2012). Cadmium binds strongly to sulfhydryl groups in proteins, leading to enzyme inactivation and cellular dysfunction (Lange and Segner, 2023). This metal induces metallothionein production as a protective response, but this mechanism can be overwhelmed during periods of high exposure or during development when protective systems are immature (Nordberg and Nordberg, 2025; Wang et al., 2025a). Additionally, cadmium interferes with essential metal homeostasis, particularly zinc and copper, leading to secondary deficiency effects that compound its direct toxic actions (Arruebarrena et al., 2023; Brzóska and Moniuszko-Jakoniuk, 2001).

Epigenetic effects of cadmium have received considerable attention in recent years. Cadmium exposure alters DNA methylation patterns, histone modifications, and microRNA expression profiles in developing tissues (Fay et al., 2018). These epigenetic changes can persist long after the initial exposure and may contribute to increased disease susceptibility later in life (Vilahur et al., 2015). Cadmium-induced epigenetic changes can be transmitted to subsequent generations, suggesting potential transgenerational effects of developmental cadmium exposure (Lawless et al., 2023; Pierron et al., 2023). Prenatal exposure to cadmium has been associated with adverse effects on child health and development, with epigenetic disruption emerging as a plausible mode of action (Vilahur et al., 2015). Studies demonstrate that cadmium alters epigenetic signatures in the DNA of the placenta and newborns, with some studies indicating marked sexual differences in cadmium-related DNA methylation changes (Sanders et al., 2014; Vilahur et al., 2015). Maternal cadmium exposure during late pregnancy causes fetal growth restriction via inhibition of placental progesterone synthesis and destruction of the placenta's morphological structure (Xiong et al., 2020). The placenta acts as a partial barrier with transfer efficiency influenced by gestational age and metallothionein expression. Placental epigenetic changes (e.g., DNA methylation of genes involved in glucocorticoid signaling such as NR3C1 and HSD11B2) may mediate some adverse developmental outcomes such as fetal growth restriction (Vilahur et al., 2015). Epigenetic modifications caused by cadmium have been shown to be involved in transgenerational inheritance of cadmium reproductive toxicity, as shown in mouse oocytes where DNA methylation and histone modifications were altered and transmitted to subsequent generations (Zhu et al., 2024). Cadmium crosses the placenta, although the placenta offers some partial barrier, leading to fetal accumulation.

3.1.3. Lead

Lead developmental toxicity research has advanced substantially since 1994, driven largely by recognition that no safe level of lead exposure exists for developing children (Sample, 2024). Major historical sources of this metal include leaded paint, gasoline, and contaminated soil; current sources include older housing, certain spices, and traditional medicines. The primary focus has shifted from preventing acute lead poisoning to understanding and preventing the subtle neurodevelopmental effects that occur at increasingly lower exposure levels. Prenatal lead exposure produces measurable cognitive deficits, behavioral problems, and academic difficulties that persist throughout childhood and into adulthood (Fruh et al., 2019; Ramírez Ortega et al., 2021). Lead exposure during development is also associated with cardiovascular effects, including increased risk of hypertension and altered cardiac autonomic regulation in later life.

Mechanistic studies have revealed that lead interferes with multiple neurodevelopmental processes including synaptogenesis, myelination, and neurotransmitter synthesis (Bjørklund et al., 2024; Neha et al., 2025). Lead substitutes for calcium in many biological processes, disrupting calcium-dependent signaling pathways that are critical for normal neural development (Virgolini and Aschner, 2021). Additionally, lead exposure increases oxidative stress in developing neural tissues, contributing to cellular damage and dysfunction (Leão et al., 2021).

In recent years, the reproductive and developmental effects of lead have been extensively studied. Lead exposure affects steroidogenesis, hormonal regulation, and gametogenic processes, with significant impacts on Leydig cells and spermatogenesis in males, and granulosa cells and theca cells in females (Aglan et al., 2021). Lead also affects placental growth, pregnancy rates, and fetal development following maternal exposure during gestation (Zhu et al., 2010). Epigenetic mechanisms have emerged as important mediators of lead developmental toxicity (Wang et al., 2025b). Lead exposure during development alters DNA methylation patterns in blood, brain, and liver tissues, with effects that vary by tissue and sex (Morgan et al., 2024). These epigenetic changes may contribute to the long-term consequences of early-life lead exposure and may explain some of the individual variability in susceptibility to lead toxicity (Gundacker et al., 2021). The epigenetic regulatory system is a critical mediator of lead-induced developmental neurotoxicity. Disruption of epigenetic gene regulation can produce profound and enduring alterations in the developing central nervous system, with effects that may persist throughout life and potentially exert transgenerational consequences (Mallick and Duttaroy, 2023). Environmental lead exposure during prenatal life or in childhood, even at blood lead concentrations below current action levels, may cause permanent neurological damage through epigenetic mechanisms (Senut et al., 2012). Lead acts as a potent epigenetic modifier, causing neurological disorders through modulation of DNA methylation, histone modifications, and non-coding RNAs (Wang et al., 2020). Emerging evidence from animal models suggests lead can induce transgenerational effects on behavior and metabolism, although the strength of evidence is less extensive than for arsenic or cadmium.

Studies in 23-year-old primates with developmental lead treatment have discovered a variety of epigenetic changes relating to Alzheimer's disease pathogenesis, providing direct evidence implicating the epigenetic basis of lead-induced neurological disorders across an entire lifespan (Wu et al., 2008; Wang et al., 2020). These findings support the concept that gestational lead exposure acts as a risk factor for neurological diseases with onset in later life, including Alzheimer's disease, Parkinson's disease, and schizophrenia (Senut et al., 2012; Wang et al., 2020). Lead has been shown to alter DNA methylation, histone modifications, and miRNA expression in experimental models and humans, implicating epigenetics in lead-induced toxicity and long-term changes in individuals (Eid and Zawia, 2016). Specific epigenetic molecules have been identified as key responses to lead neurotoxicity. Long non-coding RNA L20992 was identified as aberrantly upregulated in a lead-induced neuronal injury model, while Uc.173 was significantly decreased in lead-exposed populations, animal models, and in vitro cell lines (Wang et al., 2020). Circular RNAs have emerged as a new and promising field for association studies linking lead exposure to neurological disorders (Wang et al., 2020). Effects of developmental lead exposure on the hippocampal methylome are influenced by sex, timing, and level of exposure, with sex-specific differences documented in spatial learning and memory, motor behavior, dopamine metabolism, and brain gene expression (Senut et al., 2012; Singh et al., 2018).

Lead exposure can also disrupt global DNA methylation in human embryonic stem cells and alter their neuronal differentiation, suggesting that epigenetic modifications occur at the earliest stages of development (Senut et al., 2014). Post-translational histone modifications, particularly histone acetylation and methylation, are significantly affected by lead exposure and show sex-dependent and brain region-specific patterns in the early postnatal brain (Schneider et al., 2016). These epigenetic changes provide a mechanism by which the effects of lead exposure could be lifelong or even transgenerational (Senut et al., 2012). Lead readily crosses the placental barrier, resulting in fetal blood levels comparable to maternal levels.

3.1.4. Mercury

In recent decades, research on mercury toxicity has been transformed by the recognition that the developing nervous system is especially vulnerable to methylmercury exposure (Antunes dos Santos et al., 2018; Balali-Mood et al., 2021). The primary source of methylmercury is consumption of contaminated fish and seafood. The Minamata disease incident continues to provide critical insights into the devastating consequences of prenatal methylmercury exposure, with affected children showing severe developmental disabilities that persist throughout life. All chemical forms of mercury exert toxic effects in mammals, with methylmercury being of particular concern because of its capacity to traverse the placental barrier and accumulate in developing fetal brain tissue (Azevedo et al., 2023; Horai et al., 2025; Morgan et al., 2024). Methylmercury enters the food chain through microbial methylation in aquatic environments and bioaccumulates in fish, leading to human exposure primarily through fish consumption (Al-Sulaiti et al., 2022; Cano-Sancho et al., 2015). Methylmercury readily crosses the placenta after maternal ingestion and accumulates in the developing fetal brain (Mititelu et al., 2025). Within the nervous system, methylmercury preferentially targets the growth cone of neurons, a critical structure for axonal elongation and synaptogenesis. In physiologically normal growth cones, actin and tubulin neurofibrils maintain structural integrity and support neuronal outgrowth. However, methylmercury disrupts cytoskeletal dynamics, impairing neurofibril organization and function, which leads to developmental neurotoxicity and long-term cognitive deficits in offspring (Hu et al., 2024).

The molecular mechanisms of mercury developmental toxicity involve disruption of antioxidant systems, interference with calcium homeostasis, and induction of oxidative stress (Antunes Dos Santos et al., 2018; Kang et al., 2024). Organic mercury compounds increase intracellular calcium by accelerating calcium influx and mobilizing intracellular stores, while inorganic mercury compounds affect calcium homeostasis primarily through extracellular calcium influx (Jomova et al., 2025; Wu et al., 2024). Mercury compounds induce lipid peroxidation in liver, kidney, lung, and testis tissues, with the severity correlating with the degree of organ toxicity.

Developing animals have been shown to be more sensitive to methylmercury toxicity than adults, though the reasons for this differential sensitivity are not fully understood (Castoldi et al., 2008). Studies in young mice have demonstrated that methylmercury exposure can cause significant reductions in cell numbers in developing cerebellar regions, with evidence of mitotic arrest and altered cell cycle progression (Antunes dos Santos et al., 2016; Burke et al., 2006). These effects occur at brain mercury concentrations that would be considered relatively low in adult animals. In our laboratory, we investigated the effects of maternal stress on methylmercury-induced developmental toxicity. Colomina et al. (1995) showed that maternal restraint stress markedly enhanced methylmercury-induced toxicity at high doses, leading to increased maternal deaths, reduced weight gain, and a complete loss of viable implants at 25 mg/kg. In a subsequent study, Colomina et al. (1997) found that maternal restraint reduced weight gain in methylmercury-exposed dams but did not significantly alter physical or behavioral development in offspring. Overall, these findings indicated that severe maternal stress may potentiate methylmercury toxicity at highly toxic doses, whereas its role at lower, developmentally relevant exposures appears limited. Evidence for transgenerational effects of mercury is limited but emerging, with some studies suggesting epigenetic changes in offspring following prenatal exposure (Lozano et al., 2022). Methylmercury readily crosses the placenta, and inorganic mercury crosses to a lesser extent.

3.1.5. Uranium

Uranium developmental toxicity has received increased attention in recent years due to expanded use of depleted uranium in military applications and concerns about environmental contamination around uranium mining and processing facilities (Ma et al., 2020). Exposure sources of uranium include contaminated drinking water near mining sites and certain occupational settings. Both natural and depleted uranium have been shown to produce reproductive and developmental

toxicity in experimental animals, with effects that include reduced fertility, increased embryonic and fetal mortality, and developmental malformations (Domingo, 2001; Mirderikvand et al., 2014). Recent studies have demonstrated that uranium exposure during pregnancy can affect fetal development through multiple mechanisms (Yin et al., 2022). Uranium crosses the placental barrier and accumulates in fetal tissues, where it can interfere with normal developmental processes (Arfsten et al., 2001; Domingo et al., 2001). The metal affects cellular energy metabolism, induces oxidative stress, and interferes with essential enzyme systems required for normal development (Periyakaruppan et al., 2007).

The chemical form and route of exposure significantly influence uranium developmental toxicity. Soluble uranium compounds are generally more toxic than insoluble forms, and oral exposure typically produces different effects than inhalation or injection (Keith et al., 2013). Maternal and paternal exposure studies in rodents demonstrate that uranyl acetate can induce maternal toxicity, reduced fetal growth, and increased skeletal variations at high doses (Domingo, 2001). Albina et al. (2003) reported that maternal stress enhanced uranium-induced embryotoxicity only at levels that were already markedly toxic to the dams. In turn, in a paternal exposure study, uranium produced minimal effects on offspring development or behavior, and restraint stress did not significantly alter outcomes (Albina et al., 2005). Similarly, Sánchez et al. (2006) found that combined maternal uranium and restraint exposure produced limited interactions, with only minor alterations in specific behavioral tasks. Overall, uranium developmental toxicity appeared modest, while restraint stress only exacerbated adverse effects at doses highly toxic to the parents. Uranium crosses the placenta in rodents, leading to fetal accumulation.

3.2. Essential trace elements

3.2.1. Chromium

It is well known that essential metals can be toxic when present in excess or in inappropriate chemical forms, which is also the case for chromium (Wise et al., 2022). Occupational exposure in metallurgical and chemical industries is a primary concern. This element exists in multiple oxidation states, with trivalent chromium (Cr III) being an essential nutrient involved in glucose metabolism, while hexavalent chromium (Cr VI) is a known carcinogen and developmental toxicant (Banu et al., 2017; Sun et al., 2015). Recent studies have demonstrated that both Cr(VI) and Cr(III) can generate reactive oxygen species, leading to oxidative stress and cellular damage (Singh et al., 2022; Tian et al., 2024). Chromium-induced DNA damage includes DNA-protein crosslinks, inter- and intrastrand crosslinks, single- and double-strand breaks, and p53 point mutations (Nickens et al., 2010; Wakeman et al., 2017). These genotoxic effects are particularly concerning during development when rapidly dividing cells are most vulnerable to DNA damage (Czarnek et al., 2025; Mamyrbaev et al., 2015). Occupational exposures to chromium compounds have raised concerns about reproductive and developmental effects in exposed workers (Hessel et al., 2021). Metallurgical, refractory, and chemical industries release substantial amounts of chromium into soil, groundwater, and air, causing health issues in humans, animals, and marine life (CDCCenters for Disease Control and Prevention, 2013). Chromium (VI) crosses the placenta, while Cr(III) transfer is more limited.

3.2.2. Cobalt

Cobalt research has revealed complex relationships between its essential role in vitamin B12 metabolism and its potential toxicity when present in excess (Genchi et al., 2023). Sources of cobalt include metal-on-metal hip implants, certain occupational settings, and contaminated food/water. In its organic form, cobalt is essential for vitamin B12 (cobalamin) synthesis and contributes to amino acid and neurotransmitter formation. However, inorganic forms of cobalt can be toxic to the human body, particularly during critical developmental periods (2023Chen and Lee). Recent studies have demonstrated that cobalt deficiency during development can contribute to neural tube defects, while excess cobalt exposure can produce adverse developmental effects (Yin et al., 2020). The balance between essential function and toxicity appears to be particularly critical during embryonic and fetal development when vitamin B12-dependent processes are essential for normal neural development (González-Montaña et al., 2020). The range between essential and toxic concentrations is narrow. Thus, deficiency can occur at intakes below 0.1 μg/kg/day, while toxicity is observed at chronic intakes exceeding 10 μg/kg/day, though these thresholds can vary (ATSDR, 2024).

Metal-on-metal joint replacements have emerged as a significant source of cobalt exposure, with released metal debris causing systemic toxicity that can include neurological impairment, cardiomyopathy, and hypothyroidism. This has raised concerns about cobalt exposure during pregnancy in women with such implants (Fritzsche et al., 2012; Oppermann et al., 2015). Cobalt crosses the placenta, leading to fetal exposure.

3.2.3. Manganese

Manganese developmental toxicity has received increased attention due to recognition of its neurotoxic potential despite its essential role in cellular metabolism (Gospe Jr, 2025; Yokel et al., 2006). Exposure sources include inhalation of airborne particles in certain occupations (welding, mining) and contaminated drinking water. Manganese is required for various enzyme systems, including those involved in antioxidant defense, but excess exposure can produce neurological dysfunction like Parkinson's disease (Evans and Masullo, 2025). Manganese homeostasis is critical during development, with both deficiency and excess producing adverse effects (Bjørklund et al., 2017). The developing brain appears to be particularly vulnerable to manganese toxicity, with exposure during critical developmental windows producing long-term neurological consequences (Budinger et al., 2021). The metal accumulates preferentially in brain regions rich in dopaminergic neurons, potentially explaining its selective neurotoxicity (Nyarko-Danquah et al., 2020). It has been shown an early-life vulnerability to Mn neurotoxicity, particularly affecting the frontal cortex. Understanding environmental Mn sources, mechanisms of developmental toxicity, and effective biomarkers is crucial for prevention of neurodevelopmental disorders (Lucchini et al., 2017). Manganese readily crosses the placenta, and fetal levels are regulated by placental transporters.

3.2.4. Selenium

Selenium is an essential element for antioxidant enzyme function, particularly glutathione peroxidase. However, excess selenium exposure can produce significant developmental toxicity including neural tube defects and growth retardation (Barchielli et al., 2022). The margin between essential and toxic intake is narrow; deficiency occurs below 40 μg/day in adults, while toxicity can occur above 400 μg/day, with developmental effects observed at lower excess levels (Rayman, 2012). It has been reported that selenium status influences the toxicity of other metals, particularly mercury and cadmium (Werder et al., 2020). Selenium can provide protection against mercury toxicity through direct binding or by serving as a cofactor for antioxidant enzymes that scavenge reactive oxygen species. This protective effect has important implications for populations with mixed metal exposures (Werder et al., 2020). Geographic variations in selenium exposure continue to be a concern, with some regions having naturally high selenium levels in soil and water while others are selenium-deficient. Both extremes can produce adverse developmental effects, highlighting the narrow range between essential function and toxicity for this element (ATSDR, 2003). Selenium crosses the placenta, and fetal levels are closely related to maternal status.

3.2.5. Zinc

Zinc homeostasis is of critical importance during embryonic and fetal development (Willekens and Runnels, 2022). Zinc is essential for numerous cellular processes including DNA synthesis, protein synthesis, and cell division, making adequate zinc status crucial during periods of rapid growth and development (Padoan et al., 2024). Both zinc deficiency and excess can produce developmental abnormalities (Johnson et al., 2011). Zinc deficiency during pregnancy has been associated with neural tube defects, growth retardation, and immune system dysfunction in offspring (Wang et al., 2015). Conversely, excess zinc exposure can interfere with copper and iron absorption, leading to secondary deficiency effects that can compromise development (Stiles et al., 2024). The optimal intake range is narrow; severe deficiency occurs below 5 mg/day, while toxicity can occur with chronic intakes above 40 mg/day, though these thresholds vary by individual and life stage (Roohani et al., 2013).

The interactions between zinc and other metals have received considerable attention in recent research. Zinc competes with cadmium, lead, and other toxic metals for absorption and cellular uptake, providing some protective effects against metal toxicity. However, chronic exposure to toxic metals can deplete zinc stores, compromising this protective mechanism and potentially exacerbating metal toxicity (Hudson et al., 2025b). Zinc is actively transported across the placenta to support fetal growth.

3.3. Other elements with biological interest

3.3.1. Nickel

Nickel exposure can occur through multiple routes including inhalation of airborne particles, skin contact with nickel-containing products, and ingestion of contaminated food and water. Major sources include stainless steel production, nickel plating, and certain batteries. It has been reported that nickel exposure during development can affect multiple organ systems (Chen et al., 2018; Zhang et al., 2019). Nickel is associated with neurodevelopmental disorders and its effects on the epigenome, including alterations in DNA methylation and histone modifications, are well defined (Jose et al., 2019). Nickel interferes with cellular metal homeostasis and can substitute for essential metals in enzyme systems, leading to dysfunction of critical developmental processes. This metal also generates reactive oxygen species, contributing to oxidative stress and cellular damage during sensitive developmental periods (Das et al., 2018).

Reproductive effects of nickel have been documented in both male and female animals (Kong et al., 2014; Rizvi et al., 2020). Nickel exposure affects hormone production, gamete development, and reproductive organ function. In females, nickel can disrupt ovarian function and interfere with normal estrous cycles (Ganz et al., 2024). In males, nickel exposure affects sperm production and quality, potentially compromising fertility (Vinnikov and Syurin, 2024). Nickel crosses the placenta and has been detected in fetal tissues.

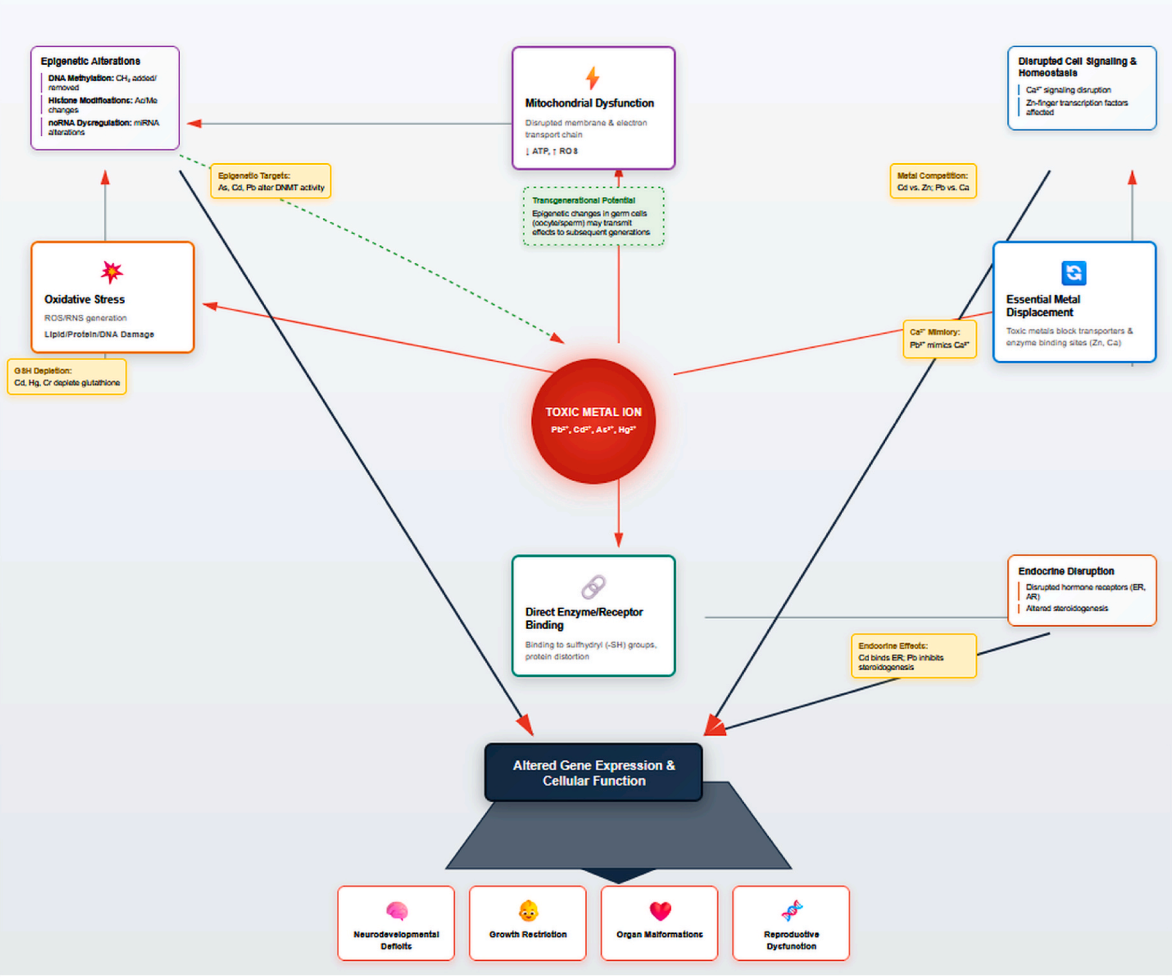


Fig. 1. Integrated schematic of key molecular mechanisms in metal-induced developmental toxicity.

3.3.2. Vanadium

Vanadium exposure during development can produce embryotoxic and teratogenic effects (Altamirano-Lozano et al., 2014; Álvarez-Barrera et al., 2022; Domingo, 1996). Exposure sources include fossil fuel combustion, steel production, and some dietary supplements. The metal interferes with cellular energy metabolism and induces oxidative stress in developing tissues. Vanadium also affects calcium homeostasis and can disrupt normal cellular signaling pathways that are critical for proper development (Aureliano et al., 2023). Vanadium compounds alter epigenetic markers, including histone modifications, which may contribute to their developmental toxicity (Altamirano-Lozano et al., 1996). The chemical form of vanadium significantly influences its toxicity, with vanadate compounds generally being more toxic than vanadyl compounds. This difference in toxicity is related to the ability of different vanadium species to cross cellular membranes and interact with intracellular targets. Vanadium crosses the placenta, though the extent of transfer depends on the chemical species.

3.4. Metals of pharmacological interest

3.4.1. Aluminum

Aluminum developmental toxicity research has undergone significant evolution since the previous review (Domingo, 1994), moving from viewing this element as relatively benign to recognizing its potential for significant developmental effects (Krewski et al., 2007; Willhite et al., 2014). Aluminum exposure has increased substantially due to widespread use in food packaging, antiperspirants, medications, and water treatment, making it ubiquitous in the human environment. It has been demonstrated that aluminum readily crosses the placental barrier and can accumulate in fetal tissues (Golub and Domingo, 1996). The developing nervous system appears to be particularly vulnerable to aluminum toxicity, with exposure during critical developmental windows producing long-term neurological consequences (Jackson and Rout, 2025).

Reproductive toxicity of aluminum has been also reported, with aluminum exposure affecting both male and female reproductive systems, with impacts on hormone production, gamete development, and reproductive organ function (Guangji et al., 2025; Yokel, 2020). In males, aluminum exposure reduces testosterone levels, affects sperm production and quality, and can cause testicular damage. In females, aluminum disrupts ovarian function and can interfere with normal reproductive cycles. The mechanism of aluminum toxicity involves generation of oxidative stress, interference with essential metal homeostasis, and direct effects on cellular membranes and organelles (Yu et al., 2025). Studies in rodents show these effects. Aluminum crosses the placenta, leading to fetal exposure.

3.4.2. Lithium

Lithium readily crosses the placental barrier and can affect fetal development, raising important questions about the balance between maternal mental health treatment and potential fetal risks (Poels et al., 2018, 2021). Lithium exposure during pregnancy can increase the risk of cardiovascular malformations, particularly Ebstein's anomaly and other cardiac defects (Patorno et al., 2017). The benefits of treating severe maternal psychiatric illness with lithium should be carefully weighed against the potential risks to the fetus. Nevertheless, careful monitoring and consideration of alternative treatments are recommended when possible (Gentile, 2012). The effects of maternal lithium exposure on placental growth and fetal development have been reported in human and animal studies (Fornaro et al., 2020).

The mechanism of lithium developmental toxicity involves interference with cellular signaling pathways, particularly those involving inositol phosphate metabolism and glycogen synthase kinase-3 (GSK-3) (Bortolozzi et al., 2024). These pathways are critical for normal cellular development and differentiation, and their disruption can lead to developmental abnormalities. Lithium also affects neural crest cell migration and differentiation, which may explain its propensity to cause cardiac and other malformations (Patorno et al., 2017). Lithium freely crosses the placenta, resulting in fetal serum concentrations similar to maternal levels.

4. Molecular mechanisms of metal-induced developmental toxicity

While the specific manifestations of toxicity vary by metal, chemical species, and developmental stage, most metal-induced developmental abnormalities arise from a core set of interconnected molecular pathways. A schematic representation of the interconnected molecular mechanisms of metal-induced developmental toxicity is presented in Fig. 1. This figure illustrates how oxidative stress, epigenetic modifications, endocrine disruption, mitochondrial dysfunction, and interference with essential metal homeostasis form an integrated network of toxic effects, with multiple feedback loops amplifying toxicity. Understanding these mechanistic interconnections is essential for interpreting the complex, multi-system effects observed in metal developmental toxicity.

4.1. Oxidative stress and antioxidant depletion

Most toxic metals generate reactive oxygen species (ROS) either directly through redox cycling or indirectly through depletion of antioxidant defense systems. During development, when antioxidant systems are immature and cellular division rates are high, oxidative stress can cause particularly severe damage. Heavy metals interfere with antioxidant defense mechanisms primarily through their interaction with intracellular glutathione and sulfhydryl groups of antioxidant enzymes including superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase (Cheng et al., 2025). The binding of metals to these critical enzymes disrupts the cellular redox balance and leads to accumulation of ROS that can damage DNA, proteins, and cellular membranes (Sun et al., 2022).

The developing embryo and fetus are particularly vulnerable to oxidative stress because their antioxidant defense systems are not fully mature, while their high metabolic rates and rapid cell division create conditions that favor oxidative damage (Divvela et al., 2025). Additionally, many developmental processes require precise regulation of redox-sensitive signaling pathways, and disruption of these pathways by metal-induced oxidative stress can lead to developmental abnormalities (Divvela et al., 2025). Metal-induced mitochondrial dysfunction represents a critical aspect of oxidative stress-mediated developmental toxicity. Heavy metals induce mitochondrial dysfunction through multiple mechanisms including disruption of the electron transport chain, mitochondrial membrane potential dissipation, alteration of mitochondrial permeability transition, and impairment of mitochondrial biogenesis (Cheng et al., 2021; Sun et al., 2022). These mitochondrial effects lead to increased reactive oxygen species production, decreased ATP synthesis, and activation of apoptotic pathways, all of which can compromise normal developmental processes (Sun et al., 2022).

4.2. Epigenetic modifications

Epigenetic mechanisms have emerged as critical mediators of metal developmental toxicity (Morgan et al., 2024). Metals can alter DNA methylation patterns, histone modifications, and microRNA expression profiles, leading to changes in gene expression that can persist throughout life and even be transmitted to subsequent generations. DNA methylation is particularly vulnerable to metal exposure because many metals interfere with the activity of DNA methyltransferases, the enzymes responsible for establishing and maintaining methylation patterns. Arsenic, cadmium, lead, and mercury have all been shown to alter global DNA methylation patterns as well as site-specific methylation of genes critical for development (Martinez-Zamudio and Ha, 2011). These changes can affect the expression of genes involved in cell cycle

Table 2
Key molecular mechanisms of metal-induced developmental toxicity.

Mechanism	Description	Affected Pathways/ Targets	Representative Metals
Oxidative Stress and ROS Generation	Direct generation of reactive oxygen species (ROS) or depletion of antioxidant defenses, particularly damaging during high cell division rates	• Glutathione depletion • SOD, catalase inhibition • Mitochondrial dysfunction • Lipid peroxidation • DNA/protein damage	As, Cd, Pb, Hg, Cr, Ni, V, U
Epigenetic Modifications	Alterations in DNA methylation, histone modifications, and microRNA expression affecting gene regulation; can persist transgenerationally	• DNA methyltransferases • Histone-modifying enzymes • Chromatin remodeling • miRNA dysregulation • Imprinted genes	As, Cd, Pb, Hg
Endocrine Disruption	Interference with hormone synthesis, transport, or receptor binding affecting reproductive and metabolic development	• Steroidogenic enzymes • Hormone receptors (ER, AR) • Thyroid function • Insulin signaling•HPG/ HPA axes	Cd, Pb, As, Hg, Mn
Essential Metal Homeostasis Disruption	Competition for absorption/ transport with essential metals leading to functional deficiencies	• Metal transporters (DMT1, ZIP) • Calcium signaling • Zinc-dependent enzymes • Iron metabolism • Copper homeostasis	Cd (Zn, Cu, Fe) Pb (Ca) Hg (Se)
Mitochondrial Dysfunction	Impairment of energy production, increased ROS, and activation of apoptotic pathways	• Electron transport chain • ATP synthesis • Mitochondrial membrane potential • Cytochrome *c* release • Mitochondrial biogenesis	As, Pb, Hg, U, Al
Calcium Homeostasis Disruption	Interference with calcium-dependent signaling critical for neural development and cellular processes	• Calcium channels • Calcium-binding proteins • Neurotransmitter release • Cell cycle regulation • Apoptosis pathways	Pb, Hg, Cd, V

regulation, apoptosis, DNA repair, and development. Histone modifications represent another important epigenetic mechanism affected by metal exposure (Chervona and Costa, 2012). Metals can interfere with histone-modifying enzymes, leading to changes in chromatin structure and gene accessibility. These changes can affect the timing and pattern of gene expression during development, potentially leading to developmental abnormalities (Kim et al., 2024). Studies have shown that the transgenerational effects of metal exposure appear to be mediated, at least in part, through epigenetic mechanisms (Nava-Rivera et al., 2021). The strength of transgenerational epigenetic evidence varies by metal, being strongest for arsenic and cadmium, with effects persisting to the F3 generation in some studies. Evidence for lead and mercury is more limited but growing, while data for other metals are sparse (Khan et al., 2019; Nava-Rivera et al., 2021; Pierron et al., 2022; Sen et al., 2015).

4.3. Endocrine disruption

It has been reported that many metals can interfere with hormone synthesis, transport, and action (Sun et al., 2022). The developing reproductive system is particularly vulnerable to endocrine disruption because it relies on precise hormonal signaling for proper differentiation and development. Metals can disrupt endocrine function through multiple mechanisms including interference with hormone synthesis enzymes, binding to hormone receptors, and disruption of hormone transport proteins (Jomova et al., 2025; Liu et al., 2023). For example, cadmium can substitute for zinc in estrogen receptors, altering receptor conformation and affecting DNA binding affinity, while lead can interfere with steroidogenic enzymes, affecting the production of sex hormones critical for reproductive development.

4.4. Interference with essential metal homeostasis

Toxic metals can interfere with the absorption, transport, and utilization of essential metals, leading to secondary deficiency effects that compound direct toxic actions (Jomova et al., 2025). Competition for absorption occurs at the level of metal transporters in the gastrointestinal tract. For example, cadmium competes with zinc, copper, and iron for absorption through shared transport mechanisms. Lead can interfere with calcium homeostasis by substituting for calcium in various cellular processes. These interactions can lead to essential metal deficiencies even when dietary intake of essential metals is adequate. The developing organism is particularly vulnerable to disruption of essential metal homeostasis because many essential metals are required as cofactors for enzymes involved in critical developmental processes (Kambe et al., 2008). Zinc is required for DNA polymerase and other enzymes involved in DNA replication and repair, while iron is essential for electron transport and cellular energy production. In turn, copper is required for collagen synthesis and neural development. Disruption of these essential functions can lead to severe developmental abnormalities. Table 2 summarizes the six principal molecular mechanisms through which metals induce developmental toxicity, highlighting the interconnected nature of these pathways and the metals most associated with each mechanism.

4.5. Complex mixtures and interaction effects

4.5.1. Multiple metal exposures

In recent years, one of the most significant developments in metal toxicology has been the recognition that real-world exposures typically involve multiple metals rather than single metal exposures (Xie et al., 2025a). These complex mixtures can produce additive, synergistic, or antagonistic effects that cannot be predicted from studies of individual metals alone. The underlying interaction mechanisms include additive or synergistic induction of oxidative stress (e.g., Pb + Cd), competitive inhibition at shared cellular transporters (e.g., DMT1 for Fe/Cd/Pb), and interactive disruption of epigenetic programming. For example, combined exposure to lead, cadmium, and arsenic shows synergistic effects on neurodevelopmental deficits in animal models, greater than the sum of individual effects (Xie et al., 2025a). The development of statistical methods for analyzing mixture effects has advanced significantly, with techniques such as Bayesian kernel machine regression being used to examine joint effects of multiple metals (Ou et al., 2025). These approaches have revealed that the health effects of metal mixtures often cannot be predicted from individual metal effects, highlighting the importance of considering real-world exposure scenarios in risk assessment. Consequently, the health risks from exposure to metal mixtures may not only be greater in magnitude but also different in nature from those predicted by the toxicity of individual components. Recent epidemiological studies using mixture analysis have demonstrated that metal mixtures are associated with adverse birth outcomes, such as reduced fetal growth, in a non-linear manner (Ou et al., 2025). Fig. 1

Table 3
Prevention and treatment strategies for metal-induced developmental toxicity.

Strategy Category	Intervention	Mechanism of Action	Target Metals/Limitations
Chelation Therapy	DMSA (meso-2,3-dimercapto-succinic acid)	• Oral bioavailability • Forms stable metal complexes • Promotes renal excretion • Lower toxicity than EDTA/BAL	Pb, Hg, As Limitation: Limited reversal of established neurobehavioral deficits
	DMPS (2,3-dimercaptopropane-1-sulfonate)	• IV or oral administration • High affinity for soft metals • Renal elimination	As, Hg Limitation: May deplete essential metals
	$CaNa_2EDTA$, BAL	• Classical chelators • Form metal chelates	Pb (EDTA), As/Hg (BAL) Limitation: Contraindicated in pregnancy; lack specificity
Antioxidant Supplementation	Vitamin E (α-tocopherol)	• Reduces lipid peroxidation • Preserves membrane integrity • Scavenges free radicals	General metal toxicity Safe adjunct therapy
	N-acetylcysteine (NAC)	• Replenishes glutathione • Direct antioxidant • Mild chelating effects	As, Pb Well-tolerated
	Selenium	• Forms Se-Hg complexes • Enhances antioxidant enzymes • Antagonizes Hg toxicity	Hg Must avoid excess
	Ascorbic acid (Vitamin C)	• Direct antioxidant • Synergistic with other antioxidants • May enhance chelator efficacy	General support High doses may be pro-oxidant
Nutritional Prevention	Iron, zinc, calcium supplementation	• Competitive inhibition of metal absorption • Supports antioxidant systems • Maintains physiological functions	Pb (Fe, Ca), Cd (Zn, Fe) Primary prevention strategy
	Folate	• Supports methylation reactions • Protects against epigenetic changes	As Critical during pregnancy
	Dietary fiber, Probiotics	• Reduces GI metal absorption • Modulates gut microbiome	General prevention Safe, low-cost intervention
Primary Prevention	Environmental control measures	• Reduce exposure sources • Screening of at-risk populations • Regulatory limits enforcement	All metals Most effective long-term strategy

Abbreviations: DMSA, meso-2,3-dimercaptosuccinic acid; DMPS, 2,3-dimercaptopropane-1-sulfonate; EDTA, ethylenediaminetetraacetic acid; BAL, dimercaprol; NAC, N-acetylcysteine; ROS, reactive oxygen species; SOD, superoxide dismutase; ER, estrogen receptor; AR, androgen receptor; HPG, hypothalamic-pituitary-gonadal; HPA, hypothalamic-pituitary-adrenal; DMT1, divalent metal transporter 1; ZIP, Zrt/Irt-like protein; GI, gastrointestinal.

schematically integrates these interconnected pathways, illustrating how metals activate molecular mechanisms that result in developmental toxicity.

5. Prevention and treatment of metal-induced developmental toxicity

Metals cross the placental barrier and interfere with fetal growth and differentiation, leading to neurodevelopmental deficits, intrauterine growth restriction, and congenital malformations. As above discussed, the underlying mechanisms include oxidative stress, mitochondrial dysfunction, disruption of essential metal homeostasis, and epigenetic alterations. In relation to this, therapeutic approaches are aimed at reducing metal burden and oxidative injury while minimizing harm to the developing organism. Current strategies combine chelation therapy, antioxidant supplementation, and nutritional optimization, with a strong emphasis on prevention.

5.1. Chelation therapy

Chelation remains the principal treatment for acute severe metal poisoning. However, during development its use mandates caution because chelators may deplete essential micronutrients or redistribute toxicants to critical tissues (Domingo, 1995, 2025). Classical chelators such as $CaNa_2EDTA$ and BAL (dimercaprol) are largely contraindicated during pregnancy due to their lack of specificity and potential to disturb micronutrient balance (Domingo, 1998). In recent years, DMSA (meso-2,3-dimercaptosuccinic acid) has been the preferred chelator for pediatric lead poisoning. It offers oral bioavailability, lower toxicity, and good clinical efficacy compared with EDTA and BAL (Blanusa et al., 2005). Although animal studies suggest DMSA reduces developmental metal burden, its ability to reverse established neurobehavioral deficits remains limited. In turn, DMPS (2,3-dimercaptopropane-1-sulfonate) is particularly effective against arsenic and mercury and can be administered orally or intravenously (Aposhian and Aposhian, 2006), while in laboratory animals, Tiopronin and Tiron also showed efficacy against certain metals such as arsenic, mercury, and vanadium (Domingo, 1995, 2025). Because chelation can also reduce the levels of essential elements, combination therapies have been proposed, such as DMSA co-administered with zinc or calcium, to preserve physiological metal balance (Flora and Pachauri, 2010).

5.2. Antioxidants and nutraceuticals

Oxidative stress plays a central role in metal-induced developmental toxicity. Thus, antioxidant therapy represents a critical adjunct to chelation. Vitamin E (α-tocopherol) reduces lipid peroxidation and preserves membrane integrity in developing tissues exposed to metals (Gurer and Ercal, 2000), while ascorbic acid acts synergistically with other antioxidants and may potentiate chelator efficacy (Flora et al., 2008). In turn, N-acetylcysteine replenishes glutathione and provides both antioxidant and mild chelating effects, protecting against arsenic and lead toxicity (Reddy et al., 2011), while selenium interacts antagonistically with mercury, forming biologically inert Se-Hg complexes and enhancing antioxidant enzyme activity (Ralston et al., 2007). On the other hand, curcumin and α-lipoic acid have demonstrated both antioxidant and chelating potential in animal models (Abdelhamid et al., 2020).

5.3. Nutritional and preventive strategies

Adequate intake of essential metals such as iron, zinc, and calcium remains a basic preventive measure. Iron deficiency enhances gastrointestinal absorption of lead (Wright et al., 2003), while calcium and zinc supplementation competitively inhibit absorption of toxic metals and mitigate oxidative injury. Dietary interventions, including probiotics and fiber, may further limit gastrointestinal metal absorption (Zhai et al., 2015). While these are promising low-cost preventive strategies supported by experimental models, their efficacy in preventing developmental toxicity in human populations requires further clinical investigation. Thus, preventive strategies can be organized hierarchically as follows: 1) primary prevention: control of metal exposure, 2) secondary prevention: nutritional optimization and screening of at-risk populations, and 3) tertiary prevention: therapeutic chelation and antioxidant support following metal exposure.

5.4. Safety considerations and future directions

Chelation therapy during pregnancy and early development should be reserved for severe, life-threatening cases under expert supervision. The risks stem from the chelators' ability to disturb essential micronutrient balance and induce transient metal redistribution. Antioxidant supplementation, while safer, requires careful dosing to avoid reductive stress. Future directions include the design of target-specific chelators with improved selectivity and biocompatibility, and the integration of nutraceutical-based adjuvants to strengthen antioxidant defenses and modulate epigenetic resilience. The interventions summarized in Table 3 represent the current state of therapeutic options, although future research may identify more targeted and effective approaches with improved safety profiles for use during critical developmental periods. A particularly promising area is the development of chelators or delivery systems that are selectively activated in metal-burdened tissues, thereby minimizing systemic disruption of essential metal homeostasis.

6. Emerging metals of concern

6.1. Technology-critical elements

The rapid advancement of technology has introduced new sources of metal exposure that were not significant concerns until recent decades (González and Domingo, 2025). Rare earth elements, lithium, cobalt, and other technology-critical elements are now present in numerous consumer products including smartphones, batteries, and electronic devices. The lifecycle of these products, from mining and manufacturing to disposal and recycling, creates new exposure pathways that may affect developmental health. Indium, gallium, and other semiconductor materials have also raised concerns due to their increasing use and limited understanding of their developmental toxicity.

6.2. Nanoparticulate metal exposures

The emergence of nanotechnology has created new forms of metal exposure that have unique toxicological properties not captured in traditional metal toxicity studies (Miazek et al., 2015; Pikula et al., 2023). Metal nanoparticles have different bioavailability, distribution, and toxicity profiles compared to conventional metal compounds, requiring new approaches to risk assessment and toxicity testing. They can cross biological barriers more readily than larger particles, potentially leading to increased bioavailability and tissue accumulation (Wang and Wang, 2020). The high surface area to volume ratio of nanoparticles may also increase their reactivity and potential for generating oxidative stress. These properties may make nanoparticulate metals more toxic than conventional forms, particularly during development when barrier systems are less mature (Engin, 2021; Zhang et al., 2022).

The environmental fate and transport of metal nanoparticles differ from conventional metals, with potential for long-range transport and accumulation in environmental compartments where they were not previously found (Bathi et al., 2022; Teng et al., 2019). The implications of these new exposure patterns for developmental health are still being investigated, but early studies suggest that caution is warranted until more definitive safety data are available.

7. Vulnerable populations and windows of susceptibility

Recognition of enhanced vulnerability during development has led to increased emphasis on protecting sensitive populations and life stages (Ortega-Romero et al., 2024). Pregnant women, infants, and children are now recognized as requiring special protection from metal exposures due to their increased vulnerability and the potential for long-term consequences of early-life exposures (Sun et al., 2025; Xie et al., 2025b). Critical windows of vulnerability have been identified for different aspects of development, with the period of organogenesis being particularly sensitive to teratogenic effects and later developmental periods being important for functional development of organ systems (Heyer and Meredith, 2017; Nangle et al., 2025). The timing of exposure relative to these critical windows can determine both the type and severity of developmental effects. It is important to note that developmental toxicity endpoints and sensitivity can vary across species commonly used in toxicological studies (e.g., rat, mouse, rabbit, primate). Differences in placental structure, metabolism, gestation length, and developmental milestones affect extrapolation to humans. For instance, the timing of brain development relative to birth differs, which is crucial for neurotoxicity assessment. These species-specific factors must be considered for robust human risk assessment (Heyer and Meredith, 2017). Individual susceptibility factors, including genetic polymorphisms affecting metal metabolism and detoxification, nutritional status, and concurrent exposures, are increasingly being incorporated into risk assessment approaches. These factors can significantly modify individual risk and help explain the variability in response to metal exposures observed in human populations.

8. Environmental justice and global health

The disproportionate impact of metal exposures on vulnerable populations, including low-income communities and developing countries, represents a significant environmental justice concern (Geron et al., 2022; Gochfeld and Burger, 2011). Understanding and addressing these disparities will require interdisciplinary approaches that combine toxicology, epidemiology, social science, and policy analysis.

On the other hand, climate change may affect metal exposures through changes in environmental fate and transport, extreme weather events that mobilize contaminated sediments, and changes in dietary patterns that affect exposure pathways (Bolan et al., 2024; Jarsjö et al., 2020). Understanding these complex interactions will be important for predicting future exposure scenarios and developing adaptive management strategies.

9. Conclusions

The past three decades have witnessed remarkable advances in the understanding of metal-induced developmental toxicity, driven by technological innovations, mechanistic insights, and growing recognition of the public health importance of this issue. The evidence clearly shows that metals continue to pose significant risks to developing organisms, with effects that can persist throughout life and even be transmitted to subsequent generations. Key findings since our previous review (Domingo, 1994) include recognition of the critical role of oxidative stress and epigenetic modifications in mediating metal developmental toxicity, the importance of metal mixtures and interactions in determining toxic outcomes, and the existence of effects at

Table 4
Comparative framework of developmental toxicity for selected metals.

Element	Relative Developmental Risk at Low Environmental Exposure	Key Mechanisms of Developmental Toxicity	Transgenerational Evidence Strength
Arsenic	High	Oxidative stress; epigenetic disruption (DNA hypo/hypermethylation, histone modifications); endocrine disruption; interference with SAM metabolism.	Strong. Well-documented in animal models (rodents), with effects persisting to F3 generation via epigenetic inheritance.
Cadmium	High	Oxidative stress; epigenetic alterations; endocrine disruption (estrogen mimicry); disruption of Zn/Ca homeostasis; placental toxicity.	Strong. Evidence for transgenerational inheritance of reproductive toxicity and disease susceptibility in animal models, linked to germline epigenetic changes.
Lead	Very High	Oxidative stress; Ca^{2+} mimicry disrupting signaling; epigenetic modifications (DNA methylation, histone modifications, ncRNAs); direct neurotoxicity.	Moderate/Emerging. Animal studies show behavioral and metabolic effects in F1–F2; evidence for epigenetic transmission is growing but less extensive than for As/Cd.
Mercury	High (Methyl-Hg)	Oxidative stress; cytoskeletal disruption in neurons; Ca^{2+} homeostasis disruption; binding to selenoproteins.	Limited/Emerging. Primarily direct developmental neurotoxicity. Some animal studies suggest epigenetic changes in offspring, but robust multigenerational evidence is sparse.
Uranium	Low–Moderate	Chemotoxicity (renal), oxidative stress; genotoxicity. Developmental toxicity typically at higher exposure levels.	Very Limited. Mainly studied for direct toxicity. No substantial evidence for transgenerational epigenetic effects reported to date.
Chromium (Cr(VI))	Moderate–High (occupational)	Genotoxicity (DNA crosslinks, strand breaks); oxidative stress.	Limited. Research focuses on carcinogenesis and direct genotoxicity. Transgenerational developmental studies are lacking.
Manganese	Moderate (excess)	Oxidative stress; neurotoxicity via dopaminergic system disruption; potential epigenetic effects.	Limited. Essential element; toxicity from excess. Evidence for transgenerational effects is minimal and not a primary focus.
Nickel	Moderate	Oxidative stress; epigenetic alterations (DNA/histone methylation); endocrine disruption; allergic sensitization.	Limited. Epigenetic effects documented in somatic cells. Transgenerational developmental studies are needed.
Aluminum	Low–Moderate	Oxidative stress; neurotoxicity; interference with Fe/Ca metabolism;	Limited. Ubiquitous exposure. Some evidence for epigenetic effects in animal models, but
Lithium	High (therapeutic doses)	epigenetic alterations in models. Interference with inositol/GSK-3 signaling; disruption of neural crest cell migration (cardiac defects).	transgenerational data are scarce. Not Applicable. Toxicity is linked to pharmacological use. Teratogenic risk is direct (Ebstein's anomaly), not typically studied in transgenerational context.

Abbreviations: SAM, S-adenosylmethionine; ncRNAs, non-coding RNAs; GSK-3, glycogen synthase kinase-3. Notes on Risk: "Low environmental exposure" refers to levels relevant to general population exposure via food, water, and air, not acute poisoning, while "Relative Risk" integrates potency, exposure prevalence, and developmental sensitivity.

exposure levels previously considered safe. The emergence of new sources of metal exposure from technology and industry requires continued vigilance and research to protect public health.

Prevention remains the most effective approach to reducing metal developmental toxicity, requiring coordinated efforts to reduce environmental contamination, identify and protect vulnerable populations, and develop effective intervention strategies. Chelation therapy continues to play an important role in treating metal poisoning, with modern agents offering improved safety and efficacy compared to earlier treatments.

Future research needs continued mechanistic studies to understand the complex pathways involved in metal developmental toxicity, development of better methods for assessing mixture effects and vulnerable populations, and translation of research findings into effective prevention and treatment strategies. Explicit knowledge gaps that should be prioritized include: 1) systematic comparative studies of low-dose, chronic multi-metal exposures; 2) elucidating the full scope and mechanisms of transgenerational inheritance for a wider range of metals; 3) developing biomarkers for early detection of mixture effects; and 4) improving in vitro and in silico models that account for human-specific pharmacokinetics and susceptibility to reduce reliance on species extrapolation. The goal remains the protection of developing organisms from the harmful effects of metal exposures while recognizing the essential roles that some metals play in normal development and health. As knowledge of metal developmental toxicity advances, this field continues to hold major relevance for public health, environmental regulation, and clinical practice. Findings from earlier studies provide valuable guidance for addressing present and emerging issues in this important area of toxicology. To facilitate comparison across metals, Table 4 provides a summary of relative developmental risk, key mechanisms, and transgenerational evidence strength for the major metals discussed.

Funding

No specific funds were received to prepare this work.

Declaration of competing interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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