Review Article

Chelation Therapy for Rare Earth Element Toxicity: Current Evidence, Challenges, and Future Directions

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The widespread and growing use of rare earth elements (REE) in modern technologies has raised concerns regarding human exposure and associated toxicological risks through occupational, environmental, and medical pathways, including mining, electronic waste, and gadolinium-based contrast agents in MRI procedures. This review evaluates REE toxicological profiles, focusing on their unique mechanisms, organ-specific effects, and therapeutic challenges. REE toxicity is primarily mediated through oxidative stress, mitochondrial dysfunction, and metal ion substitution, leading to multi-organ effects, impacting respiratory, cardiovascular, nervous, hepatic, and reproductive systems. Studies in human clinical data, animal models (e.g., rats, mice, zebrafish), and in vitro systems show adverse effects, although dose-specific data remain limited, with examples including gadolinium retention post-MRI and cerium exposure in occupational settings. Conventional chelators such as EDTA, DMSA, and DMPS demonstrate limited efficacy against most REE, with DTPA showing moderate potential particularly for gadolinium and cerium. The anticoagulant properties of lanthanides, arising from their antagonistic effects on calcium-dependent coagulation cascades, represent an additional toxicological concern that has been recognized for decades. Evidence from occupational studies, animal experiments, and clinical reports highlights the need for early exposure recognition, prevention, and individualized treatment strategies, including supportive care and REE-specific chelation when feasible. The absence of targeted regulatory frameworks and comprehensive clinical data hinders effective risk management. Chelator-assisted detoxification approaches show promise for addressing REE radionuclides from nuclear fallout, particularly for isotopes such as ^{141}Ce, ^{144}Ce/^{144}Pr, and ^{147}Pm that become prominent in late-stage fallout scenarios. Future research priorities include developing novel REE-specific chelators, establishing evidence-based therapeutic protocols, and harmonizing international regulations. This review provides healthcare professionals,

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toxicologists, and researchers with an updated synthesis of current knowledge on REE toxicity and therapeutic strategies, emphasizing the urgent need for clinical innovation and regulatory reform to address this emerging public health concern.

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1. Introduction

1.1. Background and Global Significance

Rare earth elements (REE) comprise 17 metallic elements, the 15 lanthanides (Ce, Dy, Er, Eu, Gd, Ho, La, Lu, Nd, Pr, Pm, Sm, Tb, Tm and Yb), plus scandium (Sc) and yttrium (Y), both included because of their co-occurrence and similar chemical properties with the lanthanides [1][2]. Due to their unique physicochemical properties, REE have emerged as essential components in modern technology [3][4][5][6][7]. While REE occur in substantial quantities within Earth's crust [1], their distribution patterns make commercial extraction economically challenging due to low concentration deposits, being difficult to extract and to purify given their similar chemical properties [8][9].

Nowadays, the unique magnetic, catalytic, optical, and electronic properties of REE have made them essential in numerous high-technology applications [1][10][11][12], including permanent magnets used in wind turbines and electric vehicles, catalysts for petroleum refining and automotive emission control, phosphors for display screens and LED lighting, electronic devices ranging from smartphones to advanced defense systems, renewable energy technologies including solar panels and battery systems, as well as medical imaging agents particularly gadolinium-based contrast agents used in magnetic resonance imaging procedures [11] [13][14][15][16].

Since the late 1990s, China has maintained a leading position in the global production and supply of REE, accounting for approximately 85-95% of worldwide output [11][17]. The concentration of mining and processing activities in specific geographical regions can lead to localized environmental contamination and population exposure to REE through multiple pathways including air emissions, water contamination, and soil deposition [18][19][20][21]. The increasing demand for REE has led to their widespread distribution in the environment through mining operations and industrial discharge from manufacturing facilities that process REE-containing materials, electronic waste disposal and

recycling [22][23][24]. This is particularly evident in developing countries, where informal recycling practices are common, agricultural applications where some REE are used as fertilizer additives and growth promoters, and medical waste disposal including gadolinium-containing materials and patient excreta following MRI procedures [24][25][26].

1.2. Human Exposure Pathways and Health Concerns

Human exposure to REE occurs through multiple pathways, each presenting distinct toxicological challenges [27]. Inhalation exposure is the primary route of occupational exposure in mining, processing, and manufacturing industries, where airborne REE particles can be deposited in the respiratory tract and persist for extended periods due to their biopersistent nature [28]. For the non-occupationally exposed general population, ingestion through contaminated food and water sources constitutes the main route of exposure [29]. Agricultural products grown in REE-contaminated soil accumulate these elements, while drinking water contamination occurring near mining sites, or through improper waste disposal practices, are also sources of human exposure [29][30][31][32]. In turn, dermal contact occurs primarily in occupational settings involving REE mining, processing, and manufacturing, where prolonged contact with REE-containing materials can lead to local skin effects and systemic absorption despite generally limited dermal penetration [33][34].

Iatrogenic exposure through medical applications, particularly gadolinium-based contrast agents used in MRI procedures, represents a significant and controlled source of REE exposure, which has gained increasing attention from regulatory authorities [35]. Extensive extraction and industrial application of REE over prolonged periods has generated substantial environmental contamination, presenting significant public health challenges on a worldwide scale, raising concerns regarding human health safety [36][37].Although REE have not been traditionally considered major pollutants, their increased application in new technologies requires understanding their safe exposure levels for humans and developing appropriate therapeutic interventions for cases of overexposure [28][31][34].

1.3. Regulatory Landscape and Knowledge Gaps

Despite the current widespread use and environmental presence of REE, regulatory frameworks for these elements remain underdeveloped, with no specific regulatory restrictions for REE, not even drinking water standards for human health protection [18]. However, regulatory restrictions have been implemented in China, where the critical average daily intake has been established at 70 μg/kg·day for the

sum of REE, equivalent to 4.2 mg per person. Additionally, comprehensive screening programs for REE in soils and sediments have been conducted throughout China and Japan. It means an important regulatory gap that has become increasingly concerning as evidence of REE toxicity continues to accumulate from both animal studies and human exposure scenarios [38][39]. The lack of comprehensive safety data and regulatory guidelines has led to growing concern among public health professionals and environmental scientists regarding the potential long-term health effects of chronic low-level exposure to REE, which remain poorly understood. Thus, current exposure assessment methodologies might be inadequate for evaluating the risks associated with REE exposure considering their chemical properties and biological behavior [28][40].

Scientific evidence indicates that REE can trigger cellular stress responses, compromise mitochondrial integrity, and adversely impact multiple organ systems [27][28][41]. Potential adverse effects affect pulmonary, cardiac, gastrointestinal, reproductive, and neurological functions, with toxicity patterns influenced by compound structure, exposure pathway, dosage levels, and contact duration [28][30][42]. It makes toxicity assessment highly challenging and necessitating the development of specific therapeutic approaches that differ from traditional heavy metal chelation strategies. The primary toxicological mechanism underlying REE-associated health effects involves cellular oxidative stress modulation [43], like redox pathways documented in other metallic elements, but the unique coordination chemistry and biological distribution of REE create specific challenges for developing effective antidote treatments [44] [45].

1.4. Objectives

The present review is aimed at addressing the critical knowledge gaps in understanding REE toxicity and therapy of the toxic effects of REE in mammalian systems with particular emphasis on mechanisms of toxicity and organ-specific effects. Current evidence for REE toxicity in humans including occupational, environmental, and medical exposure scenarios has been reviewed. The role of chelation therapy in intoxication treatment and its applicability to REE poisoning has been also reviewed. For this, therapeutic approaches for REE intoxication, including their limitations and potential for improvement have been evaluated, while research priorities and future directions for developing effective treatments for REE have been identified.

Thus, the primary objective of the current review has been to provide healthcare professionals, toxicologists, and researchers with a comprehensive understanding of current knowledge regarding REE

toxicity and available therapeutic options. The unique challenges posed by REE, which differentiate them from traditional heavy metals, are highlighted, along with the need to establish foundational knowledge for future research and the development of clinical practice guidelines for the management of REE intoxication. Secondary objectives include synthesizing available evidence on the effectiveness of different chelating agents for various REE, identifying specific knowledge gaps that require urgent research attention, providing practical guidance for clinicians who may encounter cases of REE poisoning, and establishing recommendations for the development of more effective therapeutic approaches considering the specific properties of REE.

2. Methods

2.1. Literature Search Strategy

To identify relevant scientific studies, an exhaustive literature search was conducted using PubMed, Web of Science, Scopus, and Google Scholar, from inception through July 31, 2025. A combination of Medical Subject Headings (MeSH) terms and keywords related to REE, chelation therapy, metal poisoning, and toxicity was used. Search terms included "rare earth elements," "REE", "lanthanides," "gadolinium", combined with "toxicity," "poisoning," "chelating agents," "antidotes," and "treatment", with searches conducted in English language.

2.2. Study Selection Criteria

Studies included involved REE toxicity in mammalian systems, human exposure studies, therapeutic interventions for metal poisoning with potential applicability to REE, chelation therapy mechanisms and effectiveness, and clinical case reports of REE poisoning or therapeutic interventions. In turn, studies were excluded if they focused solely on environmental fate without health implications, involved non-mammalian species without relevance to human health, or were purely methodological papers without toxicological content. The initial screening was based on titles and abstracts, followed by full-text review of potentially relevant articles. Priority was given to peer-reviewed publications, with gray literature included only when it provided essential information not available in peer-reviewed sources.

3. Results

3.1. Toxic Effects of REE in Mammals

3.1.1. General Toxicological Principles and Mechanisms

The toxicity of REE in mammalian systems is characterized by several key features that distinguish them from traditional heavy metals. REE not readily crossing biological membranes in their ionic form due to their large size and high charge density. However, once REE reach biological systems, they can cause significant toxicity through multiple mechanisms, mainly oxidative stress induction, mitochondrial dysfunction, protein and enzyme interference, and cellular signaling pathway disruption [31][34][46][47]. It has been demonstrated that REE can initiate cellular stress cascades, impair mitochondrial performance, and negatively affect respiratory, circulatory, digestive, reproductive, and neurological organ systems [28][48].

The main pathway through which REE causes adverse biological effects centers on disrupting cellular oxidative balance, paralleling established redox toxicity patterns seen with comparable metallic compounds [28][30][34]. REE can catalyze the formation of reactive oxygen species (ROS) through Fenton-like reactions, particularly with cerium [49], interfere with mitochondrial electron transport chains leading to increased ROS production and decreased ATP synthesis [28]. It directly inhibits antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, and bind to sulfhydryl groups in glutathione and other cellular thiols, depleting primary cellular antioxidants [42][43].

Importantly, interactions with fluoride represent a significant yet understudied aspect of REE biochemistry. Fluoride is typically present in excess over REE concentrations in body fluids, and complexation reactions between REE and fluoride have been recognized for decades, though their biological implications remain poorly characterized. Investigations of populations near electronic waste facilities have shown elevated oxidative stress indicators following REE exposure [50][51]. These results indicate that such contact triggers endocrine disruption through enhanced cellular stress, ultimately affecting hypothalamic-pituitary-thyroid regulatory mechanisms [50][52].

Furthermore, the anticoagulant activity of lanthanides represents a well-established toxicological property that has been recognized for decades. This effect arises from the antagonistic action of

lanthanides on calcium-dependent steps in the blood clotting cascade, representing a characteristic feature that distinguishes these elements from other metal toxins.

3.1.2. Mitochondrial Dysfunction and Cellular Effects

Since their role as cellular energy-producing organelles and their susceptibility to oxidative damage, mitochondria represent primary targets for REE toxicity [30][53]. The accumulation of REE in mitochondria leads to membrane integrity disruption through altered mitochondrial membrane potential and permeability, resulting in release of pro-apoptotic factors, respiratory chain inhibition interfering with electron transport complexes and reducing ATP production [48][54]. Grosjean et al. [55] [56] have reported that the primary consequence of REE administration is enhanced cellular oxidative damage resulting from element accumulation within hepatocyte nuclei and mitochondria. This is accompanied by cognitive and learning impairments due to damaged hippocampal brain cells, and pulmonary hemorrhage in neonatal mice, demonstrating the systemic nature of REE toxicity and its impact on developing organisms [57].

Mitochondrial superoxide dismutase, catalase, glutathione peroxidase, and glutathione activities in hepatocytes were significantly decreased following REE exposure [58]. It was accompanied by marked increases in malondialdehyde levels, suggesting that lanthanum, cerium, and neodymium penetrate hepatocytes and disrupt mitochondrial function through direct interference with antioxidant enzyme systems and promotion of lipid peroxidation [57][58]. REE can also interfere with protein structure and function through metal substitution displacing essential trace elements like calcium, magnesium, and zinc from metalloproteins and altering their function, protein aggregation promoting misfolding particularly affecting cytoskeletal proteins, enzyme inhibition through binding to active sites or allosteric sites, and interference with DNA-protein interactions affecting gene expression and DNA repair mechanisms [28][34].

3.1.3. Individual REE Toxicity Profiles

Light REE (La, Ce, Pr, Nd, Pm): Lanthanum shows complex dose-dependent effects with both protective and toxic properties depending on concentration and exposure conditions. High concentrations may overproduce free radicals exceeding cellular antioxidant capacity and leading to oxidative damage [59]. Hepatocyte studies showed that lanthanum, cerium, and neodymium deposition in cellular nuclei and

mitochondrial structures produces significant oxidative cellular damage, with significantly decreased mitochondrial antioxidant activities and marked increases in malondialdehyde levels [58].

Cerium compounds have been extensively investigated given their widespread industrial applications and biomedical research potential. Studies with adult male Sprague-Dawley rat pulmonary alveolar macrophages revealed that cerium chloride displayed significant cytotoxicity [60], while CeO_2 nanoparticles induced mitochondrial damage and overexpression of apoptosis in human peripheral blood monocytes and lung adenocarcinoma cells [61]. Pulmonary effects of cerium have been well-documented through studies assessing oxidative stress and molecular mechanisms involved in pulmonary inflammation caused by long-term lung toxicity in mice, demonstrating large accumulations of cerium in lungs leading to prominent increases in lung index, inflammatory cells, and lung inflammation [62].

Neodymium, particularly in the form of permanent magnets, has shown significant cytotoxic potential with neodymium-iron-boron magnets being cytotoxic against human oral mucosal fibroblasts [63]. Acute toxicity studies in zebrafish embryos revealed comparable LC_{50} values for neodymium and yttrium, suggesting probable similarity in toxicity mechanisms between light and heavy REE [64].

Middle REE (Sm, Eu, Gd, Tb, Dy, Ho): Gadolinium has received the most clinical attention among REE because of its widespread use as an MRI contrast agent, which concerns gadolinium retention in patients' bodies, including the brain, for months *to years, likely lifelong* after receiving these compounds [35]. Free gadolinium (Gd^{3+}) exhibits severe cytotoxicity due to its ability to disrupt calcium-dependent pathways, unlike stable chelated forms used in MRI contrast agents [65]. Gadolinium oxide nanoparticles have been found cytotoxic to human umbilical vein endothelial cells, inducing lipid peroxidation, ROS production, mitochondrial dysfunction, and autophagic modulation through apoptosis and necrosis [35][66].

Heavy REE (Er, Tm, Yb, Lu, Sc, Y): Yttrium toxicity has been studied more extensively than most heavy REE, with acute toxicity studies in zebrafish embryos indicating significant acute toxicity potential [64]. In turn, nanoparticles of Y_2O_3 induced apoptosis and necrosis in human cells by elevating cellular ROS levels, demonstrating that yttrium can cause significant cytotoxicity through oxidative stress mechanisms [67][68]. On the other hand, toxicokinetic studies have provided new insights into scandium toxicity through comprehensive pharmacokinetic evaluations in animal models, although comprehensive human data remain limited [69].

3.1.4. Organ-Specific Toxicity

The respiratory system represents a primary target for REE toxicity due to inhalation exposure routes and the biopersistent nature of these elements [28]. After occupational exposure, REE may remain in the human body for many years [70]. Long-term inhalation of REE-containing dust is associated with pneumoconiosis [71]. Comparative studies have shown that all types of REE nanoparticles have higher inflammatory potential than other toxic particles [72]. REE nanoparticles have demonstrated enhanced inflammatory responses compared to conventional particulate matter through increased expression of inflammatory markers, including intercellular adhesion molecule-1, interleukin-8, and monocyte chemotactic protein-1 in lung tissues [73][74]. REE exposure can also impair alveolar macrophage function, compromising the lung's ability to clear particles and pathogens and contributing to persistence of REE in lung tissue and chronic inflammatory responses [28][73].

Regarding the cardiovascular system, REE exposure correlates with diverse cardiac complications spanning direct myocardial toxicity to endothelial dysfunction, as evidenced by zebrafish studies showing pericardial fluid accumulation, cardiac rhythm disturbances, and ventricular enlargement, demonstrating adverse cardiovascular impacts [47][75][76]. Endothelial studies revealed elevated inflammatory biomarkers in human aortic cells following REE particle internalization, confirming vascular inflammatory responses [28][77]. Vascular endothelial effects include significantly increased inflammatory markers in human aortic endothelial cells that internalized REE particles, which suggests that these elements can induce inflammation in vascular endothelial cells [78]. In turn, REE can induce abnormal vascular development by activating apoptotic pathways with implications for wound healing, tissue repair, and developmental processes, being REE deposited in tissues and increasing intracellular ROS levels [34][79].

On the other hand, REE exposure has also implications for reproductive health in both males and females [80]. REE effects on male reproduction include impaired spermatogenesis, reduced sperm quality, and testicular tissue damage, while animal experiments confirmed a significant positive correlation between REE deposition in testes and sperm DNA damage following long-term exposure [81][82]. This reproductive toxicity appears related to inflammation, oxidative stress, and disruption of the blood-testis barrier, with REE disrupting mitochondrial function at the molecular level, leading to ROS production imbalances that can affect thyroid, estrogen, or androgen pathways, potentially causing hormonal imbalances [34][83]. Moreover, recent studies investigating associations between maternal urinary REE

concentrations and neonatal outcomes have reported associations with neonatal size at birth, indicating potential developmental effects from maternal REE exposure [84][85].

In relation to the hepatic system, since its role in metabolism and detoxification, the liver represents a major target organ for REE toxicity [30][86]. REE exposures trigger cellular stress pathways and NRF2 activation, elevating S-phase cell populations and associated cell cycle indicators, suggesting that chronic low-level exposure to REE mixtures can cause progressive hepatocellular dysfunction [38]. REE accumulation in hepatocytes can disrupt normal metabolic processes including glucose metabolism, lipid synthesis, and protein production [58]. These effects may have systemic implications for metabolic health, while mitochondrial antioxidant enzyme activities in hepatocytes were significantly decreased following REE exposure, indicating that REE penetrate hepatocytes and disrupt mitochondrial function [28][48].

With respect to the nervous system, given its high metabolic demands and limited regenerative capacity, it is particularly vulnerable to REE toxicity [87]. REE exposure has been reported to cause impairment of cognitive behavior and learning due to damaged hippocampal brain cells, which is of particular concern for developing organisms [42]. Various neurological effects including altered behavior and learning deficits have been reported following REE exposure to animals through mechanisms involving disruption of neurotransmitter systems and neuronal energy metabolism [88][89]. REE may cross the blood-brain barrier under certain conditions, potentially accumulating in brain tissue and causing long-term neurological effects, with exposure during critical developmental periods having particularly severe consequences for nervous system development and function [28][90][91].

A summary of the organ-specific toxic effects of key REE, including lanthanum, cerium, neodymium, gadolinium, yttrium, and samarium, is shown in Table 1. These effects highlight the diverse and systemic nature of REE toxicity, necessitating targeted therapeutic approaches.

REE	Organ/System Affected	Observed Effects
Lanthanum	Kidney, Liver	Fibrosis, enzyme alterations
Cerium	Lungs, Immune system	Inflammation, immune modulation
Neodymium	Bone, Liver	Bone metabolism disruption, oxidative stress
Gadolinium	Skin, Brain, Kidneys	Nephrogenic systemic fibrosis (NSF), neuronal deposition, renal retention
Yttrium	Lungs, Bone	Pulmonary damage, skeletal uptake
Samarium	Liver, Blood	Hematological alterations, liver toxicity

Table 1. Summary of toxic effects of some REE in mammalian systems

3.2. Human Health Evidence for REE Toxicity

3.2.1. Occupational Exposure Studies

Occupational exposure represents the most significant source of high-level REE exposure in humans [27][33]. It provides valuable insights into the health effects of these elements through comprehensive studies of workers producing ultrafine and nano-sized particles containing cerium and lanthanum oxide, particularly those at separation and packaging locations, who showed significantly elevated urinary REE levels [92][93]. Moreover, workers exposed to REE-containing dust showing various health effects including respiratory symptoms, gastrointestinal complaints, and evidence of systemic toxicity, with severity of effects correlating with both, exposure duration, and intensity [33][70].

Workers in electronic manufacturing may be exposed to multiple REE used in various components through inhalation of particulates during manufacturing processes and dermal contact with REE-containing materials [70][94][95]. Exposure patterns differ notably from mining operations through generally lower concentrations, but potentially longer duration exposures, to complex mixtures of REE including neodymium, dysprosium, terbium, and europium [33][96][95]. Urinary REE concentrations serve as valuable biomarkers of recent exposure [97], with different REE showing varying elimination kinetics and cerium and lanthanum having the highest urinary concentrations among exposed workers [38].

3.2.2. Environmental Exposure Studies

Environmental exposure to REE affects large populations living near mining sites, processing facilities, or areas with high electronic waste recycling activities [31][98]. It has been reported that people living near high-REE background areas can be affected by diarrhea, abdominal distension, anorexia, weakness, and fatigue [30][99], showing also altered blood chemistry with lower levels of total protein, globulin, albumin, and serum glutamic pyruvic transaminase and higher levels of immunoglobulin M in their blood serum [28][100]. Studies of communities living near REE mining operations have revealed elevated oxidative stress and inflammatory biomarkers. It suggests that environmental contact with REE could trigger endocrine dysfunction through enhanced cellular stress mechanisms, ultimately disrupting hypothalamic-pituitary-thyroid hormonal regulation [34][50].

The agricultural use of REE-containing fertilizers and soil amendments has also led to environmental contamination and human exposure through food and water sources [29][101]. Environmental contamination by REE has been reported in sediments that could affect food chain exposure [102][103], while drinking water contamination near agricultural areas using REE fertilizers has been reported [104] [105], although health studies remain limited.

3.2.3. Medical Exposure Studies

Gadolinium-based contrast agents used in MRI scans can remain in patients' bodies, including the brain, for months to years after administration [106]. The most recognized adverse effect linked to gadolinium retention is nephrogenic systemic fibrosis, a rare condition in patients with existing kidney failure [107] [108]. Clinicians should carefully consider retention properties when selecting contrast agents for high-risk patients, including those needing repeated exposures, pregnant women, children, and patients with inflammatory conditions [35][109]. Special consideration should be given to vulnerable populations, including fetuses, as evidenced by large epidemiological studies from Ontario, Canada, that have documented fetal loss associated with GBCA exposure. Other medical applications involving rare earth elements include radiopharmaceuticals and medical devices, which may cause combined radiological and chemical toxicity or chronic low-level exposure, though health effects data remain limited [34][110].

3.2.4. Vulnerable Populations

Children may be particularly vulnerable to REE toxicity considering their developing organ systems and higher metabolic rates [111][112]. Associations of maternal urinary REE with neonatal size at birth have shown evidence of potential developmental effects from maternal exposure [85]. Children may also to be exposed to REE due to hand-to-mouth behaviors, closer proximity to the ground where particles settle, and higher ventilation rates relative to body weight [111][113]. On the other hand, pregnancy is a critical period for both maternal and fetal health with potential for transplacental REE transfer [114][115]. However, limited data suggest that some REE may cross the placental barrier potentially affecting fetal development with the extent of transfer likely varying among different REE [116]. In turn, studies examining pregnancy outcomes in REE-exposed populations are scarce, but some evidence suggests potential effects on birth weight and gestational age [84][85].

Elderly individuals may be more susceptible to REE toxicity due to age-related changes in organ function and increased comorbidities, with decreased renal function, altered immune responses, and increased oxidative stress potentially enhancing susceptibility to REE toxicity [117][118]. Moreover, elderly patients are more likely to receive multiple MRI examinations with GBCA potentially leading to cumulative gadolinium exposure requiring special consideration in clinical practice [109][119].

3.3. Role of Chelation Therapy in Metal Intoxication

3.3.1. Principles of chelation therapy

Chelation is the main basis for the clinical treatment of metal poisoning [120]. It is a process by which a single molecule, known as a chelating agent or chelator, can form multiple bonds to a central metal ion, effectively sequestering it [121]. This process results in the formation of a stable, ring-like structure called a chelate. Structurally, chelating agents are organic compounds possessing two or more donor atoms, such as oxygen, nitrogen, or sulfur, capable of donating a pair of electrons to a metal ion to form coordinate covalent bonds. The resulting metal-ligand complex exhibits significantly enhanced stability compared to complexes formed by monodentate ligands, which can only form a single bond with the metal ion [121]. Due to their properties, chelating agents have multitude of applications, from industrial processes to water treatment [122]. In medicine, chelation therapy stands as a critical intervention for the treatment of metal intoxication, where chelators are administered to bind to toxic metal ions, facilitating

their excretion from the body [123][124][125][126][127][128][129]. A rigorous, science-based evaluation of chelator effectiveness for REEs requires two critical criteria: (a) demonstration of a high stability constant (log K) for the specific REE–chelator complex under physiologically relevant conditions, and (b) empirical evidence that the chelator facilitates measurable elimination of the target REE from the body. The standard assessment should incorporate quantitative 24-hour urine collections, both before and after chelation therapy, enabling direct comparison of REE excretion, and thereby, providing objective evidence of chelation efficacy.

3.3.2. Chelating Agents Used as Antidotes in Metal Intoxication

The following chelating agents have been most used and/or are still being used in the treatment of metal intoxication: 2,3-Dimercaptopropane-1-sulfonate (DMPS/unithiol) is a water-soluble chemical analog of dimercaprol and an effective antidote for certain forms of heavy metal poisoning, being less toxic than dimercaprol and used extensively in recent years mainly for arsenic and cadmium chelation in animal models and mercury chelation in mine workers. It has shown efficacy in mercury poisoning cases with extensive neurological symptoms, but also in lead and arsenic intoxication. DMPS can be administered orally and intravenously providing flexibility in treatment approaches [130][131].

Deferoxamine (desferrioxamine, DFO) is a chelating medication primarily approved for iron toxicity and for aluminum toxicity [132]. DFO works by binding to various forms of iron, while also increasing urinary aluminum elimination. Despite its effectiveness, DFO has significant side effects and may accumulate in dialysis patients with repeated dosing. The drug requires parenteral administration and lacks oral efficacy, prompting research into safer alternatives like dicarboxylic acids and hydroxypyridin-4-ones [133]. Deferasirox and deferiprone have been developed for chronic iron overload management (e.g., thalassemia), although their relevance to REE chelation remains unexplored. However, they can mean oral alternatives to parenteral DFO [134][135].

D-penicillamine (D-PA) is an oral chelating agent and a metabolite of penicillin, although it has no antibiotic properties. The D-isomer is used, while the L-isomer is toxic. D-PA has been a primary treatment for Wilson's disease, an inherited disorder leading to copper accumulation. It is also used for cystinuria (to prevent kidney stones) and sometimes for severe, active rheumatoid arthritis. Historically, D-PA was used for lead and mercury poisoning, although safer and more effective agents (i.e., DMSA and DMPS) are now preferred [136].

A summary of the most clinically used chelating agents, their characteristics, and main applications is presented in Table 2.

Chelator	Chemical Class	Target Metals	Route ad Dose	Clinical Use
EDTA (calcium disodium EDTA)	Polyaminocarboxylic acid	Pb, Ca, Zn	IV infusion: 1000–1500 mg/m²/day for 5 days	Lead poisoning (especially with encephalopathy), hypercalcemia
DTPA (Ca-DTPA, Zn-DTPA)	Polyaminocarboxylic acid	Pu, Am, Cm, U	IV or inhalation: 1 g/day	Internal contamination (mainly with radioactive metals)
BAL (Dimercaprol)	Dithiol	As, Hg, Pb	IM: 3–5 mg/kg every 4–6 hours	Arsenic, mercury, and lead poisoning (especially with CNS symptoms)
DMSA (Succimer)	Dithiol	Pb, Hg, As	Oral: 10 mg/kg every 8 hours for 5 days, then every 12 hours for 14 days	Pediatric lead poisoning, mercury detoxification
DMPS (Unithiol)	Dithiol	Hg, As	Oral or IV: 5–15 mg/kg/day	Mercury and arsenic poisoning
DFOA (Deferoxamine)	Hydroxamic acid	Fe, Al	IM/IV/SC: 20–40 mg/kg/day (max 6 g/day)	Iron overload (thalassemia), aluminum toxicity
Deferasirox (Exjade, Jadenu)	Tridentate chelator	Fe	Oral: 20–40 mg/kg/day	Chronic iron overload (oral alternative to DFOA)
Deferiprone (Ferriprox)	Bidentate chelator	Fe	Oral: 75–100 mg/kg/day in 3 doses	Iron overload in thalassemia major
D-Penicillamine	Thiol	Cu, Pb, Hg	Oral: 250–500 mg/day, up to 1–2 g/day	Wilson's disease, lead and mercury poisoning, cystinuria

Table 2. Most used chelating agents in the management of heavy metal poisoning:characteristics, dosing, and clinical uses

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3.3.3. Emerging Therapeutic Strategies

Newer strategies address drawbacks through combination therapy, using structurally different chelating agents, or co-administration of antioxidants. Rationale includes enhanced metal mobilization from different body compartments, synergistic effects of structurally different chelators [137][138][139] and reduced individual agent toxicity through lower dosing. Metal toxicity is often mediated through oxidative stress mechanisms leading to investigation of antioxidant supplementation during chelation therapy [140]. Then, administration of vitamins, essential metals, or amino acid supplementation can be beneficial in increasing metal mobilization and providing recoveries in altered biochemical variables [141] [142]. Antioxidants including vitamin C and E, α-lipoic acid, and others when given alone or in combination with chelating agents prove effective in mobilizing metals from soft and hard tissues [143].

Advances in nanotechnology offer promising approaches for targeted chelation therapy [144], providing advantages including targeted delivery to specific organs or tissues, reduced systemic toxicity, enhanced drug stability and bioavailability, and controlled release mechanisms [145]. New chelation therapies including polygamma-glutamic acid-coated superparamagnetic nanoparticles with high specificity for metal toxins represent cutting-edge targeted chelation therapy [146][147].

3.4. REE Chelation

3.4.1. Chemical Properties

REE possess various chemical characteristics that distinguish them from traditional heavy metals [148]. It presents specific challenges for chelation therapy, with all lanthanides sharing remarkably similar chemical properties because of their electronic configuration, making it difficult to develop selective chelating agents for individual REE [149][150]. Therefore, chelation strategies that can be effective for a certain REE may not necessarily work for others, complicating the development of antidotes. REE ions typically exhibit coordination numbers of 8-9, which are higher than most transition metals [23][151]. It allows REE to form complex structures with multiple ligands simultaneously, making displacements by chelating agents. It should be noted that more effective chelators utilize cation-exchange mechanisms, with the locus for exchange potentially located on linear arms rather than having the metal centrally positioned within the chelator structure.

3.4.2. Limitations of conventional chelators for REE

Current evidence indicates that conventional chelation does not represent an effective option for at least one of the most investigated REE: gadolinium. Various studies have reported that EDTA, DMSA and DMPS appear equally unsuccessful in increasing gadolinium elimination via the renal system [35]. The contrast agent's molecular structure determines its stability and whether it can be re-chelated by a certain chelating agent, with molecular formulas of gadolinium-DTPA and zinc-DTPA being similar as their thermodynamic stability constants [152][153][154]. However, it must be emphasized that DTPA is effective for chelating gadolinium. The model for chelators using ligands established for clinical use (with over 100 million doses of Magnevist administered worldwide) provides unique insights among REE. Understanding the principles of creating optimal ligands for GBCAs offers important guidance for developing REE chelators, particularly regarding the importance of log stability constants (thermodynamic stability) and rapid elimination pathways through kidneys and hepatobiliary routes [35].

Synthetic chelators may redistribute some REE ions to other tissues like the brain, potentially increasing neurotoxicity. They may also deactivate essential trace elements and produce deficiency states, with REE accumulating within cells particularly in mitochondria and nuclei where chelating agents can have limited access due to varying abilities to penetrate cellular membranes [155].

From soil chemistry, it is known that REE form complexes with -OH and -COOH groups of humic substances, but never with -SH groups. Therefore, the use of detoxifying agents containing -SH groups is inappropriate and should not be considered for REE chelation. Alternative approaches such as fluoride-based chelation warrant investigation. Additionally, antioxidant support appears promising for adjunctive therapy.

3.5. Current Therapeutic Approaches for REE Intoxication

3.5.1. Specific chelating agents for REE Treatment

DTPA is a pentadentate chelator that can form stable complexes with REE through multiple coordination bonds. This chelating agent has been reported to be the most promising chelator for certain REE intoxications [34][109][156]. The US FDA [157] determined that zinc-DTPA and calcium-DTPA are safe and effective for treatment of internal contamination by plutonium, americium, or curium. DTPA forms complexes with thorium, uranium, neptunium, and cerium. In turn, gadolinium-DTPA compounds are MRI contrasting agents, and some preliminary reports suggest calcium-DTPA and zinc-DTPA may be

useful for gadolinium deposition disease, but more research is still needed. On the other hand, EDTA seems to have very limited effectiveness for most REE [158]. However, EDTA combined with other chelators might show synergistic effects, which could influence efficacy and safety profiles [159]. Finally, DMSA derivatives with enhanced tissue penetration or REE specificity are still under investigation, while DMPS analogs with structural modifications could improve REE binding affinity. Nevertheless, current evidence suggests limited effectiveness of these chelators for most REE intoxications requiring the development of more specific therapeutic approaches, based on new chelating agents [160][161]. As of July 2025, no clinical trials specifically evaluating chelation therapy for REE intoxication have been identified. However, the importance of HOPO (hydroxypyridinone) chelators must be emphasized as an important emerging therapy for REE intoxication. These agents represent a significant advancement in the field and warrant inclusion in future therapeutic protocols.

3.5.2. Supportive and Adjunctive Therapies

Given the central role of oxidative stress in REE toxicity, antioxidant support might provide protective benefits through N-acetylcysteine, ascorbic acid, vitamin E, and selenium, which may help counteract REE toxicity through antioxidant mechanisms [143][162][163]. Symptomatic management includes usual therapy of heavy metal poisoning, respiratory support for patients with acute lung injury, cardiovascular support for management of cardiac arrhythmias and hemodynamic instability, neurological support for seizure control and management of encephalopathy, and renal support through hemodialysis for acute kidney injury [99][134]. Although enhanced elimination techniques including hemodialysis are not enough effective for removing tissue-bound REE, they may help eliminate chelator-REE complexes. For example, plasmapheresis, which may be considered for severe systemic toxicity, has limited evidence, while forced diuresis might enhance elimination of chelated REE complexes [127].

For most REE, the toxicity mechanism reflects an immunologic/toxic process rather than primarily radiological effects. However, radioactivity is observed in some REE isotopes, representing a separate concern that requires more rapid removal approaches. The combination of chelation therapy with corticosteroids may be beneficial, as described in recent literature on metal-induced autoimmunity in neurological disorders.

Table 3 summarizes the experimental use of chelating agents, including DTPA, EDTA, DMSA, and DMPS, against specific REE in animal and "in vitro" models, highlighting DTPA's moderate efficacy for

gadolinium and cerium compared to the limited effectiveness of other agents. These findings clearly suggest the need for further research into REE-specific chelators.

Chelating Agent	Tested REE	Experimental Model	Findings
DTPA	Gd, Ce, La	Animal models	Moderate effectiveness in reducing Gd retention; moderate effect also on Ce and La
EDTA	La, Ce, Nd	*In vitro* and animal studies	Limited efficacy; partial mobilization of REE
DMSA	Gd, Nd	Animal models	Ineffective for Gd; mild reduction for Nd
DMPS	Gd	Animal models	No significant benefit
BAL	Not tested for REE	-	Unknown effectiveness

Table 3. Some chelating agents and their experimental use against specific REE

4. Discussion

The present review shows that REE present specific toxicological challenges that distinguish them from traditional heavy metals. As above indicated, REE possess significant mammalian toxicity through multiple mechanisms, mainly involving oxidative stress and mitochondrial dysfunction [28][43], which affects respiratory, cardiovascular, digestive, reproductive, and nervous systems [47][48]. Conventional chelating agents show limited effectiveness for many REE [35], requiring development of novel therapeutic approaches specifically designed for REE characteristics [160][161].

Human exposure to REE may occur through multiple pathways including occupational exposure in mining, manufacturing, or recycling e-waste, representing significant sources of high-level exposure [33] [92][93]. In turn, environmental exposure may affect populations living near mining sites and e-waste recycling facilities [31][98], as well as through the dietary intake, including drinking water [29], while medical exposure primarily concerns gadolinium-based contrast agents in MRI procedures [35].

Vulnerable populations including children, pregnant women, and elderly individuals facing increased risks derived from REE exposure due to developmental factors, physiological changes, and cumulative exposure patterns [111][114][117]. The regulatory landscape remains underdeveloped with no specific restrictions for REE despite widespread use and environmental presence [18], creating significant gaps in protection and necessitating urgent development of exposure limits, treatment guidelines, and safety standards [28].

However, it should be noted that ambient REE levels in environmental media are generally much lower than those of traditional heavy metals. REE concentrations typically range in the ng/L range for water and µg/kg range for food items [29]. Maximum concentrations in food are found in seafood (non-fish), which is particularly relevant for Southeast Asia and China. The main uptake route may be through dust exposure. Additional concerns exist regarding REE emissions from platinum/palladium catalysts in automotive systems, where REE are released from carrier ceramics during stop-and-go driving, potentially at levels exceeding those of platinum or palladium. Data regarding REE content in cosmetics remain lacking, despite previous concerns about aluminum in cosmetic products.

Furthermore, the concept of hormesis should be considered in REE toxicology. In cases of low-dose REE exposure, defensive reactions of the organism may induce beneficial counteractions that exceed the necessary response, leading to positive effects. This mechanism has been utilized in REE additions to fertilizers and animal feeds to enhance plant growth and weight gain. It can also explain the benefits observed with some phosphate-mobilizing microorganisms.

The limited effectiveness of conventional chelating agents for REE intoxication [35][158] has significant implications for clinical practice, requiring healthcare providers to adopt different approaches compared to traditional heavy metal poisoning cases [164], with emphasis on prevention, early recognition, supportive care, and individualized treatment strategies based on specific REE involved and exposure circumstances [99]. To date, among available chelating agents, DTPA seems to be the most promising, at least for gadolinium [109][156]. DTPA has an established use for actinide contamination and ability to form stable complexes with some REE, but its use for REE is off-label and requires toxicology consultation [157]. Notwithstanding, clinical evidence remains limited and requires careful risk-benefit assessment in individual cases [152].

Clinical management should focus on immediate exposure control and decontamination as primary interventions [127], comprehensive supportive care addressing organ-specific dysfunction [164],

antioxidant support to counteract oxidative stress mechanisms [143][163], and long-term monitoring for delayed effects given the biopersistent nature of REE [70][99][134]. The use of DTPA (or other chelating) agents might help to assess body burden [38], but its clinical utility for REE remains unproven, requiring careful interpretation and correlation with clinical findings [152].

Metabolic interactions between REE and essential elements can be readily explained through interactions with iron and calcium-europium interactions, though the mechanisms are often presented in unnecessarily complex terms. A critical gap exists regarding interactions with fluoride, which is typically present in excess over REE concentrations in body fluids, despite decades of known complexation reactions.

Urgent research priorities include development of REE-specific chelating agents designed specifically for the unique coordination chemistry and biological behavior of these elements [149][150]. Chelators must focus on agents capable of accessing intracellular compartments where REE accumulate [57][58], crossing biological barriers including the blood-brain barrier [91], and selectively bind REE without affecting essential metals [165][166]. Mechanistic research is needed to better understand cellular uptake and distribution mechanisms for different REE [28][34], subcellular localization patterns and their relationship to toxicity [55][56], molecular targets and pathways affected by REE exposure [30].

Nanotechnology applications offer promising approaches for targeted chelation therapy [144] through development of nanoparticle delivery systems designed to deliver chelators to specific tissues or cell types [147], stimulus-responsive systems that release chelators in response to specific biological conditions [145], and multifunctional platforms combining chelation, antioxidant therapy, and imaging capabilities [146].

The exponential growth in global REE applications has surpassed the development of appropriate regulatory frameworks [11][17], prompting an immediate public health response. Despite evidence of potential REE toxicity and their ubiquitous presence in modern industrial processes [3][34], the absence of specific regulatory guidelines represents a critical gap that demands immediate international attention [37]. The current lack of regulatory oversight is especially concerning given the anticipated surge in demand for REE because of the global shift toward clean energy technologies and the rapid expansion of digitalization initiatives [16][36].

Comprehensive regulatory development must address multiple critical areas: establishment of science-based occupational exposure limits for workers in REE mining, processing, and manufacturing industries [33][70]; implementation of environmental monitoring standards for air, water, and soil contamination [20][31]; development of biomonitoring protocols for high-risk populations including industrial workers and communities near REE facilities [38][97]; and creation of standardized risk assessment frameworks that account for the unique physicochemical properties and toxicological profiles of individual REE compounds [1][40]. Moreover, healthcare regulations require particular attention to gadolinium-based contrast agents [13][35].

Environmental regulatory frameworks must encompass stringent controls for REE extraction and processing operations, which generate substantial volumes of toxic waste [8][21], alongside comprehensive requirements for proper disposal and recycling of REE-containing consumer products [22] [23]. The establishment of environmental contamination thresholds, remediation standards for contaminated sites, and long-term monitoring protocols is essential given the persistent nature of REE environmental contamination [102][103]. Occupational health regulations must include enhanced protective measures for the growing workforce exposed to REE [94], including industry-specific personal protective equipment standards, continuous workplace air monitoring, and comprehensive medical surveillance programs with particular focus on respiratory, renal, and neurological health endpoints [70] [71].

The global nature of REE supply chains, concentrated primarily in regions with varying regulatory standards [17], necessitates unprecedented international coordination to prevent regulatory arbitrage and ensure consistent protection standards. Environmental contamination risks, evidenced by long-range atmospheric transport of REE-containing particles from processing facilities [73][74], further underscore the critical need for harmonized international regulatory approaches.

Critical societal implications include the urgent need for comprehensive public campaigns addressing REE exposure risks in both occupational and consumer contexts [27], systematic training programs for healthcare providers to enhance recognition and management of REE toxicity syndromes [99], and development of emergency response capabilities for acute exposure incidents in specific areas [127]. Ethical considerations regarding acceptable risk thresholds for beneficial REE technologies must be transparently addressed through inclusive stakeholder engagement processes that balance technological advancement with worker and community protection [36].

The anticipated increase in REE demand driven by renewable energy deployment, electric vehicle adoption, and advanced technology development [4][10], will inevitably intensify both occupational exposures in expanding REE industries, and environmental releases from increased mining and processing activities [19]. It demands a fundamentally proactive approach to risk assessment and management [28], with robust regulatory frameworks, enhanced worker protections, and comprehensive environmental monitoring systems implemented before widespread health impacts become irreversible.

5. Limitations

5.1. Literature and Data Limitations

This review is constrained by several significant limitations in the available literature including limited human studies with most evidence derived from animal models [41][53], also rather scarce, and "in vitro" studies [61][72]. It may not accurately reflect human responses to REE exposure [27], making extrapolation to clinical scenarios challenging and uncertain [42]. Case reports and observational studies predominate in human literature [33][92][93] with few controlled clinical trials available for REE chelation therapy [152], limiting the strength of evidence for therapeutic recommendations and requiring reliance on lower-quality evidence sources that may be subject to bias and confounding factors [99].

The heterogeneity of REE exposure scenarios [31][34] makes it difficult to develop unified treatment approaches, with different REE having distinct chemical properties and biological effects [148][149], various exposure routes and durations, requiring different therapeutic considerations [95][96]. Limited data on mixture effects when multiple REE are present simultaneously as commonly occurs in real-world exposure situations [38] is another issue. Methodological limitations in existing studies include inconsistent exposure assessment methods across studies [27], variable outcome measures making comparison difficult [30], limited long-term follow-up data for chronic effects [70], and insufficient consideration of confounding factors that can influence results [28].

Additionally, studies regarding ambient levels in environmental media remains limited in the databases. Contrary to initial assumptions, the water solubility, soil-to-plant transfer, and gastrointestinal uptake of REE are considerably lower than those of traditional heavy metals.

5.2. Therapeutic development challenges

The development of effective REE chelation therapy faces significant scientific and practical challenges including the chemical similarity among REE making selective chelation difficult [1][150], limited understanding of optimal therapeutic targets within cells and tissues [55][58], uncertainty about chelator access to sites of REE accumulation [155], and potential for redistribution toxicity when chelators mobilize REE from storage sites [159]. Regulatory pathways for REE-specific chelating agents are unclear given the limited precedent for this class of compounds [120], potential classification as orphan drugs due to -until now- small patient populations [167], complex safety evaluation requirements for novel chelating agents [165], and international regulatory harmonization challenges for global approval [164].

5.3. Clinical practice limitations

Current clinical practice faces significant limitations in managing REE intoxication [99] including lack of standardized diagnostic criteria for REE toxicity [34], limited availability of REE measurement in biological samples [38][97], absence of evidence-based treatment guidelines [134], and insufficient training of healthcare providers in REE toxicity recognition and management [70]. Monitoring and assessment challenges include difficulty distinguishing REE toxicity from other conditions with similar presentations [30], limited biomarkers for early detection of REE effects [53], uncertainty about optimal timing and duration of treatment [127], and lack of validated tools for assessing treatment response and long-term outcomes [48].

6. Conclusions and Recommendations

6.1. Conclusions

The expanding use of REE in industrial, technological, and medical activities [11][12], has led to increasing human exposure and consequent toxicological concerns [31][34]. The present review highlights the significant health hazards posed by REE, distinguishing them from other much more studied heavy metals [164]. REE possess unique coordination chemistry [148][149], biological persistence [70], and multifactorial mechanisms of toxicity [28]. They exert toxicity primarily through oxidative stress and mitochondrial dysfunction [43][48], leading to damage across multiple organ systems, including respiratory, cardiovascular, hepatic, reproductive, and neurological tissues [30][41]. The biopersistence and

capacity of REE to accumulate in intracellular compartments, including mitochondria and nuclei [55][58], pose long-term health threats, particularly in vulnerable populations such as children, pregnant women, and individuals with preexisting health conditions [111][114][117].

Human exposure pathways are multifaceted, encompassing occupational settings (e.g., mining and manufacturing) [33][92][93], environmental contamination (e.g., e-waste and agricultural runoff) [31][98], and iatrogenic sources (essentially gadolinium-based contrast agents) [35]. Despite this broad exposure potential, there is a striking paucity of regulatory oversight at international levels [18]. Existing regulatory frameworks fail to establish exposure thresholds, biomonitoring protocols, or standardized therapeutic guidelines specific to REE [28]. This regulatory vacuum remarks the lack of validated biomarkers for early detection [53] and insufficient clinical awareness of REE-related toxicopathology [99].

From a therapeutic perspective, conventional chelation strategies used for the treatment of heavy metal intoxication [123][127], show limited or negligible efficacy in mobilizing or enhancing the excretion of REE [35][158], being gadolinium the most investigated [152][153]. Among existing agents, DTPA and its calcium and zinc salts, has shown the most promising for certain REE [109][156], although clinical evidence remains sparse [157]. Furthermore, current chelators often fail to cross cellular membranes or access compartments where REE accumulate [155], and they can disrupt the homeostasis of essential trace elements [165][166].

As shown in this review, the therapeutic management of REE intoxication is primarily supportive [99][134], as no standardized antidotes currently exist [127]. Experimental approaches, such as chelation therapy and adjunctive antioxidant co-treatment [140][152, are under investigation but have not yet been established as standard protocols [120]. The lack of REE-specific antidotes, coupled with insufficient clinical trials [152], means considerable challenge to evidence-based medical management [164]. Therefore, addressing the toxicological, clinical, and regulatory gaps is imperative for protecting public health as REE utilization continues to expand [4][28].

6.2. Recommendations

Clinicians should maintain a high index of suspicion for REE toxicity in patients presenting multi-system symptoms and histories suggestive of occupational, environmental, or medical exposure [27][99]. If chelation is indicated, DTPA (particularly Ca-DTPA followed by Zn-DTPA) remains the preferred agent for certain REE [109][156], although off-label use should be accompanied by toxicological consultation [157].

Use of traditional chelators (EDTA, DMSA, DMPS) should be approached cautiously due to their limited efficacy [35][158] and potential for adverse redistribution or depletion of essential elements [166][159]. Treatment regimens should emphasize organ-specific support [164] and antioxidant therapy (e.g., N-acetylcysteine, vitamin E, selenium) to mitigate oxidative damage [143] [162] [163].

There is an urgent need for developing novel chelators based on the coordination chemistry of REE [149] [150]. These agents must demonstrate high selectivity, ability to penetrate cellular and organelle membranes [58][91], low toxicity, and minimal interference with essential trace elements [165][166]. Research into nano-formulated chelators or multifunctional platforms incorporating both chelation and antioxidant properties [144][146] is another promising issue for overcoming current pharmacokinetic limitations [145]. These systems could enable organ-targeted therapy and improve treatment outcomes [147]. For this, further elucidation of REE toxicokinetics, tissue distribution, and molecular targets [28][34], particularly those affecting mitochondrial bioenergetics [48], redox balance [43], and endocrine regulation [50][52], is essential. Comparative studies among different REE and across exposure routes will aid in refining treatment strategies [28][64].

On the other hand, it is very important that national and international regulatory organizations define acceptable REE exposure thresholds for occupational, environmental, and medical contexts [18][40], based on current toxicological evidence [30][34]. Given the global nature of REE production and application [11] [17], harmonization of safety standards, environmental monitoring practices [20], and treatment protocols is basic to ensure equitable health protection across regions [37].

Future investigations should focus on the critical need for studies examining concentrations and dosages involved in REE toxicity, including ambient levels, no-effect levels, daily intakes, and hormetic responses. The lack of comprehensive dose-response data represents a fundamental gap in our understanding of REE risk assessment. Finally, it is important to note that from soil chemistry perspectives, REE complexation with humics involves -OH and -COOH groups but never -SH groups. This has important implications for chelation therapy design, suggesting that fluoride-based approaches and antioxidant supports be more promising than sulfhydryl-containing detoxifying agents.

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Conflicts of interests

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