Environmental Health

REVIEW

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Adverse effects and underlying mechanism of rare earth elements

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Abstract

Background Rare earth elements (REEs) have found broad application in a range of industries, including electronics, automotive, agriculture, and healthcare. However, their widespread utilization and release into the environment pose potential risks of human exposure. Despite extensive research on REEs toxicity, the relationship between exposure and subsequent health concerns remains ambiguous. Given that the biological effects of REEs can vary based on their design and application, assessing their toxicity can be highly challenging.

Objective This review is to offer a thorough comprehension of REEs' application and toxicity, guiding future research and policy-making to safeguard public health and environmental integrity.

Methods A systematic search across PubMed, Web of Science, Cochrane Library, and Embase was conducted using the terms: ("rare earth" OR "lanthanoid") AND ("health hazard" OR "toxic" OR "adverse health effect"). From 5,924 initial records, 89 studies were selected through deduplication and two-stage screening to assess systemic toxicity of REEs. An additional 100 articles on REEs mechanisms and applications were incorporated via citation tracking. All selections followed PRISMA guidelines with dual-author verification to ensure rigor.

Conclusion The review emphasizes REEs' applications in various domains and documents potential environmental pathways. Furthermore, it elaborates on current processes to assess REEs-related toxicity across different model organisms and cell lines, estimating health threats posed by REEs exposure. Finally, based on the findings of both in vivo and in vitro experiments, the potential toxic mechanisms of REEs are detailed. To guide future research and policy development to safeguard public health and environmental integrity.

Keywords REEs, Applications, Systemic damage, Mechanism of toxicity

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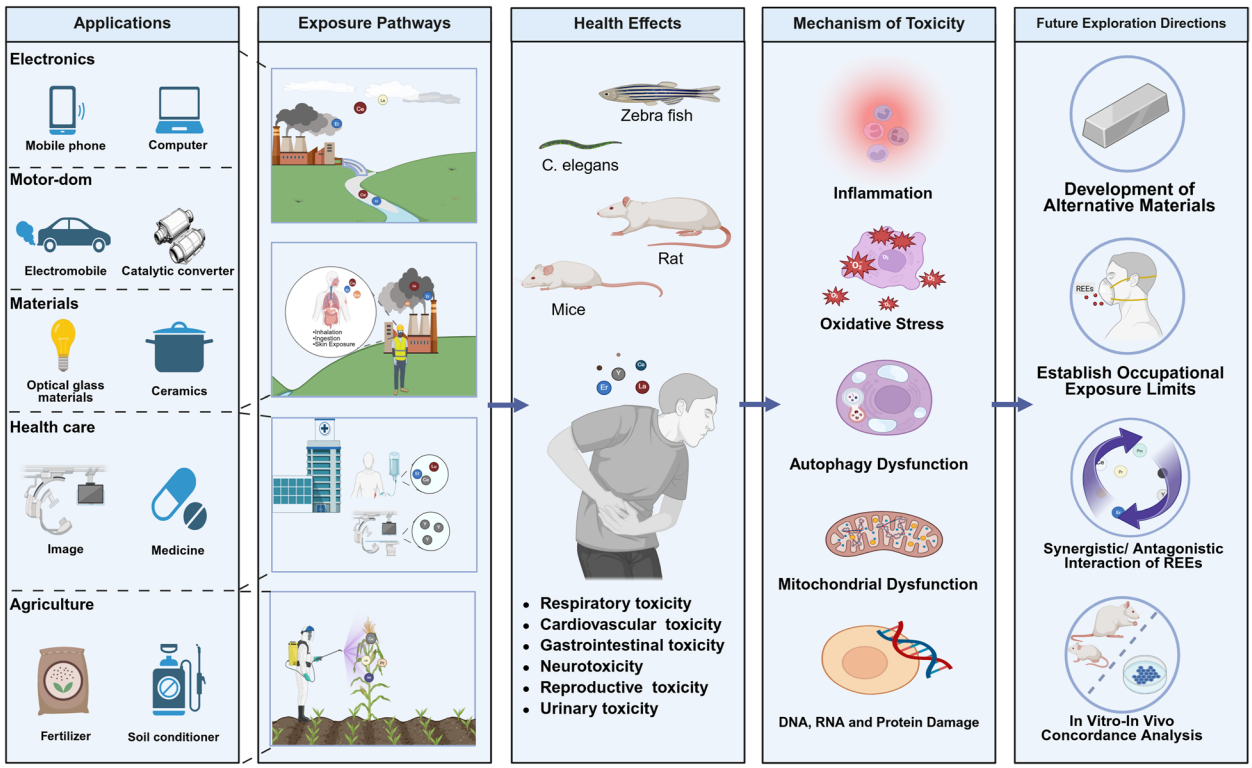
Graphical Abstract



Introduction

REEs comprise the 15 lanthanides (atomic numbers 57–71), scandium (Sc, atomic number 21), and yttrium (Y, atomic number 39), due to their co-occurrence and similar chemical properties Connelly [37] (Table S1). These elements are subdivided into light rare earth elements (LREEs) and heavy rare earth elements (HREEs) based on distinctions in ionic radius, electron configuration, and coordination chemistry [60]. Major REEs mining regions around the world include the Bayan Obo mine in China, the Mountain Pass mine in the United States, the Mount Weld mine in Australia, and REEs resources in eastern Canada [114]. The proven reserves of REEs resources are 43.5 million tons, Bayan Obo mining area accounts for 83.7% of the national total and 37.8% of the global total (G). Currently, China contributes to over 60% of the world's total output [142, 146]. The REEs are categorized into light and heavy types based on atomic electron configuration and are primarily found in minerals such as phosphates, silicates, carbonates, oxides, and halides [45, 148]. Light REEs oxides and chlorides are pivotal in catalysis and coordination chemistry, utilized notably in hybrid car battery production, petroleum refining, and water treatment [100], while heavy REEs oxides and chlorides are vital for magnetic materials and high-temperature superconductors [19]. Nano oxides derived from REEs have applications in catalysis, sensing, and biomedical imaging [10]. These diverse applications drive the continuous growth in the market demand for REEs.

REEs demonstrate long-lasting presence in the human body even years after being exposed to them in a work environment [94]. As far back as 1965, Haley provided detailed insights into the pharmacological and toxicological properties of REEs [63]. The REEs can enter the human body through ingestion, inhalation, or intravenous injection, as seen in the use of pharmaceuticals and food products [82, 104]. Additionally, during the production, manufacturing, usage, fertilizers, livestock feeds, or disposal of REEs containing materials, these elements can be released into the environment through waste management processes, sewage treatment plants, and recycling systems [61, 150]. This leads to their eventual dissemination into air, soil, surface water, and sediments, posing exposure risks to humans [123, 124, 130]. Observational studies have found that workers inhaling REEs

particles are more susceptible to acquiring respiratory illnesses, such as airway inflammation and fibrosis [25, 69]. Similarly, Wingard et al. report that Cerium oxide nanoparticles (CeO_2 NPs) activate mast cells, causing lung inflammation, decreased vascular relaxation, and enhanced cardiac ischemia/reperfusion damage [158]. Huang et al. reported that children living near REEs mining areas had increased levels of lead and REEs in their hair, correlating with a higher percentage of abnormal IQs [76]. REEs have been identified in many human samples, including hair, nails, urine, blood, semen, breast milk, and tissues, raising concerns about their pollution and bioaccumulation [29, 128, 182]. The US Environmental Protection Agency classifies REEs as emerging contaminants present in trace amounts [145].

According to earlier research, modest doses of REEs can have beneficial impacts on animals and plants, whereas long-term consumption of REE-contaminated food may lead to chronic poisoning, involving hormonal imbalances, carcinogenic consequences, and neurological damage [81, 189]. In contrast, Xu et al. found that early pregnancy exposure to lower levels of REEs combination was related to a higher likelihood of gestational diabetes [170]. Therefore, it is necessary to conduct long-term assessments of the health status of residents in areas with high concentrations of REEs. In recent years, numerous studies have demonstrated the toxic effects of REEs on various biological systems, encompassing the respiratory [110, 118, 126], cardiovascular [9, 51, 58], hepatic [6, 21, 109], neurological (Fig. 4a) [54], immune [155], and reproductive systems [22, 125, 129]. However, the toxicological evaluation of REEs lags significantly behind the rapidly developing rare earth field and the expanding market demand. Based on current laboratory research evidence, the health damage caused by REEs may be attributed to the migration of REEs into the systemic circulation, or secondary organ changes induced by inflammation, oxidative stress, or other factors following local tissue damage [123, 124]. Despite extensive research, current literature reveals considerable inter-study variability and contradictory findings, leaving the toxicological mechanisms inadequately understood.

Therefore, the review delves into understanding the applications, toxicity, and mechanisms of REEs. A literature search on October 30, 2023, across PubMed, Web of Science, Cochrane Library, and Embase retrieved a total of 2764, 3033, 3, and 124 articles, respectively. Search terms include: 'rare earth', 'rare earth elements', 'rare earth oxides', 'rare earth metals', 'earth metals', 'health damaged degree', 'health hazard', 'adverse health effects', 'health risks', 'health harmful'. Combine search terms using Boolean logical operators (AND, OR). We included articles related to rare earths and health damage, screened titles and abstracts to determine relevance, and duplicated articles, reviews without original data, and studies not related to REEs were excluded. We added a flowchart to illustrate the article selection process (Fig. 1). We provide detailed analysis of the toxic effects of REEs on humans, aiming to identify limitations and suggest new research directions. Additionally, we explore the release pathways and human risks of REEs, analyzing their toxicity through evidence from in vivo and in vitro experiments. By integrating these insights, we aim to comprehensively understand the applications and environmental consequences of REEs while identifying research gaps and hazards.

Applications

REEs have been in high demand across various industries, including electronics, military, energy, and other high-technology sectors, due to their low melting point and ductility [36, 105]. The following sections will detail the specific applications of REEs in traditional materials, new materials, agriculture, and medicine (Fig. 2).

Traditional materials

REEs are increasingly crucial in traditional materials due to advanced technologies (Fig. 2a). They enhance physical properties when added to aluminum, steel, and other metals, and serve as crucial catalysts in the petroleum industry and air pollution control [27]. Additionally, rare earth glass ceramics are foundational in industry and daily life, such as CeO_2 used in cathode ray tube (CRT) glass to reduce electron emission browning and as a glass polishing compound [70]. However, rising REEs demand raises environmental concerns, with increased risks of these elements entering freshwater and marine environments [143]. Bau and Dulski [12] and studies by Khan et al. reported elevated REEs levels in aquatic environments [12, 86]. In spite of REEs contamination, heavy metal and U pollution are severe consequences of REEs mining and processing [66]. The mining process necessary for REEs has also had a negative impact on human well-being and ecosystems, resulting in geological challenges such as soil degradation, disruptions of geological structures, and alterations of hydrogeological systems [16]. Implementing effective REEs recycling and recovery techniques can reduce the ecological impact of mining and promote energy reuse, making the advancement of recovery technologies highly urgent.

New materials

Advancements in technology have significantly expanded the applications of REEs in new materials (Fig. 2b), making them indispensable in high-tech fields, particularly in the production of permanent magnets [74].

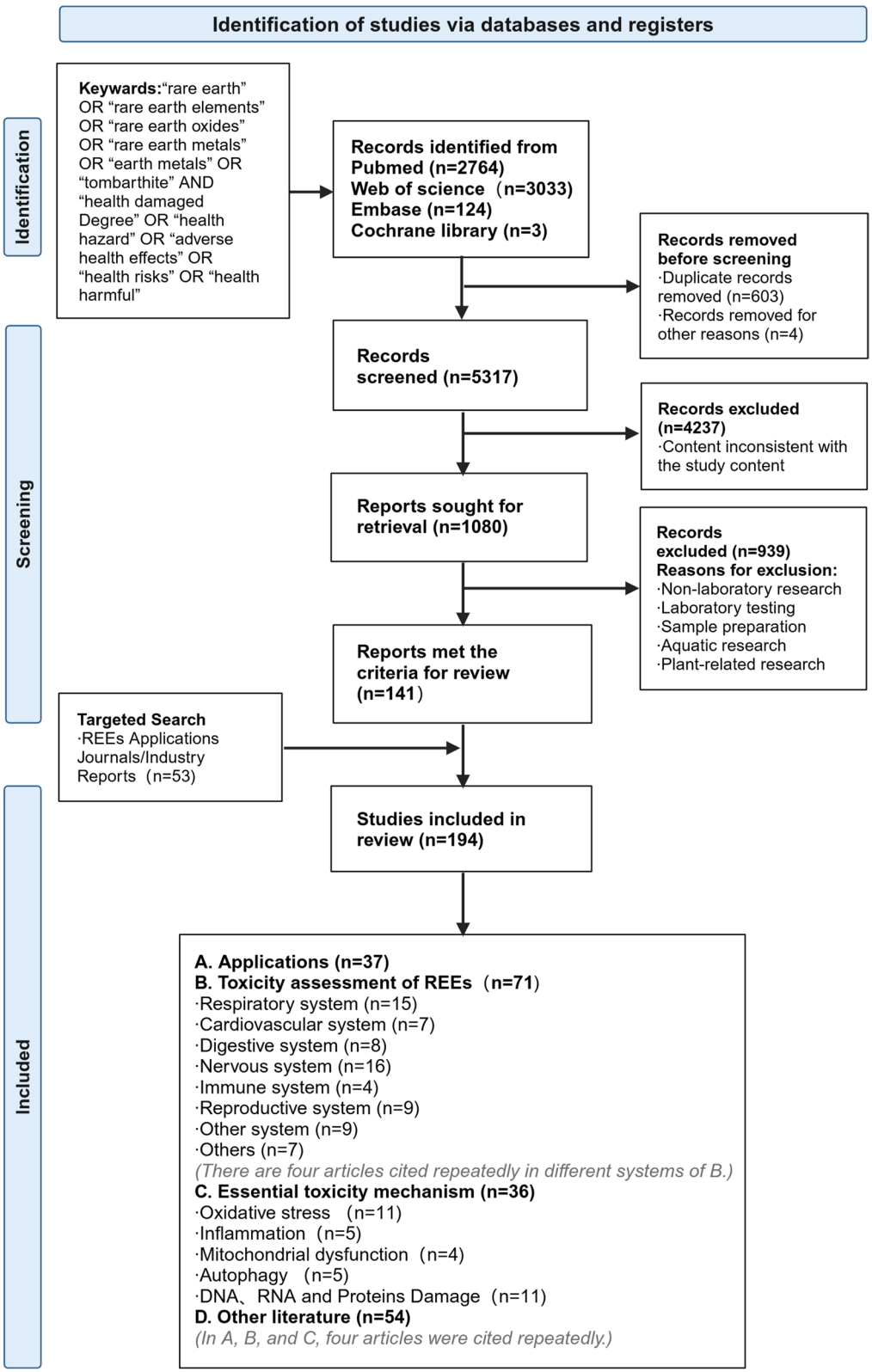


Fig. 1 Article screening process for scoping reviews. Created with BioRender.com

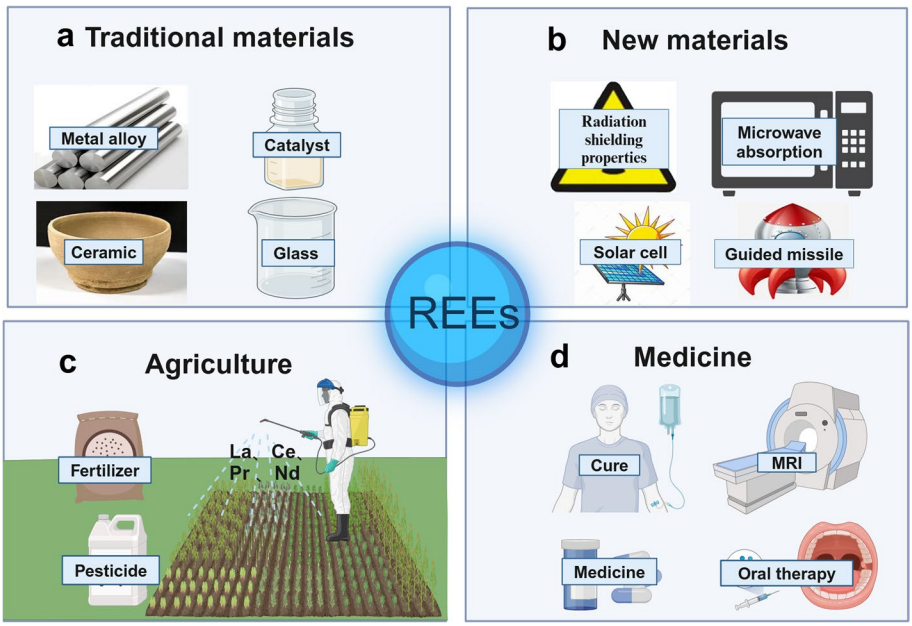


Fig. 2 The application of REEs. **a** REEs in traditional materials. **b** REEs in new materials. **c** REEs in agriculture. **d** REEs in medicine. Created with BioRender.com

Neodymium-iron-boron magnets are crucial for military weapons systems, while samarium-cobalt magnets excel in high-temperature applications such as precision-guided missiles and smart bombs [89]. Superconducting materials made from barium base oxide modified by barium yttrium copper oxygen elements, marking a breakthrough in the development of superconducting materials [175]. Catalysis, energy materials, environmental pigments, thermoelectric materials, analytical instruments, optical materials, and magnetic materials are among the applications of rare earth sulfides [95, 169, 181]. Rare earth compounds function as corrosion inhibitors for aluminium alloys, providing significant protection and meeting military standards. Rare earth tantalates offer thermal and oxidative protection for high-temperature components in aero-engines and gas turbines. Rare earth fluorides are used in arc carbon for lighting purposes [122, 152]. Azimi et al. demonstrate that these rare earth fluoride can also be added to arc carbon as a wick, which was employed for a diverse array of illumination purposes [4]. The quick use of REEs in new materials has resulted in an increased exposure to these elements, necessitating careful consideration of their benefits and potential risks.

Agriculture

The impact of REEs in agriculture has increased substantially over the past few decades, primarily due to the use of REEs-based fertilizers to enhance crop growth and yield (Fig. 2c). The chemical characteristics of REEs are similar to those of Ca due to their similar ionic radius. For example, the addition of La could alleviate the symptoms of Ca deficiency in plants [61]. Moreover, REEs regulate plant growth and development in a dose-dependent manner. However, the long-term application of REEs-rich fertilizers and extractive mining activities release significant amounts of these elements into the environment [42]. Studies have shown that after applying rare earth fertilizers to maize, except for Sc and Lu, all other REEs demonstrated significant cumulative effects in maize roots within ten days [171]. Specifically, low concentrations of La slightly increased root and shoot biomass, but excessive La concentrations negatively affected cell division, Deoxyribonucleic acid (DNA) structure and nutrient absorption, causing toxicity symptoms [40]. For example, high La concentrations inhibited the growth of soybeans [48]. Furthermore, vegetables can accumulate REEs from the soil, and the potential toxicity of this accumulation remains unclear [13]. Given the increasing use of REEs in agriculture, it is crucial to conduct further research and monitoring to understand their long-term effects on both plant health and food safety.

Medicine

REEs have widespread applications in the medical field (Fig. 2d), including biomolecular detection, imaging, oxidant detection, and as contrast agents in magnetic resonance imaging (MRI) [17, 156]. For instance, CeO_2 NPs

are used to develop fluorescent nano biosensors for rapid DNA methylation detection [3]. These nanoparticles possess antioxidant, antibacterial, anti-inflammatory, anticancer, and biocompatibility properties [8, 30, 156], and are widely applied in dental adhesives, caries prevention, and implant coatings [2, 49, 55]. They also show potential in treating cancer, eye diseases, neurodegenerative diseases, ischemic cardiomyopathy, and diabetes [121], yet their safety remains uncertain (S [80]). Gd^{3+} is crucial in medical applications, especially for light therapy in cancer treatment, where it reduces cell proliferation and induces apoptosis [144]. However, its salt form has been shown toxic in animal studies since the 1960s [38], primarily accumulating in the kidneys, skin, liver, lungs, spleen, femoral muscle, diaphragm, and heart [133]. In conclusion, while REEs offer significant medical benefits, it is vital to continue researching and monitoring their potential human toxicity.

Biological distribution of REEs

REEs can penetrate the body through multiple routes, including respiratory inhalation, digestive ingestion, and dermal contact [104, 116, 151]. The biological distribution of REEs is greatly influenced by the mode of entry, inhalation through the respiratory or dietary tract is the common route of exposure [66, 190]. For example, the daily REEs intake through inhalation ranged from 5.09×10^{-7} to 2.25×10^{-5} mg/kg/day in Baotou [96]. Inhaled REEs penetrate the alveolar epithelium, breach the alveolar air-blood barrier in the lungs, and then circulate throughout the body, reaching extra-pulmonary organs such as the heart, liver, and kidneys [123, 124]. REEs can also penetrate the human body through the food chain, as they are used as feed additives, pesticides, herbicides, and fertilizers [1]. REEs can enter the cell cytosol through various mechanisms, potentially altering the cell membrane structure and permeability upon binding [162]. Long-term exposure to low levels of REEs may affect blood pressure, blood cells, neural reflexes, and bone quality [178, 179]. Some REEs exhibit a propensity to accumulate within human bones and teeth, posing challenges in terms of excretion and potentially affecting bone health [18, 44]. In summary, the distribution and bioaccumulation of REEs can negatively impact multiple human health systems, especially with long-term exposure.

Toxicity assessment of REEs

In recent years, various model organisms have been used to study the toxic effects of REEs. For instance, research using sea urchins has demonstrated that REEs affect fertilization, embryonic development, skeletal formation, and the regulation of gene expression during embryogenesis [115]. Studies show that Ce exposure in Lake Taihu increases microcystin pollution by enhancing endocytosis in M. aeruginosa [174]. Research on zebrafish embryos has shown that exposure to high concentrations (0.46 to 1000 mg/L) of REEs such as La and Pr leads to increased DNA damage and apoptotic activity [186]. These findings highlight the developmental risks that REEs pose to aquatic ecosystems. In ecotoxicology, Caenorhabditis elegans (C. elegans) is a canonical model organism that demonstrates how REEs exposure can induce neural damage, inhibit body length, and reduce movement frequency [168]. Additionally, rodent studies provide further insights, showing detailed physiological impacts of REEs exposure. For example, He et al. reported that water contaminated with REEs such as Sc may cause significant DNA genetic damage in rats [68]. Furthermore, human health studies have indicated potential risks associated with environmental exposure to REEs, particularly in areas with elevated levels of these elements, which have been linked to abnormal blood biochemical indicators or fetal neural tube defects [157, 180]. This section summarizes the most widely available evidence regarding the health effects of REEs on various systems or organs (Fig. 3).

Respiratory system

In vitro models

Alveolar macrophages are primarily responsible for creating pro-inflammatory mediators and are considered one of the primary lines of protection against ingested particles [83]. Palmer et al. conducted a study using rat pulmonary alveolar macrophages to reveal the potential impacts of different REEs, such as $LaCl_3$, $CeCl_3$, and Nd_2O_3, on lung tissue. The results indicated that these REEs fumes are cytotoxic, with $LaCl_3$ (LC50 = 52 μM), $CeCl_3$ (LC50 = 29 μM), and Nd_2O_3 (LC50 = 101 μM) showing significant cytotoxicity. This suggests that these fumes could potentially be fibrogenic [125]. Similarly, Huang et al. revealed that exposure to Nd_2O_3 can cause cell damage and enhance the synthesis and release of inflammatory chemokines through experiments on rat NR8383 alveolar macrophages [77]. Furthermore, Verstraelen et al. conducted a study on the exposure of Cobalt Oxid Nanoparticles (CoO NPs) and CeO2 NPs to alveolar A549 and bronchial BEAS- 2B epithelial cells. They found that CoO NPs and CeO_2 NPs primarily induced downregulation of gene transcription, with BEAS- 2B cells being more delicate [149].

In vivo models

Haley et al. demonstrated that REEs inhalation can lead to pulmonary toxicity, with the severity of effects influenced by factors such as particle size, duration, and

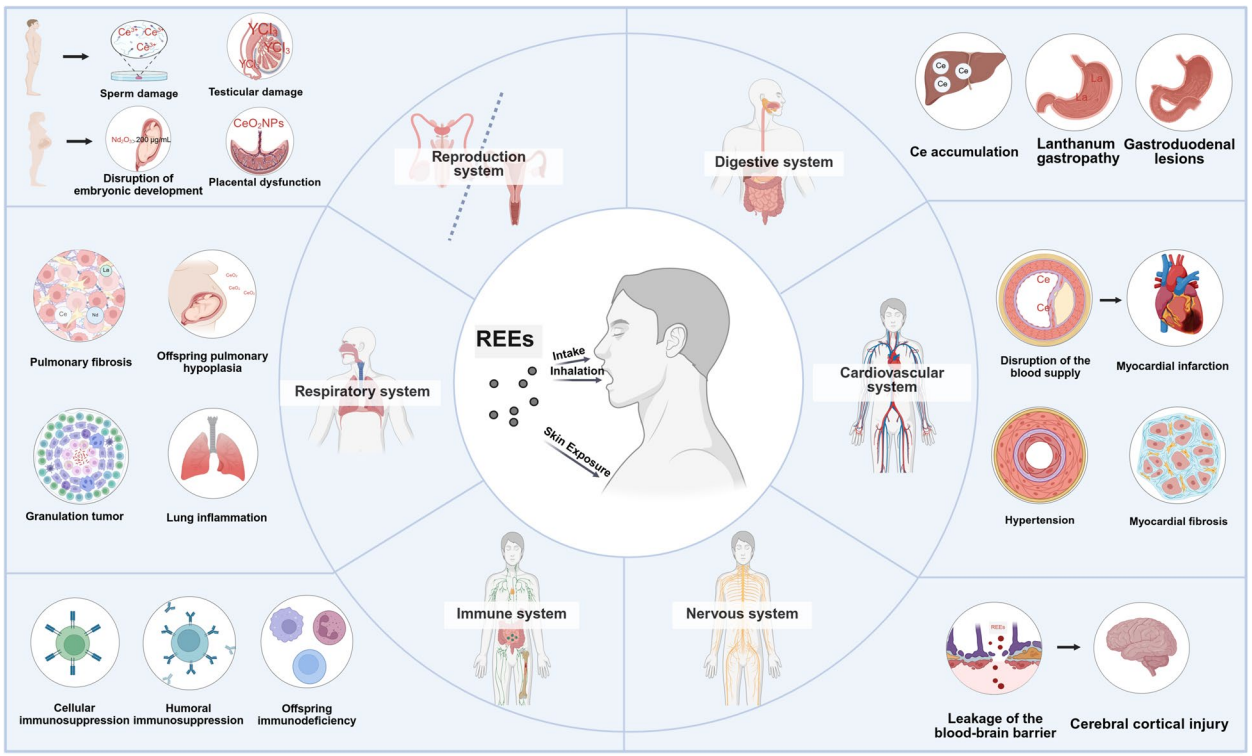


Fig. 3 Potential health risks associated with REEs exposure. The diagram illustrates the adverse effects of REEs on various organs and tissues, as observed in numerous laboratory studies. Created with BioRender.com

dose of exposure [62, 88]. Huang's study observed size-dependent toxic effects of REEs, finding that smaller CeO_2 NPs (23 nm) significantly induced more acute pro-inflammatory lung responses in mice compared to larger CeO_2 particles (88 nm) [77]. Besides, Sisler et al. demonstrate that there are indeed differences in the lung responses to CoO (72 nm) and lanthanum oxide nanoparticles (La_2O_3 NPs) (25 nm) in the induction of acute vs. long-time pulmonary responses [138]. Such discrepancies reflect unfavourable outcome pathways for these compounds [120]. Shin et al. conducted a study in which male rats were exposed to La_2O_3 and observed La_2O_3 deposition in lung tissue, alveolar proteinosis, lung inflammation, and increased total cell counts, suggesting that the target organ of lanthanum was the lung [137]. Furthermore, Ahmad et al. reported that Nd_2O_3 exhibit the capability to A549 cancer cell death via Reactive Oxygen Species (ROS) generation and genotoxicity study pathways [5]. Wu et al. reported that long-term gavage exposure to $Ce(NO_3)_3$ could induce the incidence of foreign body granulomatous lesions in the lungs, which may also contribute to the development of fibrosis in multiple organs [160, 161]. At the same time, the findings of Schwotzer et al. also emphasized the potential long-term health effects of CeO_2 NPs, indicating the need for further research on nanoparticle risk assessment and the establishment of safety thresholds [135]. Keller et al. exposed rats to CeO_2 NPs at concentrations of 0.5, 5, and 25 mg/m^3 for 1 or 4 weeks, with observations at 24 or 129 days post-exposure. They found that higher concentrations impaired lung clearance, leading to prolonged retention and an inflammatory response whose severity was linked to the duration and dose of exposure [85]. Solid evidence has confirmed that CeO_2 exposure is associated with pulmonary phospholipid deposition, fibrosis, and sustained inflammatory responses, with the severity of inflammation in the lung tissue increasing with both the duration and concentration of exposure [59, 111]. Given that the respiratory tract is likely the primary route of human exposure to REEs, it is crucial to pay close attention to the potential lung diseases induced by REEs (Fig. 4a).

Cardiovascular system

In vitro models

Because of their minuscule size, the largest numbers of REEs NPs have the capability to penetrate the air-blood barrier and travel through the bloodstream. Throughout this process, they unavoidably interact with the vasculature and eventually reach the heart. Xiong et al.

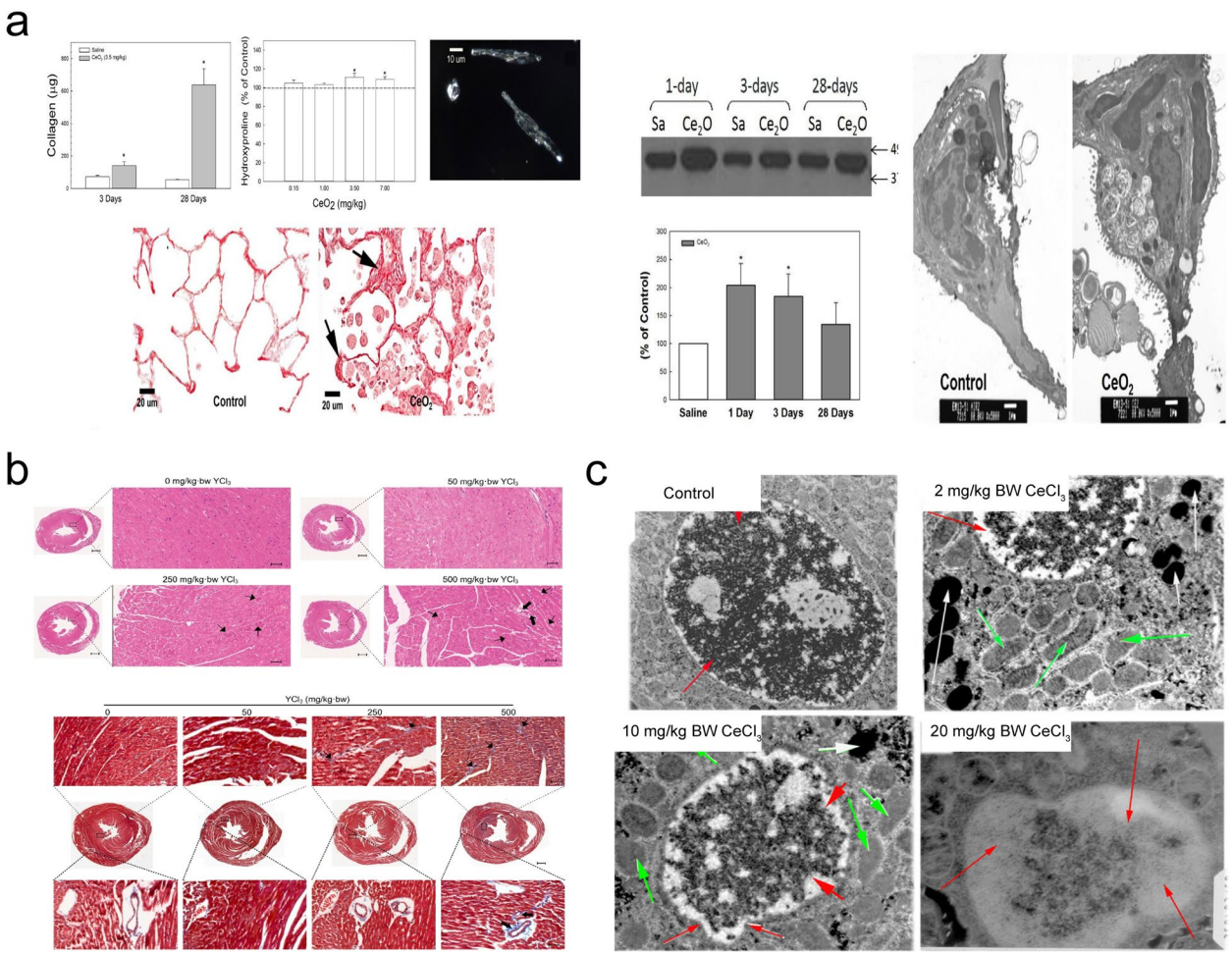


Fig. 4 REEs induced adverse effects on the respiratory, cardiovascular, and digestive systems. **a** Cerium oxide (CeO_2) exposure induced pulmonary fibrosis. Reprint from ref [110], reproduced under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/). **b** Cardiovascular damage induced by YCl_3 exposure. The images illustrate significant myocardial hypertrophy, necrosis, and fibrosis in left ventricular tissue across different YCl_3 doses, highlighting the dose-dependent progression of cardiac injury. Reprint from ref [166]. **c** Ultrastructural changes in mouse liver after 60 days of $CeCl_3$ exposure. The TEM images reveal dose-dependent liver damage, including nuclear chromatin condensation, mitochondrial swelling, cytoplasmic lipid droplets, and nuclear vacuolization, highlighting progressive hepatic injury across varying $CeCl_3$ doses. Reprint from ref [183]

conducted experiments to assess the cytotoxicity of YCl_3 on rat H9c2 cardiomyocytes across various concentrations. Their findings revealed that exposure to YCl_3 resulted in DNA damage mediated by ROS and a notable increase in gamma-H2ax levels [165]. Gojova et al. reported that Y_2O_3 particles are taken up by aortic endothelial cells and enter vesicles, leading to a significant inflammatory response [57]. Moreover, Zhao et al. reported that $LaCl_3$ inhibits calcium deposition in vascular smooth muscle cells at low concentrations but promotes calcium deposition and induces apoptosis at high concentrations, which suggests that the use of $LaCl_3$ may carry a risk of toxic effects on vascular health [183, 185]. Kuruvilla et al. proved through in vitro cell experiments that Ce directly stimulated subendocardial fibroblasts could cause cardiac lesions in endocardial myocardial fibrosis [90]. While these studies reveal REEs'cardiovascular toxicity, further research is needed on interactions between different REEs, as well as protective strategies due to their persistence.

In vivo models

The cardiovascular effects of REEs have also been demonstrated in vivo studies (Fig. 4b). Minarchick et al. investigated the impact of pulmonary CeO_2 NPs exposure on microvascular function using isolated mesenteric and coronary arteries. They found that CeO_2 NPs impair endothelium-dependent and independent arteriolar

dilation in a dose-dependent manner, with mesenteric microvessels being more sensitive than coronary arteries. These changes may contribute to cardiovascular dysfunction and increased mean arterial pressure in some groups [119]. Besides, Zhao et al. proved that REEs have detrimental effects on the swimming action and cardiac morphology of zebrafish, particularly in the case of La and Pr, where cardiac hypertrophy and myocardial contraction are two critical toxic pathways [186]. Chen et al. reported that neodymium sesquioxide (Nd_2O_3 NPs) disrupt early development in zebrafish embryos, leading to increased mortality, malformations, heart arrhythmias and elevated apoptosis [31]. Given the evidence from these studies, conducting long-term studies to assess the chronic effects of REEs exposure on cardiovascular health, which are currently underexplored, is crucial.

Digestive system

Studies have shown that REEs can enter the body through the digestive tract and have toxic effects on the digestive system, particularly on liver function (Fig. 4c). Subacute exposure to $CeCl_3$ was reported to induce liver apoptosis and alter the expression levels of genes related to metal detoxification, metabolism regulation, and radical scavenging in mice (Fig. 4b) [183, 185]. Marzi et al. demonstrated that, compared to short-term exposure, which showed minimal toxicity, long-time exposure to CeO_2 NPs led to significant toxicity in various cell lines, with HepG2 cells being especially sensitive [39]. Moreover, Cheng et al. found that long-term exposure to $CeCl_3$ can lead to Ce accumulation, liver inflammation, and hepatocyte necrosis, along with significant alterations in gene expression profiles related to immune response, apoptosis, and metabolic processes in the liver [33, 34]. In vivo models further investigated REEs'impact, showing irreversible accumulation of La, Ce, Pd, Nd, and Gd in the liver of SD rats, underscoring the liver as a critical organ affected by these elements [21]. For example, administration of $Pr(NO_3)_3$ to rats resulted in fatty liver [92]. Acute toxic effects of La on the gills and liver of the Gobiocypris rarus [75]. Furthermore, La deposition in the upper gastrointestinal tract was associated with clinical symptoms such as dysphagia, nausea, vomiting, and reflux, long-term La carbonate administration can lead to multiple forms of gastroduodenal lesions [67]. Intriguingly, Yabuki et al. revealed that oral administration of $LaCl_3$ (1000 mg/day) for more than 2 weeks in rats caused La deposition in the gastric mucosa and led to histological changes, including glandular atrophy, fibrosis, mucous neck cell hyperplasia, and ulcers [172]. These findings collectively underscore the significant impact of REEs on the digestive system, particularly on liver function, necessitating further research into their toxicological effects and mechanisms. (Table 1).

Nervous system

In vitro models

REEs are known to exert neurotoxic effects, impacting neuronal function and health through various mechanisms elucidated in vitro models (Fig. 5a). Gao et al. investigated the neurotoxic effects of $LaCl_3$ in vitro, revealing that it induces autophagy by inhibiting the Akt/mTOR signalling pathway and activating the AMPK/mTOR signalling pathway [54]. Moreover, $LaCl_3$ decreased the expression of VAPB-PTPP51, BAP 31-FIS 1, and MFN2-MFN1, resulting in abnormal cultured rat cortical neurons and neuronal damage [103]. Ariyani et al. recently found that gadolinium-based contrast agents (GBCAs) enhance astrocyte migration and adhesion by activating integrin αvβ3 and related signalling pathways, which may adversely affect brain development with repeated use [7]. Meanwhile, similar results were also confirmed by Sun et al., who reported that $LaCl_3$ inhibits lactate production and transport in astrocytes, leading to learning and memory impairment, which may be related to disruptions in lactate metabolism [141].

In vivo models

In vivo studies have shed light on the neurotoxic insults and behavioral deficits induced by REEs exposure (Table 2). Notably, chronic exposure to La may compromise learning, potentially because of disturbances in trace elements, enzymes, and neurotransmitter systems in the brain [46]. La exposure causes neurotoxic insults and behavioural deficits in C. elegans. La $(NO_3)_3\ 6H_2O$ inhibits C. elegans growth, and also inhibits or activates neurotransmitter transporters and receptors (glutamate, serotonin, and dopamine) that regulate behavioral and motor function. In addition, ROS was significantly increased in stage L4 C. elegans exposed to La [64]. In rats, La exposure leads to excessive oxidative stress in hippocampal neurons, resulting in elevated ROS levels and increased transcription of autophagy-related genes through the JNK/c-jun and JNK/FoxOs signalling pathways [53]. Furthermore, research find that $LaCl_3$ administration has been found to alter TP activity and cause partial brain cell damage in Wistar rats, along with reductions in the expression levels of pCaMK IV, pMAPK, pCREB, c-fos, and egr1 in the hippocampus, potentially impairing offspring memory [173]. Moreover, adult rats exposed to La after weaning exhibit reduced plasma neurotransmitter levels of acetylcholine and norepinephrine, as well as decreased neuron numbers in the CA1 region of the hippocampus [164]. GBCAs commonly used in clinical practice, have raised concerns regarding

Table 1 Toxicological effects of REEs on respiratory, cardiovascular, and digestive systems

Organ	Element	drug delivery route	Test model	Main effects	References
Lung	$LaCl_3$、$CeCl_3$、Nd_2O_3		Male Sprague–Dawley rat	Lung fibrosis	[125]
	Nd_2O_3	Nd_2O_3 exposure on rat NR8383	Rat NR8383 alveolar macrophages	Caused cell damage and enhanced synthesis and release of inflammatory chemokines	[77]
	CeO_2 NPs	Expose	Alveolar A549 and bronchial BEAS- 2B epithelial cells	Downregulation of gene transcription	[149]
	CeO_2、TiO_2	Oropharyngeal	CD- 1 mice	Lung inflammatory	[88]
	La_2O_3	Expose nose to La_2O_3	Male rats	Alveolar protein deposition and pulmonary inflammation	[137]
	CeO_2	Endotracheal instillation	Male Sprague–Dawley rat	Lung phospholipid deposition and fibrosis	[111]
	CeO_2	Inhalation	Rat	Lung inflammation	[135]
	La_2O_3	Whole-body inhalation exposure	C57BL/6 J mice	Chronic inflammatory changes and mild fibrosis	[138]
	CeO_2	Intratracheal instillation	Male Sprague–Dawley	Lung fibrosis	[110]
	CeO_2	Intratracheal instillation	C57BL/6 J mice	Damage to lung development	[126]
Heart	YCl_3	Different concentrations of YCl_3	Rat H9c2 cardiomyocytes	DNA damage	[165]
	YCl_3	Intragastric administration	Male Kunming mice	Lipid peroxidation and inflammation in the heart	[166]
	Ce	Treated with $CeCl_3$	Wistar rat	Endomyocardial fibrosis	[90]
	CeO_2 NPs	Nose-only inhalation to CeO_2 NPs	C57BL/6 J mice, mice prone to cardiovascular disease and a mouse model of neurological disease	Cardiovascular dysfunction	[41]
	16 REEs ($LaCl_3$, $CeCl_3$, $PrCl_3$, $SmCl_3$, $TbCl_3$, $DyCl_3$, $YbCl_3$, $ScCl_3$ $NdCl_3$, $EuCl_3$, $GdCl_3$, $HoCl_3$, $ErCl_3$, $TmCl_3$, $LuCl_3$, and YCl_3)	Exposure of 16 REEs	Zebrafish embryo	Cardiac hypertrophy and myocardial contraction	[186]
Liver	CeO_2 NPs	Expose in CeO_2 NPs	A549, $CaCo_2$, and HepG2 cell lines	Toxic to all tested cell lines	[39]
	La, Ce, Pd, Nd, and Gd	Intragastric administration	SD rats	The accumulation of REEs in the liver was irreversible	[21]
	$Pr(NO_3)_3$	Intravenous injection	Female Wistar rats	Fatty livers	[92]
	$CeCl_3$	Oral administration	Male CD- 1 mice	Liver inflammation, and hepatocyte necrosis	[34]
	La	Intragastric administration	Male CD- 1 mice	Impairing liver function	[33]

their neurotoxicity. Intravenous exposure to GBCAs has been associated with neuronal tissue deposition, with elevated Gd levels observed in various brain regions and across the intact blood–brain barrier in patients with relatively normal renal function [117]. Furthermore, the neurotoxicity of REEs is closely related to their ability to penetrate the blood–brain barrier (BBB) and disrupt its integrity. Studies have shown that La and Gd can cross the BBB through multiple mechanisms, including direct penetration, diffusion via cerebrospinal fluid, and perivascular pathways along cortical arteries [127]. For example, $LaCl_3$ significantly increases BBB permeability in young rats by downregulating tight junction proteins and upregulating matrix metalloproteinase- 9 activity [160, 161].

In the C. elegans model, $La(NO_3)_3{\cdot}6H_2O$ crosses the BBB-like barrier and induces motor and behavioral deficits by degenerating dopaminergic and GABAergic neurons, promoting abnormal alpha-synuclein

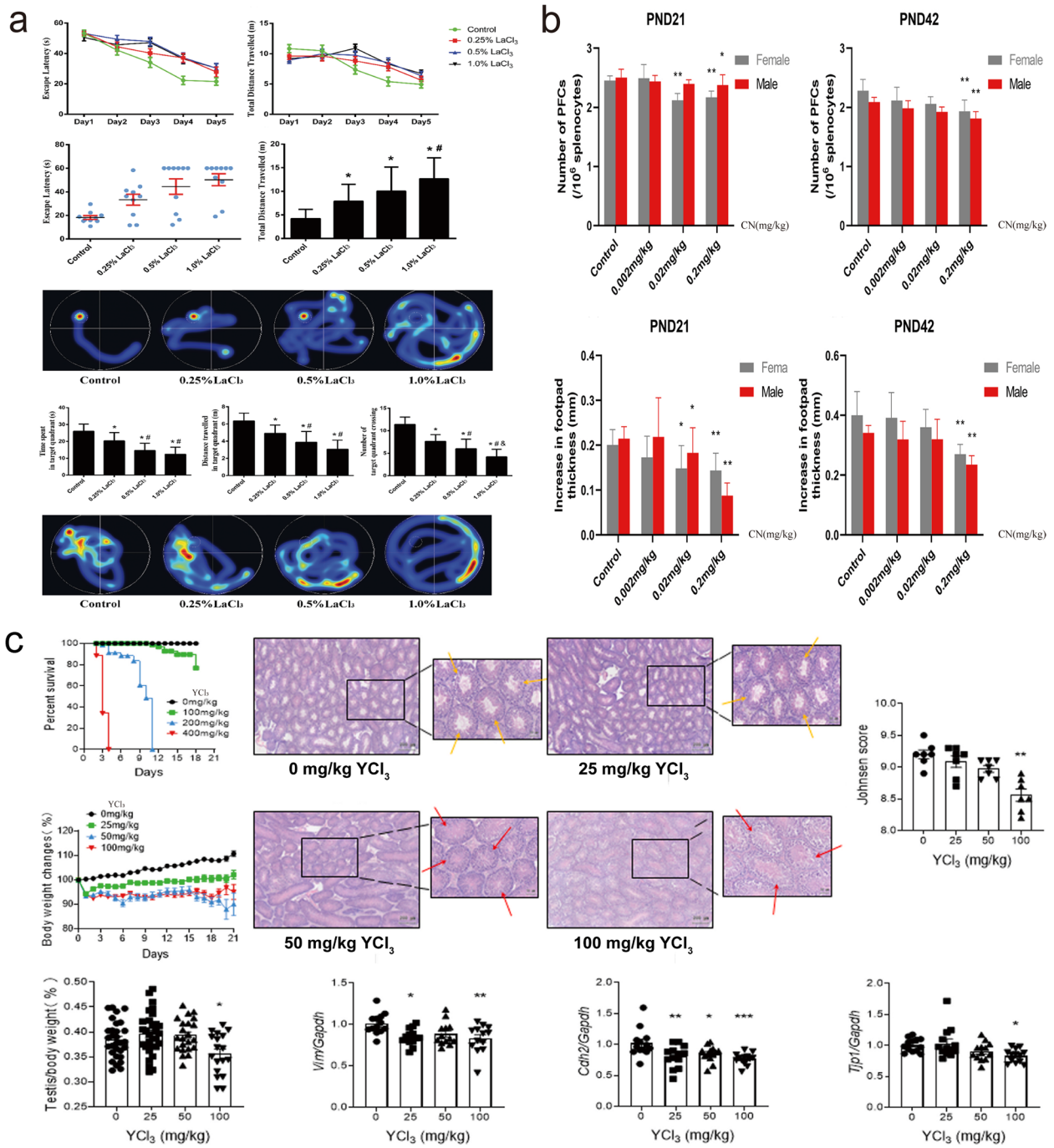


Fig. 5 REEs have adverse effects on the nervous system, immune system, and reproductive system. **a** The effects of $LaCl_3$ on spatial learning and memory in rats. The graphs show escape latency and total distance traveled over the first five training days, indicating a dose-dependent decline in cognitive performance with increasing $LaCl_3$ concentrations [53]. Reproduced under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/). **b** Cerium nitrate (CN) exposure induces immunotoxicity in BALB/c mouse offspring. As evidenced by changes in PFC numbers and increased footpad thickness on PND 21 and PND 42. Bar graphs show mean ± SD (n = 10), with significant differences from the control group indicated. Reprint from ref [56]. **c** YCl_3 exhibits toxic effects on the testes of adult male mice. Reduced survival rates, weight loss, decreased testes-to-body weight ratios, and histopathological changes, including impaired varicocele function, lower sperm counts, and alterations in the expression of genes related to the blood-testes barrier, clearly demonstrate this toxicity. Reprinted from ref [73]

Table 2 Damaging effects of REEs on nervous, immune and reproductive systems

Organ	Element	drug delivery route	Test model	Main effects	References
Brain	La	$LaCl_3$ treatment	Wistar rats	Increase in key proteins associated with autophagy	[54]
	$LaCl_3$	Expose to $LaCl_3$ via the maternal placenta	Female Wistar rats	Neuronal damage	[103]
	Gd	Expose in GBCA	Astrocyte -enriched cultures of the cerebral cortex、C6 clonal cells and U87MG clonal cells	Migration of astrocytes	[7]
	$LaCl_3$	Treated with $LaCl_3$	Primary culture of rat cortical astrocytes	La-induced learning-memory damage	[141]
	$La(NO_3)_3$·6H2O	$La(NO_3)_3$·$6H_2O$ was dissolved in K-medium	C. elegans strains	Neurotoxic insults and behavioral deficits in C. elegans	[64]
	$LaCl_3$	Maternal rats were exposed to $LaCl_3$	Male Wistar rats	Learning and memory impairment induced by $LaCl_3$ may be related to excessive autophagy	[53]
	$LaCl_3$	Exposed to $LaCl_3$ in distilled drinking water	Wistar rats	Partial brain cell damage	[173]
	$La(NO_3)_3$	Gavage	Sprague Dawley rats	Decreased neuron numbers in the CA1 region of the hippocampus	[164]
	La	Oral administration	Wistar rats	Impair the learning ability	[46]
	$LaCl_3$	Exposed to $LaCl_3$ in drinking water	Wistar rats	Blood–brain barrier leakage	[160]
Skeleton	Ln	Orally exposed	Male CD- 1 mice	Affected the cell and humoral immunity	[33]
	Ce $(NO_3)_3$	Oral gavage	BALB/C mouse	Reduces the proportion of NK cells in peripheral blood and spleen	[56]
	Gd_2O_3	Intravenous injection	Mice	Expanded populations of hematopoietic stem cells, multipotent progenitors in both the bone marrow	[52]
	$CeCl_3$	Gavage	Male CD- 1 mice	Decreases in white blood cell, lymphocyte, platelet counts, reticulum count, and neutrophil percentage	[34]
Testis、placenta and so on	Nd_2O_3	Adding the Nd_2O_3 NPs	Zebrafish	Disrupted embryo development	[31]
	Ce and Yb		7367 pregnant women from Wuhan Children's Hospital	Reduced TSH levels	[107]
	YCl_3	Intraperitoneal injection	Male C57BL/6 J mice	Induce testicular damage	[73]
	CeO_2 NPs	Tail vein	Female and male BALB/c mice	Impair placental development	[32]
	La_2O_3 NPs	Intragastric administration	Kunming mice	Apoptosis in the mice testes	[177]
	Ce^{3+}	Intragastric administration	Male Kunming mice	Risk factor for infertility or aberrations	[28]
	CeO_2 NPs	CeO_2 NPs were dissolved in dimethyl sulfoxide	Female CD- 1 mice	Negative effect on spermatogenesis and germ cell	[91]

aggregation, and disrupting neurotransmitter systems [64]. Notably, the size and surface modifications of REEs nanoparticles significantly influence their BBB penetration efficiency. Smaller nanoparticles exhibit higher BBB permeability, while targeted modifications enhance intracerebral delivery, providing insights into the neurotoxicity mechanisms of REEs nanoparticles [136]. REEs cause subclinical damage to the cerebral cortex through the blood–brain barrier [188], cause depression, anxiety behavior, memory impairment and neural tube defects [101, 157]. In summary, REEs pose multiple risks of neurotoxicity by disrupting BBB integrity, activating oxidative stress and interfering with neuronal signaling pathways, and its mechanism of action is closely related to particle physicochemical properties and targeted delivery strategies. All this evidence suggests that REEs should be a novel threat to the nervous system, which should be of great concern.

Immune system

Some research shows that REEs can damage the immune system (Fig. 5b). Cheng et al. documented that exposure to lanthanoids (Ln) impacts both cellular and humoral immunity in mice [33, 34]. Moreover, $Ce_2(NO_3)_3$ significantly inhibits the cytotoxicity of natural killer NK cells, reduces the proportion of NK cells in peripheral blood and spleen (Fig. 5b), suppresses T/B lymphocyte proliferation, and dampens humoral and cellular immune responses [56]. Exposure to $CeCl_3$ is associated with notable decreases in white blood cell, lymphocyte, platelet counts, reticulum count, and neutrophil percentage, as well as in the A/G ratio. Conversely, it leads to significant increases in alkaline phosphatase, lactate dehydrogenase, and cholinesterase activity, as well as in triglyceride and total cholesterol concentrations [33, 34]. Additionally, Gd_2O_3 increases the number of monocyte-derived macrophages and myeloid-derived dendritic cells (M-DCs) in the liver. It also induces infiltration of neutrophils, M-DCs, and B cells in the spleen. Furthermore, Gd_2O_3 leads to expanded populations of hematopoietic stem cells, multipotent progenitors, and common lymphoid progenitors in both the bone marrow and spleen [52].

Reproductive system

Numerous studies have highlighted the potential reproductive system damage associated with REEs exposure [91, 97–99]. Once these elements enter an organism, they tend to accumulate and disrupt the normal function of the reproductive system [15]. Chen et al. reported that when the concentration of Nd_2O_3 NPs exceeded 200 μg/mL, embryonic development was adversely affected [31]. Similarly, Hou et al. confirmed that YCl_3 disrupts antioxidant stress signalling pathways and, through ROS-Ca^{2+} axis activation, causes apoptosis (Fig. 5c) and autophagy in testicular cells, leading to testicular injury as well as impaired male reproductive function [73]. Additionally, research has shown that maternal exposure to CeO_2 NPs impairs placental development, resulting in placental dysfunction, fetal loss, or growth restriction, and increases the risk of spontaneous abortion [32, 187]. Animal experiments further revealed that La_2O_3 NPs could induce apoptosis by inhibiting the Nrf- 2/ARE pathway and the expression of NQO1, HO- 1, and GSH-Px. Additionally, La_2O_3 NPs altered testicular ultrastructure, inducing oxidative stress and inflammatory responses in the testes of exposed mice [177]. Excessive exposure to REEs has thus been implicated as a risk factor for infertility or developmental abnormalities [28]. In conclusion, mounting evidence suggests that REEs may adversely affect the reproductive health of both males and females, representing a significant public health concern.

Other systems

In addition to the aforementioned systemic toxicities, REEs also exert effects on various other systems. Several studies have demonstrated that REEs bind to biofilms, altering membrane structure and permeability, thereby facilitating their entry into erythrocytes [162]. For instance, $La(NO_3)_3$ inhibits lipogenesis and impacts cell proliferation in 3 T3-L1 preadipocytes [167]. Additionally, CeO_2 NPs exposure has been associated with cell transformation, and the toxicity induced by Ce exposure is linked to tumorigenesis [11]. In animal models, REEs have demonstrated mild oncogenic activity, highlighting potential carcinogenic risks [134]. Long-term environmental and occupational exposure to REEs leads to their accumulation, resulting in decreased levels of iron and Ca due to competitive binding. This phenomenon collectively induces bone metabolic disorders and subsequently reduces bone mineral density [102]. Furthermore, Lutetium- 177 shows promise in the treatment of early-stage prostate cancer but may cause myelosuppression [26]. Intravascular gadolinium-based contrast is an alternative to iodinated contrast [24]. Nephrogenic systemic fibrosis can lead to severe complications and even death, and it is associated with exposure to GBCAs used in MRI [79]. In mice with normal renal function, gadolinium contrast agents have been shown to cause metabolic disorders and kidney damage, and the damaging effects of gadolinium contrast are exacerbated by obesity [43].

Essential toxicity mechanism

REEs can permeate the human body through multiple methods, associated with a variety of diseases. By inducing oxidative stress, inflammation, autophagy dysfunction, and mitochondrial dysfunction, REEs can cause health-related issues in the human body. The fate of the cell will be determined by the interaction between these subcellular effects (Fig. 6).

Oxidative stress

The chemical properties and biological activities of REEs depend on factors such as their valence state, structure, and environmental conditions [112]. ROS overproduction and oxidative stress are acknowledged as fundamental mechanisms driving the detrimental impacts of REEs on organisms. Mechanistically, CeO_2 can inhibit ROS production and induce cell resistance to exogenous oxidative stress [163]. However, The Gd_2O_3 and CeO_2-Gd NPs were also seen to generate ROS in U- 87 MG cells after irradiation [108]. Under other conditions, REEs may interact with oxidation–reduction reaction participants, leading to the generation of oxidative damage, but the molecular mechanisms are not clear completely. REEs exhibit dual effects, possibly influenced by their

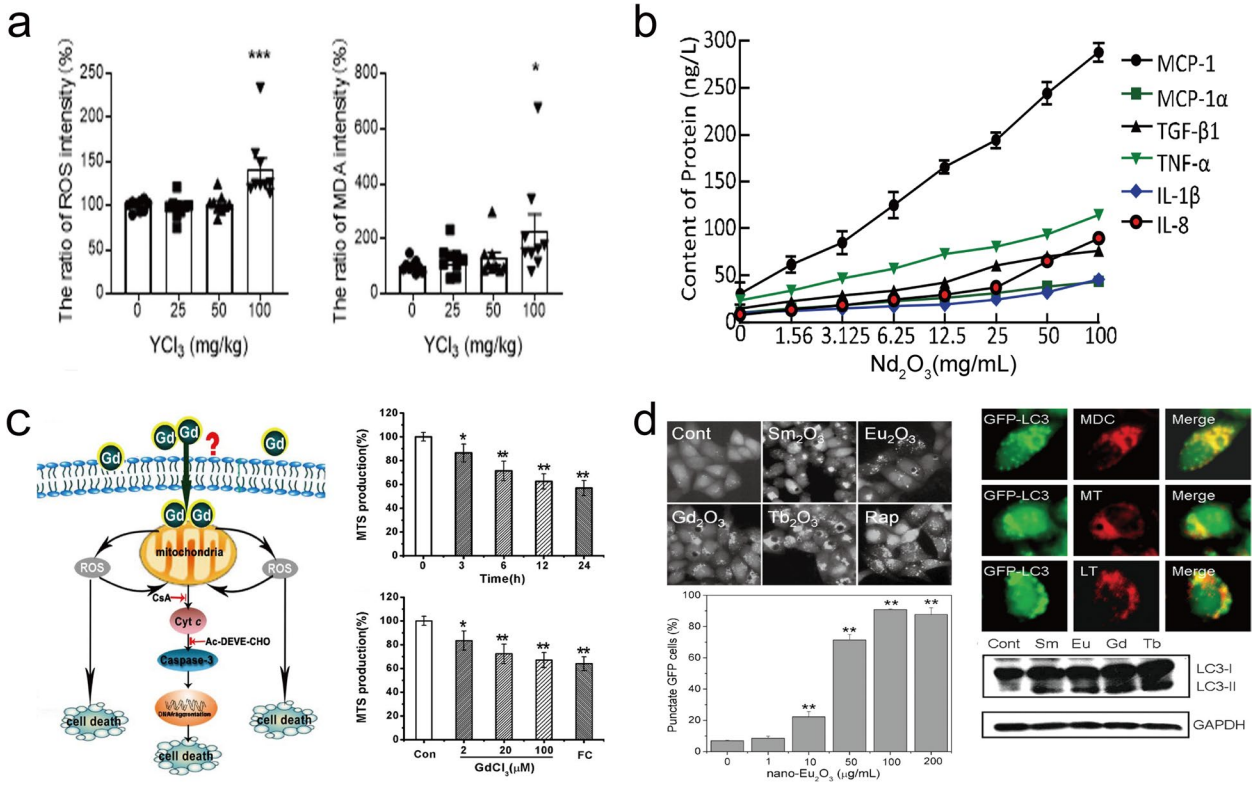


Fig. 6 The fundamental mechanisms underlying REEs-induced toxicity. **a** YCl_3 increases ROS and MDA levels in mouse testes, indicating oxidative stress. Reproduced from Hou et al. [73], reproduced under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/). **b** Nd_2O_3 elevates inflammatory cytokine levels in NR8383 cells after 24 h of treatment. Reproduced from Huang et al. [77]. **c** Gd induces neuronal apoptosis by impairing mitochondrial function. Reproduced from Feng et al. [47]. **d** Sm_2O_3, Eu_2O_3, Gd_2O_3, and Tb_2O_3 trigger autophagy in HeLa cells. Reproduced from Yu et al. [176]

concentration, morphology, and exposure duration. Li et al. demonstrated that $La(NO_3)_3$ could restore the redox homeostasis that was disrupted by ethanol by provoking the Keap 1/Nrf2/p62 signalling pathway at low concentrations [97–99]. However, at high concentrations, they may overproduce free radicals, exceeding the antioxidant capacity of cells, leading to the occurrence of oxidative damage. Khosa et al. concluded that the accumulation of La, Ce, and Nd in the nuclei and mitochondria of hepatocytes results in oxidative stress [87]. In addition, different forms of REEs (such as nanoparticles, solutions, ions, etc.) may have different effects on their actions, affecting their oxidation status on cells. Wang et al. concluded that CeO_2 NPs with a small specific surface area induced more cell apoptosis, leading to increased mitochondrial membrane potential (MMP), ROS, and glutathione (GSH). This reflects a compensatory antioxidant response, but when oxidative stress overwhelms cellular defenses, it reduces the ability to remove hydroxyl radicals, ultimately causing toxicity in human hepatocellular carcinoma cells [153].

Additionally, the dual effects of REEs may be related to cell type and physiological state. Different cell types may respond differently to REEs, and some cells may be more susceptible to their oxidative damage, while others may be more resistant. For instance, Sun et al. have concentrated on the oxidative stress induced by La in choroid plexus epithelial cells. This stress can significantly impede the normal function of the blood-cerebrospinal fluid barrier, resulting in central nervous system dysfunction [140]. Some studies suggest that $LaCl_3$ exerts oxidative stress effects on the kidney, increasing the production of ROS, increasing lipid, protein, and DNA peroxidation levels, and reducing the activity of superoxide dismutase (SOD) [184]. In mice exposed to La, Ce, and Nd, the activities of hepatic nuclear SOD and catalase (CAT) were reduced, while glutathione peroxidase (GPx), GSH, and malondialdehyde (MDA) levels were increased. Notably, mitochondrial SOD, CAT, GPx, and GSH activities in hepatocytes were significantly decreased, accompanied by a marked increase in MDA levels, suggesting that La, Ce, and Nd may penetrate hepatocytes and disrupt mitochondrial function [78]. In contrast, Leite et al.

observed that exposure to praseodymium in the mussel species Mytilus galloprovincialis increased SOD activity at lower concentrations (≤ 40 μg/L) and significantly enhanced glutathione reductase (GR) activity at the highest concentration (80 μg/L). These findings indicate that Pr, within a specific concentration range, may enhance cellular antioxidant capacity by activating antioxidant enzymes [93]. On the contrary, $La(NO_3)_3$ ameliorates atherosclerosis by regulating lipid metabolism, oxidative stress and endothelial dysfunction in mice [97–99]. Therefore, in the study of oxidative stress damage of REEs, the above factors should be comprehensively considered, and the mechanism of action should be further explored through systematic experimental design and analysis.

Inflammation

REEs NPs exposure can additionally stimulate inflammatory responses in target organs. When macrophages are exposed to intratracheal instillation, they can cause inflammation and produce pro-inflammatory cytokines, chemokines, and growth factors. In the liver, the increased population of monocyte-derived macrophages may enhance liver damage by secreting pro-inflammatory cytokines [52]. As an important participant in the inflammatory process, mast cells may play a key role in lung inflammation [20]. Wingard et al. showed that CeO_2 has the ability to directly stimulate mast cells, leading to the production of inflammatory cytokines and chemokines, using laboratory tests in C57BL/6 mice. Collectively, these data suggest that mast cell activation may act as a neglected inflammatory mechanism when exposed to CeO_2 [158]. Hong et al. conducted a study to assess the oxidative stress and molecular mechanism involved in pulmonary inflammation caused by long-term lung toxicity in mice. The animals were treated with injected $CeCl_3$ for a period of 90 consecutive days. Their experiment proved that a large number of Ce accumulation in the lung, leading to a prominent increase in lung index, inflammatory cells as well as produce lung inflammation [71]. At the same time, by comparing REEs NPs with other toxic particles, Han et al. concluded that all types of REEs NPs have higher inflammatory potential than other toxic particles [65].

Mitochondrial dysfunction

Mitochondria function as vital hubs for cellular metabolism, facilitating energy production and metabolic processes. They are renowned for their pivotal role in ATP synthesis through oxidative phosphorylation, a cornerstone of cellular catabolism [147]. Studies have revealed that the $CeCl_3$ efficient activation of caspase- 3 and- 9, inhibition of Bcl- 2, increased the levels of Bax and cytochrome c, and promoted the accumulation of ROS in the mouse hippocampus, implying that $CeCl_3$ induced apoptosis in the mouse hippocampus is triggered by a mitochondria-mediated pathway [35]. Wu et al. reported that collapse the MMP, release cytochrome c into the cytosol, and increase the activated caspase- 3 expression, triggering the mitochondrial apoptotic pathway in cortical neurons. $LaCl_3$ elevated intracellular $Ca.^{2+}$ concentration, promoting the generation of ROS, up-regulates pro-apoptotic Bax, and downregulates anti-apoptotic Bcl- 2 expression, thereby changing the Bcl- 2 ratio, ultimately leading to mitochondrial apoptosis in neurons. In summary, the toxicity of La in cortical neurons may be partly attributed to enhanced mitochondrial apoptosis [159]. Besides, exposure to Gd causes disruption of the oxidative state, mitochondrial dysfunction, apoptosis, necrosis, and autophagy [47]

Autophagy

REEs have emerged as significant players in cellular responses, particularly in the induction of autophagy, a pivotal process crucial for cell survival. Autophagy is typically activated by food and ATP depletion, but ROS production and oxidative stress also play important roles in autophagy regulation [84]. rare earth oxide nanocrystals is a novel class of autophagy inducers [113]. The rare-earth Y causes cell death and autophagy in the male reproductive system via the ROS-Ca^{2+}-CamkII/AMPK axis [73]. Moreover, Le et al. revealed that rare earth oxide nanocrystals activate autophagy in HeLa cells (Fig. 6d) [176]. Further elucidation of the molecular pathways involved unveils the complex mechanisms underlying REEs-induced autophagy. For instance, $LaCl_3$ can activation of ROS-AMPK-mTOR signaling pathway, increase the expression level of autophagy-related proteins, and lead to abnormal enhancement of autophagy [103]. Additionally, understanding the cellular uptake mechanisms and intracellular trafficking of REEs provides crucial insights into their modes of action. The interplay between REEs and cellular organelles, such as lysosomes and endoplasmic reticulum, further elucidates the multifaceted nature of REEs-induced autophagy.

DNA, RNA and Proteins Damage

REEs exhibit significant interactions with DNA, ribonucleic acid(RNA) and proteins, influencing their structural integrity and biological functions (Table S2). Ln are particularly effective catalysts for the hydrolytic cleavage of phosphate ester bonds, including those in DNA [50]. Recent studies have shown that exposure to La metal–organic frameworks can alter the expression of DNA methylation and demethylation enzymes,

suggesting potential epigenetic modifications even at low concentrations [23]. Additionally, single-effect analyses indicate that Y, La, and Tb significantly elevate mitochondrial DNA copy number (MtDNACN), with Y posing the highest risk for genetic damage [72]. REEs also play a critical role in stabilizing DNA secondary structures. For instance, Satapathy et al. [132] demonstrated that low concentrations of LREEs can stabilize G-quadruplex structures in human telomere sequences, which has potential applications in the design of functional nanomaterials and molecular switches [132]. Furthermore, Bhanjadeo et al. [14] found that $LaCl_3$ strongly binds to the phosphate backbone of Z-DNA, suggesting its role as an inducer of left-handed DNA conformations [14]. These findings highlight the ability of REEs to modulate DNA topology, which may influence gene regulation and disease mechanisms.

Occupational and environmental exposure studies further underscore the biological impact of REEs. For example, Bai et al. [9] reported that simultaneous exposure to REEs in factory workers may synergistically enhance DNA damage, emphasizing the need for careful monitoring of mixed exposures [9]. Moreover, Ln cations have been shown to induce DNA compaction in a concentration- and force-dependent manner, which could affect chromatin organization and gene expression [131]. Population-based studies have also linked maternal REEs exposure during the third trimester to increased neonatal mitochondrial DNA content, suggesting potential transgenerational effects [106]. Mechanistically, REEs can induce DNA damage through oxidative stress pathways. Song et al. reported that $LaCl_3$ decreased the expression of LKB1, p-LKB1, STRAD and MO25 proteins, and directly or indirectly affected the expression of LKB1, leading to axonal abnormalities in offspring rats [139]. Xiong et al. [165] demonstrated that YCl_3 induces DNA damage by causing intracellular ROS overproduction and inhibiting antioxidant defense mechanisms [165]. These findings collectively highlight the dual role of REEs in both stabilizing DNA structures and inducing damage, depending on the context and concentration. The toxicity mechanisms of REEs are still under active investigation. Beyond the mechanisms previously discussed, epigenetic alterations have emerged as significant contributors. Wang et al. analyzed the expression profiles of miRNA, lncRNA, circRNA, and mRNA in mouse testicular tissue after exposure to Nd_2O_3 through RNA sequencing and found that the abnormal expression of these RNA molecules is closely related to reproductive damage [154].

Conclusions

Despite the notable industrial benefits of REEs, their extensive production and use have led to significant environmental contamination, creating serious risks for both human health and ecosystems. REEs can permeate the human body through various routes—such as inhalation, ingestion, dermal contact, and medical procedures—leading to their accumulation and damage across multiple organ systems. Research suggests that REEs may induce oxidative stress, disrupt mitochondrial function, and cause harmful effects on the respiratory, cardiovascular, digestive, reproductive, and nervous systems. Nonetheless, the exact link between in vivo and in vitro toxicity and the mechanisms involved remain unclear. There is a critical need for further epidemiological studies to confirm animal model findings and explore the long-term effects of REEs exposure. Key issues to address include: the functional mediators involved, their activation by REEs, their interactions, and the upstream factors that regulate relevant signaling pathways. The lack of official occupational exposure limits for REEs underscores the necessity for detailed guidelines and protective measures, to reduce worker exposure. Tackling these issues requires continued research and the establishment of effective safety standards.

Abbreviations

BBB	Blood-brain barrier
Ca	Calcium
Ca^{2+}	Calcium ion
CAT	Catalase
Ce	Cerium
$CeCl_3$	Cerium chloride
CeO_2	Cerium dioxide
CeO_2 NPs	Cerium oxide nanoparticles
CeO_2-Gd NPs	Cerium oxide-gadolinium composite nanoparticles
$Ce(NO_3)_3$	Cerium nitrate
CN	Cerium nitrate
CoO	Cobaltous oxide
CoO NPs	Cobalt Oxide Nanoparticles
C. elegans	Caenorhabditis elegans
CRT	Cathode ray tube
DNA	Deoxyribonucleic acid
$DyCl_3$	Dysprosium chloride
$ErCl_3$	Erbium chloride
$EuCl_3$	Europium chloride
GBCAs	Gadolinium-based contrast agents
Gd	Gadolinium
Gd^{3+}	Gadolinium ion
$GdCl_3$	Gadolinium chloride
Gd_2O_3	Gadolinium Oxide
GR	Glutathione reductase
GSH	Glutathione
GDL	Gastroduodenal lesions
HREEs	Heavy rare earth elements
$HoCl_3$	Holmium chloride
IQs	Intelligence Quotient
La	Lanthanum
$LaCl_3$	Lanthanum chloride
$La(NO_3)_3$	Lanthanum nitrate
La_2O_3	Lanthanum oxide
La_2O_3 NPs	Lanthanum oxide nanoparticles

Ln	Lanthanoids
LREEs	Light rare earth elements
Lu	Lutetium
$LuCl_3$	Lutetium chloride
M-DCs	Myeloid-derived dendritic cells
MDA	Malondialdehyde
MMP	Mitochondrial membrane potential
MRI	Magnetic resonance imaging
MtDNACN	Mitochondrial DNA copy number
Nd	Neodymium
$NdCl_3$	Neodymium chloride
Nd_2O_3	Neodymium oxide
Nd_2O_3 NPs	Neodymium oxide nanoparticles
Pd	Palladium
Pr	Praseodymium
$PrCl_3$	Praseodymium chloride
$Pr(NO_3)_3$	Praseodymium nitrate
REEs	Rare earth elements
RNA	Ribonucleic acid
ROS	Reactive oxygen species
Sc	Scandium
$ScCl_3$	Scandium chloride
$SmCl_3$	Samarium chloride
SOD	Superoxide dismutase
TiO_2	Titanium dioxide
$TmCl_3$	Thulium chloride
U	Uranium
Y	Yttrium
YCl_3	Yttrium chloride
Y_2O_3	Yttrium oxide
Yb	Ytterbium
$YbCl_3$	Ytterbium chloride

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-025-01178-3.

Supplementary Material 1: Table S1. REEs: Abbreviations, Applications, and Toxicity. Table S2 Interaction of REEs,with DNA, RNA and proteins.

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Authors' contributions
Xuemei Wang, Feiyu Wang, Lirong Yan: literature collection, writing, preparation of all the tables and figures, Zhixiang Gao: Supervision, Visualization. Shengbo Yang: Investigation. Zhigang Su: Investigation, Methodology. Wenting Chen: Supervision. Yanan Li: Writing – review & editing, Methodology, Visualization, Conceptualization. Fenhong Wang: Writing – review & editing, Investigation, Visualization, Conceptualization. All authors read and approved the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Consent for publication wasbtained from the participants.

Competing interests
The authors declare no competing interests.

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References

1. Abdelnour SA, Abd El-Hack ME, Khafaga AF, Noreldin AE, Arif M, Chaudhry MT, Losacco C, Abdeen A, Abdel-Daim MM. Impacts of rare earth elements on animal health and production: Highlights of cerium and lanthanum. Sci Total Environ. 2019;672:1021–32. https://doi.org/10.1016/j.scitotenv.2019.02.270.
2. Abuid, N. J., M. E. Urdaneta, K. M. Gattas-Asfura, C. Zientek, C. I. Silgo, J. A. Torres, K. J. Otto and C. L. Stabler (2021). "Engineering the Multi-Enzymatic Activity of Cerium Oxide Nanoparticle Coatings for the Antioxidant Protection of Implants." Adv Nanobiomed Res 1(8), https://doi.org/10.1002/anbr.202100016.
3. Adampourezare M, Nikzad B, Amini M, Sheibani N. Fluorimetric detection of DNA methylation by cerium oxide nanoparticles for early cancer diagnosis. Heliyon. 2024;10(7):e28695. https://doi.org/10.1016/j.heliyon.2024.e28695.
4. Azimi G, Dhiman R, Kwon HM, Paxson AT, Varanasi KK. Hydrophobicity of rare-earth oxide ceramics. Nat Mater. 2013;12(4):315–20. https://doi.org/10.1038/nmat3545.
5. Ahmad J, Wahab R, Siddiqui MA, Farshori NN, Saquib Q, Ahmad N, Al-Khedhairy AA. Neodymium oxide nanostructures and their cytotoxic evaluation in human cancer cells. J Trace Elem Med Biol. 2022;73:127029. https://doi.org/10.1016/j.jtemb.2022.127029.
6. Almukhlafi H, Ali D, Almutairi B, Yaseen KN, Alyami N, Almeer R, Alkahtani S, Alarifi S. Role of Oxidative Stress in La(2)O(3) Nanoparticle-Induced Cytotoxicity and Apoptosis in CHANG and HuH-7 Cells. Int J Nanomedicine. 2021;16:3487–96. https://doi.org/10.2147/ijn.S302478.
7. Ariyani W, Miyazaki W, Tsushima Y, Koibuchi N. Gadolinium-based contrast agent accelerates the migration of astrocyte via integrin αvβ3 signaling pathway. Sci Rep. 2022;12(1):5850. https://doi.org/10.1038/s41598-022-09882-7.
8. Arumugam A, Karthikeyan C, Haja Hameed AS, Gopinath K, Gowri S, Karthika V. Synthesis of cerium oxide nanoparticles using Gloriosa superba L. leaf extract and their structural, optical and antibacterial properties. Mater Sci Eng C Mater Biol Appl. 2015;49:408–15. https://doi.org/10.1016/j.msec.2015.01.042.
9. Bai Y, Long C, Hu G, Zhou D, Gao X, Chen Z, Wang T, Yu S, Han Y, Yan L. Association of blood chromium and rare earth elements with the risk of DNA damage in chromate exposed population. Environ Toxicol Pharmacol. 2019;72: 103237. https://doi.org/10.1016/j.etap.2019.103237.
10. Balaram, V. (2019). "Rare earth elements: A review of applications, occurrence, exploration, analysis, recycling, and environmental impact." Geoscience Frontiers 10(4): 1285–1303, https://doi.org/10.1016/j.gsf.2018.12.005.
11. Ballesteros S, Barguilla I, Marcos R, Hernández A. Nanoceria, alone or in combination with cigarette-smoke condensate, induce transforming and epigenetic cancer-like features in vitro. Nanomedicine (Lond). 2021;16(4):293–305. https://doi.org/10.2217/nnm-2020-0367.
12. Bau, M. and P. Dulski (1996). "Anthropogenic origin of positive gadolinium anomalies in river waters." Earth and Planetary Science Letters 143(1): 245–255, https://doi.org/10.1016/0012-821X(96)00127-6.
13. Ben, Y., M. Cheng, L. Wang, Q. Zhou, Z. Yang and X. Huang (2021). "Low-dose lanthanum activates endocytosis, aggravating accumulation of lanthanum or/and lead and disrupting homeostasis of essential elements in the leaf cells of four edible plants." Ecotoxicology and Environmental Safety 221: 112429, https://doi.org/10.1016/j.ecoenv.2021.112429.
14. Bhanjadeo, M. M., P. S. Nial, C. Sathyaseelan, A. K. Singh, J. Dutta, T. Rathinavelan and U. Subudhi (2022). "Biophysical interaction between

lanthanum chloride and (CG)n or (GC)n repeats: A reversible B-to-Z DNA transition." International Journal of Biological Macromolecules 216: 698–709, https://doi.org/10.1016/j.ijbiomac.2022.07.020.
15. Blomqvist, L., G. F. Nordberg, V. M. Nurchi and J. O. Aaseth (2022). "Gadolinium in Medical Imaging-Usefulness, Toxic Reactions and Possible Countermeasures-A Review." Biomolecules 12(6), https://doi.org/10.3390/biom12060742.
16. Borges de Lima, I. and W. L. Filho (2016). Chapter 26 - Highlights on Rare Earths: Research Advances, Possibilities, Challenges, and Trends Based on Authors' Findings and Views. Rare Earths Industry. I. Borges De Lima and W. Leal Filho. Boston, Elsevier: 395–424.
17. Bouzigues C, Gacoin T, Alexandrou A. Biological applications of rare-earth based nanoparticles. ACS Nano. 2011;5(11):8488–505. https://doi.org/10.1021/nn202378b.
18. Brown CJ, Chenery SR, Smith B, Mason C, Tomkins A, Roberts GJ, Sserunjogi L, Tiberindwa JV. Environmental influences on the trace element content of teeth–implications for disease and nutritional status. Arch Oral Biol. 2004;49(9):705–17. https://doi.org/10.1016/j.archoralbio.2004.04.008.
19. Brown DN, Wu Z, He F, Miller DJ, Herchenroeder JW. Dysprosium-free melt-spun permanent magnets. J Phys Condens Matter. 2014;26(6): 064202. https://doi.org/10.1088/0953-8984/26/6/064202.
20. Brown JM, Swindle EJ, Kushnir-Sukhov NM, Holian A, Metcalfe DD. Silica-Directed Mast Cell Activation Is Enhanced by Scavenger Receptors. Am J Respir Cell Mol Biol. 2007;36(1):43–52. https://doi.org/10.1165/rcmb.2006-0197OC.
21. Cao B, Wu J, Xu C, Chen Y, Xie Q, Ouyang L, Wang J. The Accumulation and Metabolism Characteristics of Rare Earth Elements in Sprague-Dawley Rats. Int J Environ Res Public Health. 2020;17(4): https://doi.org/10.3390/ijerph17041399.
22. Cao Z, Yang M, Gong H, Feng X, Hu L, Li R, Xu S, Wang Y, Xiao H, Zhou A. Association between prenatal exposure to rare earth elements and the neurodevelopment of children at 24-months of age: A prospective cohort study. Environ Pollut. 2024;343:123201. https://doi.org/10.1016/j.envpol.2023.123201.
23. Carrillo-Cocom LM, Juárez-Méndez L, Rincón S, Rivera-Villanueva JM, Nic-Can GI, Zepeda A. Induction of cytotoxic effects and changes in DNA methylation-related gene expression in a human fibroblast cell line by the metal-organic framework [H(2)NMe(2)](3) [Tb(III)(2,6 pyridinedicarboxylate)(3)] (Tb-MOF). Environ Sci Pollut Res Int. 2023;30(16):46685–96. https://doi.org/10.1007/s11356-023-25314-z.
24. Cashion W, Weisbord SD. Radiographic Contrast Media and the Kidney. Clin J Am Soc Nephrol. 2022;17(8):1234–42. https://doi.org/10.2215/cjn.16311221.
25. Censi PTE, Speziale S, Zuddas P, Randazzo LA, Punturo R, Cuttitta A, Aricò P. Yttrium and lanthanides in human lung fluids, probing the exposure to atmospheric fallout. J Hazard Mater. 2011.
26. Chandran E, Figg WD, Madan R. Lutetium-177-PSMA-617: A Vision of the Future. Cancer Biol Ther. 2022;23(1):186–90. https://doi.org/10.1080/15384047.2022.2037985.
27. Charalampides, G., K. I. Vatalis, B. Apostoplos and B. Ploutarch-Nikolas (2015). "Rare Earth Elements: Industrial Applications and Economic Dependency of Europe." Procedia Economics and Finance 24: 126–135, https://doi.org/10.1016/S2212-5671(15)00630-9.
28. Chen J, Xiao H-J, Qi T, Chen D-L, Long H-M, Liu S-H. Rare earths exposure and male infertility: the injury mechanism study of rare earths on male mice and human sperm. Environ Sci Pollut Res. 2015;22(3):2076–86. https://doi.org/10.1007/s11356-014-3499-y.
29. Chen Q, Hong J, Lai G, Yang X, Chen G, Xu N, Li X, Hu K, Chen T, Song Y, Wan Y. What are exposure biomarkers of rare earth elements for the ionic rare earth occupational population? Environ Poll. 2024;345: 123499, https://doi.org/10.1016/j.envpol.2024.123499.
30. Chen S, Hou Y, Cheng G, Zhang C, Wang S, Zhang J. Cerium oxide nanoparticles protect endothelial cells from apoptosis induced by oxidative stress. Biol Trace Elem Res. 2013;154(1):156–66. https://doi.org/10.1007/s12011-013-9678-8.
31. Chen Y, Zhu W, Shu F, Fan Y, Yang N, Wu T, Ji L, Xie W, Bade R, Jiang S, Liu X, Shao G, Wu G, Jia X. Nd(2)O(3) Nanoparticles Induce Toxicity and Cardiac/Cerebrovascular Abnormality in Zebrafish Embryos via the Apoptosis Pathway. Int J Nanomedicine. 2020;15:387–400. https://doi.org/10.2147/ijn.S220785.
32. Chen Z, Geng Y, Gao R, Zhong H, Chen J, Mu X, Chen X, Zhang Y, Li F, He J. Maternal exposure to CeO(2)NPs derails placental development through trophoblast dysfunction mediated by excessive autophagy activation. J Nanobiotechnology. 2022;20(1):131. https://doi.org/10.1186/s12951-022-01334-8.
33. Cheng J, Cheng Z, Hu R, Cui Y, Cai J, Li N, Gui S, Sang X, Sun Q, Wang L, Hong F. Immune dysfunction and liver damage of mice following exposure to lanthanoids. Environ Toxicol. 2014;29(1):64–73. https://doi.org/10.1002/tox.20773.
34. Cheng J, Fei M, Fei M, Sang X, Sang X, Cheng Z, Gui S, Zhao X, Sheng L, Sun Q, Hu R, Wang L, Hong F. Gene expression profile in chronic mouse liver injury caused by long-term exposure to CeCl3. Environ Toxicol. 2014;29(7):837–46. https://doi.org/10.1002/tox.21826.
35. Cheng Z, Li N, Cheng J, Hu R, Gao G, Cui Y, Gong X, Wang L, Hong F. Signal pathway of hippocampal apoptosis and cognitive impairment of mice caused by cerium chloride. Environ Toxicol. 2012;27(12):707–18. https://doi.org/10.1002/tox.20696.
36. Coimbra S, Rocha S, Sousa NR, Catarino C, Belo L, Bronze-da-Rocha E, Valente MJ, Santos-Silva A. Toxicity Mechanisms of Gadolinium and Gadolinium-Based Contrast Agents-A Review. Int J Mol Sci. 2024;25(7), https://doi.org/10.3390/ijms25074071.
37. Connelly NG, Damhus T, Hartshorn RM, Hutton AT. Nomenclature of Inorganic Chemistry: IUPAC Recommendations 2005. Royal Society of Chemistry; 2005.
38. de Haën C. Conception of the first magnetic resonance imaging contrast agents: a brief history. Top Magn Reson Imaging. 2001;12(4):221–30. https://doi.org/10.1097/00002142-200108000-00002.
39. De Marzi L, Monaco A, De Lapuente J, Ramos D, Borras M, Di Gioacchino M, Santucci S, Poma A. Cytotoxicity and genotoxicity of ceria nanoparticles on different cell lines in vitro. Int J Mol Sci. 2013;14(2):3065–77. https://doi.org/10.3390/ijms14023065.
40. de Oliveira C, Ramos SJ, Siqueira JO, Faquin V, de Castro EM, Amaral DC, Techio VH, Coelho LC, e Silva PH, Schnug E, Guilherme LR. Bioaccumulation and effects of lanthanum on growth and mitotic index in soybean plants. Ecotoxicol Environ Saf. 2015;122:136–44. https://doi.org/10.1016/j.ecoenv.2015.07.020.
41. Dekkers S, Miller MR, Schins RPF, Römer I, Russ M, Vandebriel RJ, Lynch I, Belinga- Desaunay MF, Valsami-Jones E, Connell SP, Smith IP, Duffin R, Boere JAF, Heusinkveld HJ, Albrecht C, de Jong WH, Cassee FR. The effect of zirconium doping of cerium dioxide nanoparticles on pulmonary and cardiovascular toxicity and biodistribution in mice after inhalation. Nanotoxicology. 2017;11(6):794–808. https://doi.org/10.1080/17435390.2017.1357214.
42. Dinali, G. S., R. A. Root, M. K. Amistadi, J. Chorover, G. Lopes and L. R. G. Guilherme (2019). "Rare earth elements (REY) sorption on soils of contrasting mineralogy and texture." Environment International 128: 279–291, https://doi.org/10.1016/j.envint.2019.04.022.
43. Do C, Ford B, Lee DY, Tan C, Escobar P, Wagner B. Gadolinium-based contrast agents: Stimulators of myeloid-induced renal fibrosis and major metabolic disruptors. Toxicol Appl Pharmacol. 2019;375:32–45. https://doi.org/10.1016/j.taap.2019.05.009.
44. Duan, L., Y. Li, J. Hu, Q. Ma, T. Yu, C. Zhang, F. Luo, J. Xu and C. Dou (2021). "Light rare earth elements hinder bone development via inhibiting type H vessels formation in mice." Ecotoxicology and Environmental Safety 218: 112275, https://doi.org/10.1016/j.ecoenv.2021.112275.
45. Dushyantha, N., N. Batapola, I. M. S. K. Ilankoon, S. Rohitha, R. Premasiri, B. Abeysinghe, N. Ratnayake and K. Dissanayake (2020). "The story of rare earth elements (REEs): Occurrences, global distribution, genesis, geology, mineralogy and global production." Ore Geology Reviews 122: 103521, https://doi.org/10.1016/j.oregeorev.2020.103521.
46. Feng L, Xiao H, He X, Li Z, Li F, Liu N, Zhao Y, Huang Y, Zhang Z, Chai Z. Neurotoxicological consequence of long-term exposure to lanthanum. Toxicol Lett. 2006;165(2):112–20. https://doi.org/10.1016/j.toxlet.2006.02.003.
47. Feng X, Xia Q, Yuan L, Yang X, Wang K. Impaired mitochondrial function and oxidative stress in rat cortical neurons: Implications for gadolinium-induced neurotoxicity. NeuroToxicology 2010;31(4): 391–398, https://doi.org/10.1016/j.neuro.2010.04.003.
48. Fiket, Ž. and G. Medunić (2023). "Dataset of rare earth elements distribution in soils and vegetables." Results in Earth Sciences 1: 100004, https://doi.org/10.1016/j.rines.2023.100004.

49. Foong LK, Foroughi MM, Mirhosseini AF, Safaei M, Jahani S, Mostafavi M, Ebrahimpoor N, Sharifi M, Varma RS, Khatami M. Applications of nanomaterials in diverse dentistry regimes. RSC Adv. 2020;10(26):15430–60. https://doi.org/10.1039/d0ra00762e.
50. Franklin SJ. Lanthanide-mediated DNA hydrolysis. Curr Opin Chem Biol. 2001;5(2):201–8.
51. Gaman L, Delia CE, Luzardo OP, Zumbado M, Badea M, Stoian I, Gilca M, Boada LD, Henríquez-Hernández LA. Serum concentration of toxic metals and rare earth elements in children and adolescent. Int J Environ Health Res. 2020;30(6):696–712. https://doi.org/10.1080/09603123.2019.1626353.
52. Gao J, Wang S, Tang G, Wang Z, Wang Y, Wu Q, Yang X, Liu Y, Hu L, He B, Qu G, Jiang. Inflammation and accompanied disrupted hematopoiesis in adult mouse induced by rare earth element nanoparticles. Sci Total Environ. 2022;831:155416. https://dx.doi.org/10.1016/j.scitotenv.2022.155416.
53. Gao X, Yang J, Li Y, Yu M, Liu S, Han Y, Lu X, Jin C, Wu S, Cai Y. Lanthanum chloride induces autophagy in rat hippocampus through ROS-mediated JNK and AKT/mTOR signaling pathways. Metallomics. 2019;11(2):439–53. https://doi.org/10.1039/c8mt00295a.
54. Gao X, Yu M, Sun W, Han Y, Yang J, Lu X, Jin C, Wu S, Cai Y. Lanthanum chloride induces autophagy in primary cultured rat cortical neurons through Akt/mTOR and AMPK/mTOR signaling pathways. Food Chem Toxicol. 2021;158:112632. https://doi.org/10.1016/j.fct.2021.112632.
55. Garcia IM, Leitune VC, Takimi AS, Bergmann CP, Samuel SM, Melo MA, Collares FM. Cerium Dioxide Particles to Tune Radiopacity of Dental Adhesives: Microstructural and Physico-Chemical Evaluation. J Funct Biomaterials. 2020;11 https://doi.org/10.3390/jfb11010007.
56. Ge J, Wang X, Meng Q, Tang M, Jiang W, Jiang J, Xiao Q, Hao W, Wei X. Maternal cerium nitrate exposure induces developmental immunotoxicity in BALB/c mouse offspring. Toxicol Lett. 2023;374:57–67. https://doi.org/10.1016/j.toxlet.2022.12.008.
57. Gojova A, Guo B, Kota RS, Rutledge JC, Kennedy IM, Barakat AI. Induction of inflammation in vascular endothelial cells by metal oxide nanoparticles: effect of particle composition. Environ Health Perspect. 2007;115(3):403–9. https://doi.org/10.1289/ehp.8497.
58. Gómez-Aracena J, Riemersma RA, Gutiérrez-Bedmar M, Bode P, Kark JD, Garcia-Rodríguez A, Gorgojo L, Van't Veer P, Fernández-Crehuet J, Kok FJ, Martin-Moreno JM. Toenail cerium levels and risk of a first acute myocardial infarction: the EURAMIC and heavy metals study. Chemosphere. 2006;64(1):112–20. https://doi.org/10.1016/j.chemosphere.2005.10.062.
59. Gosens I, Mathijssen LE, Bokkers BG, Muijser H, Cassee FR. Comparative hazard identification of nano- and micro-sized cerium oxide particles based on 28-day inhalation studies in rats. Nanotoxicology. 2014;8(6):643–53. https://doi.org/10.3109/17435390.2013.815814.
60. Gupta CK, Krishnamurthy N. Extractive metallurgy of rare earths. Int Mater Rev. 1992;37(1):197-248 https://doi.org/10.1179/imr.1992.37.1.197
61. Gwenzi, W., L. Mangori, C. Danha, N. Chaukura, N. Dunjana and E. Sanganyado (2018). "Sources, behaviour, and environmental and human health risks of high-technology rare earth elements as emerging contaminants." Science of The Total Environment 636: 299–313, https://doi.org/10.1016/j.scitotenv.2018.04.235.
62. Haley PJ. Pulmonary toxicity of stable and radioactive lanthanides. Health Phys. 1991;61(6):809–20. https://doi.org/10.1097/00004032-199112000-00011.
63. Haley TJ. Pharmacology and toxicology of the rare earth elements. J Pharm Sci. 1965;54(5):663–70. https://doi.org/10.1002/jps.2600540502.
64. Han GC, Jing HM, Zhang WJ, Zhang N, Li ZN, Zhang GY, Gao S, Ning JY, Li GJ. Effects of lanthanum nitrate on behavioral disorder, neuronal damage and gene expression in different developmental stages of Caenorhabditis elegans. Toxicology. 2022;465: 153012. https://doi.org/10.1016/j.tox.2021.153012.
65. Han Y, Lee DK, Kim SH, Lee S, Jeon S, Cho WS. High inflammogenic potential of rare earth oxide nanoparticles: the New Hazardous Entity. Nanotoxicology. 2018;12(7):712–28. https://doi.org/10.1080/17435390.2018.1472311.
66. Hao Z, Li Y, Li H, Wei B, Liao X, Liang T, Yu J. Levels of rare earth elements, heavy metals and uranium in a population living in Baiyun Obo, Inner Mongolia, China: A pilot study. Chemosphere. 2015;128: 161–170, https://doi.org/10.1016/j.chemosphere.2015.01.057.
67. Haratake J, Yasunaga C, Ootani A, Shimajiri S, Matsuyama A, Hisaoka M. Peculiar histiocytic lesions with massive lanthanum deposition in dialysis patients treated with lanthanum carbonate. Am J Surg Pathol. 2015;39(6):767–71. https://doi.org/10.1097/pas.0000000000000385.
68. He X, Yuan T, Jiang X, Yang H, Zheng C. Effects of contaminated surface water and groundwater from a rare earth mining area on the Biology and the Physiology of Sprague-Dawley rats. Sci Total Environ. 2020;761:144123. https://doi.org/10.1016/j.scitotenv.2020.144123.
69. He X, Zhang H, Ma Y, Bai W, Zhang Z, Lu K, Ding Y, Zhao Y, Chai Z. Lung deposition and extrapulmonary translocation of nano-ceria after intratracheal instillation. Nanotechnology. 2010;21(28):285103. https://doi.org/10.1088/0957-4484/21/28/285103.
70. Hedrick, J. B. (2004). Rare earths in selected US defense applications. 40th forum on the geology of industrial minerals.
71. Hong J, Yu X, Pan X, Zhao X, Sheng L, Sang X, Lin A, Zhang C, Zhao Y, Gui S, Sun Q, Wang L, Hong F. Pulmonary toxicity in mice following exposure to cerium chloride. Biol Trace Elem Res. 2014;159(1–3):269–77. https://doi.org/10.1007/s12011-014-9953-3.
72. Hong S, Zhang Y, Zhang Q, Su Z, Hu G, Wang L, Yu S, Zhu X, Jia G. Health risks of rare earth elements exposure: Impact on mitochondrial DNA copy number and micronucleus frequency. J Environ Sci (China). 2025;151:150–60. https://doi.org/10.1016/j.jes.2024.01.054.
73. Hou F, Huang J, Qing F, Guo T, Ouyang S, Xie L, Ding Y, Yu J, Li Y, Liu X, He TS, Fan X, Liu Z. The rare-earth yttrium induces cell apoptosis and autophagy in the male reproductive system through ROS-Ca(2+)-CamkII/Ampk axis. Ecotoxicol Environ Saf. 2023;263:115262. https://doi.org/10.1016/j.ecoenv.2023.115262.
74. Hsu, W.-T., E. Petavratzi, M. Zils, S. Einarsson, E. K. Morasae, O. Lysaght and P. Hopkinson (2024). "Mapping the flows and stocks of permanent magnets rare earth elements for powering a circular economy in the UK." Sustainable Production and Consumption 47: 37–46, https://doi.org/10.1016/j.spc.2024.03.027.
75. Hua D, Wang J, Yu D, Liu J. Lanthanum exerts acute toxicity and histopathological changes in gill and liver tissue of rare minnow (Gobiocypris rarus). Ecotoxicology. 2017;26(9):1207–15. https://doi.org/10.1007/s10646-017-1846-8.
76. Huang F, Wang H, Chen L, Wang Y. Effects of co-exposure of rare earth elements and lead on children's intelligence. J Mod Med Health. 2020;36(16):2534–8.
77. Huang LH, Yang H, Su X, Gao YR, Xue HN, Wang SH. Neodymium Oxide Induces Cytotoxicity and Activates NF-κB and Caspase-3 in NR8383 Cells. Biomed Environ Sci. 2017;30(1):75–8. https://doi.org/10.3967/bes2017.010.
78. Huang P, Li J, Zhang S, Chen C, Han Y, Liu N, Xiao Y, Wang H, Zhang M, Yu Q, Liu Y, Wang W. Effects of lanthanum, cerium, and neodymium on the nuclei and mitochondria of hepatocytes: accumulation and oxidative damage. Environ Toxicol Pharmacol. 2011;31(1):25–32. https://doi.org/10.1016/j.etap.2010.09.001.
79. Issa N, Poggio ED, Fatica RA, Patel R, Ruggieri PM, Heyka RJ. Nephrogenic systemic fibrosis and its association with gadolinium exposure during MRI. Cleve Clin J Med. 2008;75(2): 95–97, 103–104, 106 passim, https://doi.org/10.3949/ccjm.75.2.95.
80. Jairam LS, Chandrashekar A, Niranjana Prabhu T, Kotha SB, Girish MS, Devraj IM, Dhanya Shri M, Prashantha K. A review on biomedical and dental applications of cerium oxide nanoparticles - Unearthing the potential of this rare earth metal. J Rare Earths. 2023;41(11):1645–61. https://doi.org/10.1016/j.jre.2023.04.009.
81. Jiang DG, Yang J, Zhang S, Yang DJ. A Survey of 16 Rare Earth Elements in the Major Foods in China. Biomedical Environmental Sci. 2012;25(3):267–271, https://doi.org/10.3967/0895-3988.2012.03.003.
82. Jin S, Huang Y, Hu Y, Qiao M, Wang X, Wang F, Li J, Xiang M, Xu F. Rare earth elements content and health risk assessment of soil and crops in typical rare earth mine area in Jiangxi Province. Huanjing Kexue Xuebao/Acta Scientiae Circumstantiae 2014;34: 3084–3093, https://doi.org/10.13671/j.hjkxxb.2014.0799.
83. Joshi N, Walter JM, Misharin AV. Alveolar Macrophages. Cell Immunol. 2018;330:86–90. https://doi.org/10.1016/j.cellimm.2018.01.005.
84. Kaushik, S. and A. M. Cuervo (2006). "Autophagy as a cell-repair mechanism: Activation of chaperone-mediated autophagy during oxidative stress." Molecular Aspects of Medicine 27(5): 444–454, https://doi.org/10.1016/j.mam.2006.08.007.

85. Keller J, Wohlleben W, Ma-Hock L, Strauss V, Gröters S, Küttler K, Wiench K, Herden C, Oberdörster G, van Ravenzwaay B, Landsiedel R. Time course of lung retention and toxicity of inhaled particles: short-term exposure to nano-Ceria. Arch Toxicol. 2014;88(11):2033–59. https://doi.org/10.1007/s00204-014-1349-9.
86. Khan AM, Yusoff I, Bakar NKA, Bakar AFA, Alias Y. Assessing anthropogenic levels, speciation, and potential mobility of rare earth elements (REEs) in ex-tin mining area. Environ Sci Pollut Res Int. 2016;23(24):25039–55. https://doi.org/10.1007/s11356-016-7641-x.
87. Khosa, T., M. Ben Said, Z. U. Rehman, M. Ali, S. Jamil, Q. Fatima, H. Hussain, R. Iqbal, A. Khan and F. Iqbal (2022). "Varying Doses of Rare-Earth-Metal-Based Neodymium Zirconate Zinc Sulfide Nanocomposite Disrupt Blood and Serum Parameters, as well as Markers of Oxidative Stress in the Selected Organs of Albino Mice." Genes (Basel) 13(12), https://doi.org/10.3390/genes13122262.
88. Kim YH, Boykin E, Stevens T, Lavrich K, Gilmour MI. Comparative lung toxicity of engineered nanomaterials utilizing in vitro, ex vivo and in vivo approaches. J Nanobiotechnology. 2014;12:47. https://doi.org/10.1186/s12951-014-0047-3.
89. King AH, Eggert RG. Chapter 10 - Critical materials for permanent magnets. Modern Permanent Magnets. J. Croat and J. Ormerod: Woodhead Publishing; 2022. p. 343–70.
90. Kuruvilla L, Kartha CC. Cerium depresses endocardial endothelial cell-mediated proliferation of cardiac fibroblasts. Biol Trace Elem Res. 2006;114(1–3):85–92. https://doi.org/10.1385/bter:114:1:85.
91. Lee WY, Park HJ. Toxicity of cerium oxide nanoparticles on neonatal testicular development in mouse organ culture. Reprod Toxicol. 2022;111:120–8. https://doi.org/10.1016/j.reprotox.2022.05.014.
92. Lehmann BV, Oberdisse E, Grajewski O, Arntz HR. Subcellular distribution of phospholipids during liver damage induced by rare earths. Arch Toxicol. 1975;34(2):89–101. https://doi.org/10.1007/bf00353309.
93. Leite C, Russo T, Pinto J, Polese G, Soares AMVM, Pretti C, Pereira E, Freitas R. From the cellular to tissue alterations induced by two rare earth elements in the mussel species Mytilus galloprovincialis: Comparison between exposure and recovery periods. Sci Total Environment 2024;915: 169754, https://doi.org/10.1016/j.scitotenv.2023.169754.
94. Li J, Hong M, Yin X, Liu J. Effects of the accumulation of the rare earth elements on soil macrofauna community. J Rare Earths 2010;28(6): 957–964, https://doi.org/10.1016/S1002-0721(09)60233-7.
95. Li J, Mao N, Zhang X, Wang S, Yang F, Lu W, Yang H, Yang W, Zhang L, Wu D, Guo X. Effect of gadolinium addition on microstructure, mechanical properties and corrosion behavior of titanium alloys for spent fuel storage and neutron shielding. J Rare Earths. 2024. https://doi.org/10.1016/j.jre.2024.06.013.
96. Li K, Liang T, Wang L, Tian S. Inhalation exposure and potential health risk estimation of lanthanides elements in PM(2.5) associated with rare earth mining areas: a case of Baotou city, northern China. Environ Geochem Health. 2018;40(6):2795–805. https://doi.org/10.1007/s10653-018-0146-4.
97. Li M, Zhuang L, Zhang G, Lan C, Yan L, Liang R, Hao C, Li Z, Zhang J, Lu Q, Wang B. Association between exposure of light rare earth elements and outcomes of in vitro fertilization-embryo transfer in North China. Sci Total Environ. 2021;762: 143106. https://doi.org/10.1016/j.scitotenv.2020.143106.
98. Li R, Yu L, Qin Y, Zhou Y, Liu W, Li Y, Chen Y, Xu Y. Protective effects of rare earth lanthanum on acute ethanol-induced oxidative stress in mice via Keap 1/Nrf2/p62 activation. Sci Total Environ. 2021;758: 143626. https://doi.org/10.1016/j.scitotenv.2020.143626.
99. Li R, Zhou Y, Liu W, Li Y, Qin Y, Yu L, Chen Y, Xu Y. Rare earth element lanthanum protects against atherosclerosis induced by high-fat diet via down-regulating MAPK and NF-κB pathways. Ecotoxicol Environ Saf. 2021;207: 111195. https://doi.org/10.1016/j.ecoenv.2020.111195.
100. Li XZ, Tian CB, Sun QF. Coordination-Directed Self-Assembly of Functional Polynuclear Lanthanide Supramolecular Architectures. Chem Rev. 2022;122(6):6374–458. https://doi.org/10.1021/acs.chemrev.1c00602.
101. Lin C, Liu G, Huang Y, Liu S, Tang B. Rare-earth nanoparticles induce depression, anxiety-like behavior, and memory impairment in mice. Food Chem Toxicol. 2021;156: 112442. https://doi.org/10.1016/j.fct.2021.112442.
102. Liu HM, Liu HY, Yang ZH, Wang KZ. Bone Mineral Density in Population Long-Term Exposed to Rare Earth Elements from a Mining Area of China. Biol Trace Elem Res. 2021;199(2):453–64. https://doi.org/10.1007/s12011-020-02165-0.
103. Liu J, Wang L, Ge L, Sun W, Song Z, Lu X, Jin C, Wu S, Yang J. Lanthanum decreased VAPB-PTPP51, BAP31-FIS1, and MFN2-MFN1 expression of mitochondria-associated membranes and induced abnormal autophagy in rat hippocampus. Food Chem Toxicol. 2022;161: 112831. https://doi.org/10.1016/j.fct.2022.112831.
104. Liu WS, Guo MN, Liu C, Yuan M, Chen XT, Huot H, Zhao CM, Tang YT, Morel JL, Qiu RL. Water, sediment and agricultural soil contamination from an ion-adsorption rare earth mining area. Chemosphere. 2019;216:75–83. https://doi.org/10.1016/j.chemosphere.2018.10.109.
105. Liu Y, Wang D, Shi J, Peng Q, Li Y. Magnetic tuning of upconversion luminescence in lanthanide-doped bifunctional nanocrystals. Angew Chem Int Ed Engl. 2013;52(16):4366–9. https://doi.org/10.1002/anie.201209884.
106. Liu Y, Wu M, Liu B, Song L, Bi J, Wang L, Upadhyaya Khatiwada S, Chen K, Liu Q, Xiong C, Li Y, Xia W, Xu S, Wang Y, Zhou A. Association of prenatal exposure to rare earth elements with newborn mitochondrial DNA content: Results from a birth cohort study. Environ Int. 2020;143: 105863. https://doi.org/10.1016/j.envint.2020.105863.
107. Liu Y, Wu M, Zhang L, Bi J, Song L, Wang L, Liu B, Zhou A, Cao Z, Xiong C, Yang S, Xia W, Li Y, Wang Y. Prenatal exposure of rare earth elements cerium and ytterbium and neonatal thyroid stimulating hormone levels: Findings from a birth cohort. Study Environ Int. 2019;133:105222. https://dx.doi.org/https://doi.org/10.1016/j.envint.2019.10522.
108. Lu VM, Crawshay-Williams F, White B, Elliot A, Hill MA, Townley HE. Cytotoxicity, dose-enhancement and radiosensitization of glioblastoma cells with rare earth nanoparticles. Artif Cells Nanomed Biotechnol. 2019;47(1):132–43. https://doi.org/10.1080/21691401.2018.1544564.
109. Luo X, Wei L, Liu S, Wu K, Huang D, Xiao S, Guo E, Lei L, Qiu X, Zeng X. Correlation between urinary rare earth elements and liver function in a Zhuang population aged 35–74 years in Nanning. J Trace Elem Med Biol. 2024;84:127426. https://doi.org/10.1016/j.jtemb.2024.127426.
110. Ma J, Bishoff B, Mercer RR, Barger M, Schwegler-Berry D, Castranova V. Role of epithelial-mesenchymal transition (EMT) and fibroblast function in cerium oxide nanoparticles-induced lung fibrosis. Toxicol Appl Pharmacol. 2017;323:16–25. https://doi.org/10.1016/j.taap.2017.03.015.
111. Ma JY, Young SH, Mercer RR, Barger M, Schwegler-Berry D, Ma JK, Castranova V. Interactive effects of cerium oxide and diesel exhaust nanoparticles on inducing pulmonary fibrosis. Toxicol Appl Pharmacol. 2014;278(2):135–47. https://doi.org/10.1016/j.taap.2014.04.019.
112. Malhotra, N., H. S. Hsu, S. T. Liang, M. J. M. Roldan, J. S. Lee, T. R. Ger and C. D. Hsiao (2020). "An Updated Review of Toxicity Effect of the Rare Earth Elements (REEs) on Aquatic Organisms." Animals (Basel) 10(9), https://doi.org/10.3390/ani10091663.
113. Man N, Yu L, Yu SH, Wen LP. Rare earth oxide nanocrystals as a new class of autophagy inducers. Autophagy. 2010;6(2):310–1. https://doi.org/10.4161/auto.6.2.11138.
114. Marginson H, MacMillan GA, Grant E, Gérin-Lajoie J, Amyot M. Rare earth element bioaccumulation and cerium anomalies in biota from the Eastern Canadian subarctic (Nunavik). Sci Total Environ. 2023;879:163024. https://doi.org/10.1016/j.scitotenv.2023.163024.
115. Martino, C., T. Chianese, R. Chiarelli, M. C. Roccheri and R. Scudiero (2022). "Toxicological Impact of Rare Earth Elements (REEs) on the Reproduction and Development of Aquatic Organisms Using Sea Urchins as Biological Models." Int J Mol Sci 23(5), https://doi.org/10.3390/ijms23052876.
116. Mauro, M., M. Crosera, M. Monai, T. Montini, P. Fornasiero, M. Bovenzi, G. Adami, G. Turco and F. L. Filon (2019). "Cerium Oxide Nanoparticles Absorption through Intact and Damaged Human Skin." Molecules 24(20), https://dx.doi.org/10.3390/molecules24203759.
117. McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, Williamson EE, Eckel LJ. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. Radiology. 2015;275(3):772–82. https://doi.org/10.1148/radiol.15150025.
118. Meldrum K, Robertson SB, Römer I, Marczylo T, Dean LSN, Rogers A, Gant TW, Smith R, Tetley TD, Leonard MO. Cerium dioxide nanoparticles exacerbate house dust mite induced type II airway inflammation. Part Fibre Toxicol. 2018;15(1):24. https://doi.org/10.1186/s12989-018-0261-5.
119. Minarchick VC, Stapleton PA, Porter DW, Wolfarth MG, Çiftyürek E, Barger M, Sabolsky EM, Nurkiewicz TR. Pulmonary cerium dioxide

nanoparticle exposure differentially impairs coronary and mesenteric arteriolar reactivity. Cardiovasc Toxicol. 2013;13(4):323–37. https://doi.org/10.1007/s12012-013-9213-3.
120. Nel A, Xia T, Meng H, Wang X, Lin S, Ji Z, Zhang H. Nanomaterial toxicity testing in the 21st century: use of a predictive toxicological approach and high-throughput screening. Acc Chem Res. 2013;46(3):607–21. https://doi.org/10.1021/ar300022h.
121. Nelson BC, Johnson ME, Walker ML, Riley KR, Sims CM. Antioxidant Cerium Oxide Nanoparticles in Biology and Medicine. Antioxidants (Basel). 2016;5(2). https://doi.org/10.3390/antiox5020015.
122. O'Keefe MJ, Geng S, Joshi S. Cerium-based conversion coatings as alternatives to hex chrome: Rare-earth compounds provide resistance against corrosion for aluminum alloys in military applications. Metal Finishing. 2007;105(5): 25–28, https://doi.org/10.1016/S0026-0576(07)80547-2.
123. Pagano G, Aliberti F, Guida M, Oral R, Siciliano A, Trifuoggi M, Tommasi F. Rare earth elements in human and animal health: State of art and research priorities. Environmental Res. 2015;142: 215–220, https://doi.org/10.1016/j.envres.2015.06.039.
124. Pagano G, Guida M, Tommasi F, Oral R. Health effects and toxicity mechanisms of rare earth elements-Knowledge gaps and research prospects. Ecotoxicol Environ Saf. 2015;115:40–8. https://doi.org/10.1016/j.ecoenv.2015.01.030.
125. Palmer RJ, Butenhoff JL, Stevens JB. Cytotoxicity of the rare earth metals cerium, lanthanum, and neodymium in vitro: comparisons with cadmium in a pulmonary macrophage primary culture system. Environ Res. 1987;43(1):142–56. https://doi.org/10.1016/s0013-9351(87)80066-x.
126. Paul E, Franco-Montoya ML, Paineau E, Angeletti B, Vibhushan S, Ridoux A, Tiendrebeogo A, Salome M, Hesse B, Vantelon D, Rose J, Canouï-Poitrine F, Boczkowski J, Lanone S, Delacourt C, Pairon JC. Pulmonary exposure to metallic nanomaterials during pregnancy irreversibly impairs lung development of the offspring. Nanotoxicology. 2017;11(4):484–95. https://doi.org/10.1080/17435390.2017.1311381.
127. Prybylski, J. P., E. Maxwell, C. Coste Sanchez and M. Jay (2016). "Gadolinium deposition in the brain: Lessons learned from other metals known to cross the blood–brain barrier." Magnetic Resonance Imaging 34(10): 1366–1372, https://doi.org/10.1016/j.mri.2016.08.018.
128. Qiao, X., W. Cui, S. Gao, Q. Zhi, B. Li, Y. Fan, L. Liu, J. Gao and H. Tan (2022). "Occupational exposure to rare earth elements: Assessment of external and internal exposure." Environmental Pollution 309: 119801, https://doi.org/10.1016/j.envpol.2022.119801.
129. Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association Between MRI Exposure During Pregnancy and Fetal and Childhood Outcomes. JAMA. 2016;316(9):952–61. https://doi.org/10.1001/jama.2016.12126.
130. Ribeiro PG, de Oliveira C, Guerra MBB, de Carvalho TS, Martins GC, W. V. d. S. Pereira, S. J. Ramos and L. R. G. Guilherme,. Rare Earths as Emerging Trace Element Contaminants in the Soil. Current Pollution Reports. 2024. https://doi.org/10.1007/s40726-024-00312-y.
131. Ru XM, Yang ZY, Ran SY. Lanthanide ions induce DNA compaction with ionic specificity. Int J Biol Macromol. 2022;210:292–9. https://doi.org/10.1016/j.ijbiomac.2022.04.182.
132. Satapathy SN, Nial PS, Tulsiyan KD, Subudhi U. Light rare earth elements stabilize G-quadruplex structure in variants of human telomeric sequences. Int J Biol Macromol. 2024;254(Pt 2):127703. https://doi.org/10.1016/j.ijbiomac.2023.127703.
133. Sato T, Ito K, Tamada T, Kanki A, Watanabe S, Nishimura H, Tanimoto D, Higashi H, Yamamoto A. Tissue gadolinium deposition in renally impaired rats exposed to different gadolinium-based MRI contrast agents: evaluation with inductively coupled plasma mass spectrometry (ICP-MS). Magn Reson Imaging. 2013;31(8):1412–7. https://doi.org/10.1016/j.mri.2013.03.025.
134. Schroeder, H. A. and M. Mitchener (1971). "Scandium, Chromium(VI), Gallium, Yttrium, Rhodium, Palladium, Indium in Mice: Effects on Growth and Life Span." The Journal of Nutrition 101(10): 1431–1437, https://doi.org/10.1093/jn/101.10.1431.
135. Schwotzer D, Ernst H, Schaudien D, Kock H, Pohlmann G, Dasenbrock C, Creutzenberg O. Effects from a 90-day inhalation toxicity study with cerium oxide and barium sulfate nanoparticles in rats. Part Fibre Toxicol. 2017;14(1):23. https://doi.org/10.1186/s12989-017-0204-6.
136. Shilo M, Sharon A, Baranes K, Motiei M, Lellouche JP, Popovtzer R. The effect of nanoparticle size on the probability to cross the blood-brain barrier: an in-vitro endothelial cell model. J Nanobiotechnology. 2015;13:19. https://doi.org/10.1186/s12951-015-0075-7.
137. Shin SH, Lim CH, Kim YS, Lee YH, Kim SH, Kim JC. Twenty-eight-day repeated inhalation toxicity study of nano-sized lanthanum oxide in male sprague-dawley rats. Environ Toxicol. 2017;32(4):1226–40. https://doi.org/10.1002/tox.22319.
138. Sisler JD, Li R, McKinney W, Mercer RR, Ji Z, Xia T, Wang X, Shaffer J, Orandle M, Mihalchik AL, Battelli L, Chen BT, Wolfarth M, Andrew ME, Schwegler-Berry D, Porter DW, Castranova V, Nel A, Qian Y. Differential pulmonary effects of CoO and La2O3 metal oxide nanoparticle responses during aerosolized inhalation in mice. Part Fibre Toxicol. 2016;13(1):42. https://doi.org/10.1186/s12989-016-0155-3.
139. Song Z, Mao H, Liu J, Sun W, Wu S, Lu X, Jin C, Yang J. Lanthanum Chloride Induces Axon Abnormality Through LKB1-MARK2 and LKB1-STK25-GM130 Signaling Pathways. Cell Mol Neurobiol. 2023;43(3):1181–96. https://doi.org/10.1007/s10571-022-01237-0.
140. Sun J, Zhang Y, Yan L, Liu S, Wang W, Zhu Y, Wang W, Li S, He B, Wu L, Zhang L. Action of the Nrf2/ARE signaling pathway on oxidative stress in choroid plexus epithelial cells following lanthanum chloride treatment. J Inorg Biochem. 2022;231: 111792. https://doi.org/10.1016/j.jinorgbio.2022.111792.
141. Sun Y, Yang J, Hu X, Gao X, Li Y, Yu M, Liu S, Lu X, Jin C, Wu S, Cai Y. Lanthanum chloride reduces lactate production in primary culture rat cortical astrocytes and suppresses primary co-culture rat cortical astrocyte-neuron lactate transport. Arch Toxicol. 2018;92(4):1407–19. https://doi.org/10.1007/s00204-017-2148-x.
142. Survey, U. S. G. (2023). Mineral commodity summaries 2023. from https://www.usgs.gov/publications/mineral-commodity-summaries-2023.
143. Trapasso, G., S. Chiesa, R. Freitas and E. Pereira (2021). "What do we know about the ecotoxicological implications of the rare earth element gadolinium in aquatic ecosystems?" Science of The Total Environment 781: 146273, https://doi.org/10.1016/j.scitotenv.2021.146273.
144. Unruh, C., N. Van Bavel, M. Anikovskiy and E. J. Prenner (2020). "Benefits and Detriments of Gadolinium from Medical Advances to Health and Ecological Risks." Molecules 25(23), https://doi.org/10.3390/molecules25235762.
145. USEPA. Rare Earth Elements: a Eeview of Production, Processing, Recycling,and Associated Environmental Issues. EPA600/R-12/572. US Environmental Protection Agency. 2012. www.epa.gov/ord.,
146. U.S. Geological Survey. Mineral commodity summaries 2022. Reston: U.S. Geological Survey; 2022. Accessed at https://doi.org/10.3133/mcs2022.
147. Vakifahmetoglu-Norberg H, Ouchida AT, Norberg E. The role of mitochondria in metabolism and cell death." Biochemical and Biophysical Research Communications. 2017;482(3): 426–431, https://doi.org/10.1016/j.bbrc.2016.11.088.
148. Van Gosen BS, Verplanck PL, Long KR, Gambogi J, Seal Ii RR. The rare-earth elements: Vital to modern technologies and lifestyles. Fact Sheet. Reston, VA: 2014;4.
149. Verstraelen S, Remy S, Casals E, De Boever P, Witters H, Gatti A, Puntes V, Nelissen I. Gene expression profiles reveal distinct immunological responses of cobalt and cerium dioxide nanoparticles in two in vitro lung epithelial cell models. Toxicol Lett. 2014;228(3):157–69. https://doi.org/10.1016/j.toxlet.2014.05.006.
150. Viana LN, Soares APS, Guimarães DL, Rojano WJS, Saint'Pierre TD. Fluorescent lamps: A review on environmental concerns and current recycling perspectives highlighting Hg and rare earth elements. J Environmental Chemical Engineering. 2022;10(6): 108915, https://doi.org/10.1016/j.jece.2022.108915.
151. Wang B, Yan L, Huo W, Lu Q, Cheng Z, Zhang J, Li Z. Rare earth elements and hypertension risk among housewives: A pilot study in Shanxi Province, China. Environ Pollut. 2017;220(Pt B):837–42. https://doi.org/10.1016/j.envpol.2016.10.066.
152. Wang J, Li J, Jiang C, Song J, Yang X, Ma X, Luo K, Wu P, Chong X, Feng J. Advanced rare earth tantalate RETaO4 (RE=Dy, Gd and Sm) with excellent oxygen/thermal barrier performance. J Rare Earths. 2024.https://doi.org/10.1016/j.jre.2024.05.012.

153. Wang L, Ai W, Zhai Y, Li H, Zhou K, Chen H. Effects of Nano-CeO_2 with Different Nanocrystal Morphologies on Cytotoxicity in HepG2 Cells. Int J Environ Res Public Health. 2015;12(9):10806–19. https://doi.org/10.3390/ijerph120910806.
154. Wang S, Bu N, Yun Y, Shi X, Wang S, Gao Y. RNA-Seq Analysis of Testes from Mice Exposed to Neodymium Oxide. Toxics 2023;11(12). https://doi.org/10.3390/toxics11120952.
155. Wang X, Tang M, Ge J, Jiang W, Li Z, Xiao Q, Meng Q, Jiang J, Hao W, Wei X. Effects of intrauterine and lactational exposure to lanthanum nitrate on BALB/c offspring mice: Developmental immunotoxicity and self-recovery. Toxicol Lett. 2022;362:17–25. https://doi.org/10.1016/j.toxlet.2022.01.013.
156. Wason MS, Lu H, Yu L, Lahiri SK, Mukherjee D, Shen C, Das S, Seal S, Zhao J. Cerium Oxide Nanoparticles Sensitize Pancreatic Cancer to Radiation Therapy through Oxidative Activation of the JNK Apoptotic Pathway. Cancers (Basel). 2018;10(9), https://doi.org/10.3390/cancers10090303.
157. Wei J, Wang C, Yin S, Pi X, Jin L, Li Z, Liu J, Wang L, Yin C, Ren A. Concentrations of rare earth elements in maternal serum during pregnancy and risk for fetal neural tube defects. Environ Int. 2020;137: 105542. https://doi.org/10.1016/j.envint.2020.105542.
158. Wingard CJ, Walters DM, Cathey BL, Hilderbrand SC, Katwa P, Lin S, Ke PC, Podila R, Rao A, Lust RM, Brown JM. Mast cells contribute to altered vascular reactivity and ischemia-reperfusion injury following cerium oxide nanoparticle instillation. Nanotoxicology. 2011;5(4):531–45. https://doi.org/10.3109/17435390.2010.530004.
159. Wu J, Yang J, Liu Q, Wu S, Ma H, Cai Y. Lanthanum induced primary neuronal apoptosis through mitochondrial dysfunction modulated by Ca^{2+} and Bcl-2 family. Biol Trace Elem Res. 2013;152(1):125–34. https://doi.org/10.1007/s12011-013-9601-3.
160. Wu J, Yang J, Lu X, Jin C, Wu S, Zhang L, Hu X, Ma H, Cai Y. Lanthanum Chloride Impairs the Blood-Brain Barrier Integrity by Reduction of Junctional Proteins and Upregulation of MMP-9 in Rats. Biol Trace Elem Res. 2019;187(2):482–91. https://doi.org/10.1007/s12011-018-1402-2.
161. Wu Y, Tang X, Yang W, Fan J, Tang L, Wang C, Yu Z, Jia XD, Fan B. Subchronic toxicity of cerium nitrate by 90-day oral exposure in wistar rats. Regul Toxicol Pharmacol. 2019;108: 104474. https://doi.org/10.1016/j.yrtph.2019.104474.
162. Wu YP, Mi Y, Shen H, Yao HY, Cheng Y, Wang X, Zhang JX. Studies of rare earth element distribution and action in human erythrocyte and animal hepatocyte by PIXE. Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms. 2002;189(1): 459–463, https://doi.org/10.1016/S0168-583X(01)01125-9.
163. Xia T, Kovochich M, Liong M, Mädler L, Gilbert B, Shi H, Yeh JI, Zink JI, Nel AE. Comparison of the mechanism of toxicity of zinc oxide and cerium oxide nanoparticles based on dissolution and oxidative stress properties. ACS Nano. 2008;2(10):2121–34. https://doi.org/10.1021/nn800511k.
164. Xiao X, Yong L, Jiao B, Yang H, Liang C, Jia X, Liu Z, Sang Y, Song Y. Postweaning exposure to lanthanum alters neurological behavior during early adulthood in rats. Neurotoxicology. 2021;83:40–50. https://doi.org/10.1016/j.neuro.2020.12.012.
165. Xiong L, Huang J, Wang S, Yuan Q, Yang D, Zheng Z, Wu Y, Wu C, Gao Y, Zou L, Hu G. Yttrium chloride-induced cytotoxicity and DNA damage response via ROS generation and inhibition of Nrf2/PPARγ pathways in H9c2 cardiomyocytes. Arch Toxicol. 2022;96(3):767–81. https://doi.org/10.1007/s00204-022-03225-1.
166. Xiong L, Huang J, Wu C, Yuan Q, Wang S, Zhu L, Li Z, Sun Z, Fang Y, Li W, Hu G. Yttrium chloride induces ferroptosis in cardiomyocytes via iron accumulation and triggers cardiac lipid peroxidation and inflammation that cause heart adverse events in mice. Ecotoxicol Environ Saf. 2023;263:115279. https://dx.doi.org/10.1016/j.ecoenv.2023.115279.
167. Xu L, Xiao Q, Kang C, Wei X, Hao W. Lanthanum nitrate inhibits adipogenesis in 3T3-L1 preadipocytes with a disorder of mitotic clonal expansion process. J Appl Toxicol. 2023;43(3):402–15. https://doi.org/10.1002/jat.4391.
168. Xu T, Zhang M, Hu J, Li Z, Wu T, Bao J, Wu S, Lei L, He D. Behavioral deficits and neural damage of Caenorhabditis elegans induced by three rare earth elements. Chemosphere. 2017;181:55–62. https://doi.org/10.1016/j.chemosphere.2017.04.068.
169. Xu W, Bai G, Pan E, Li D, Zhang J, Xu S. Advances, optical and electronic applications of functional materials based on rare earth sulfide semiconductors. Materials Design. 2024;238: 112698, https://doi.org/10.1016/j.matdes.2024.112698.
170. Xu X, Wang Y, Han N, Yang X, Ji Y, Liu J, Jin C, Lin L, Zhou S, Luo S, Bao H, Liu Z, Wang B, Yan L, Wang HJ, Ma X. Early Pregnancy Exposure to Rare Earth Elements and Risk of Gestational Diabetes Mellitus: A Nested Case-Control Study. Front Endocrinol (Lausanne). 2021;12: 774142. https://doi.org/10.3389/fendo.2021.774142.
171. Xu X, Zhu W, Wang Z, Witkamp GJ. Distributions of rare earths and heavy metals in field-grown maize after application of rare earth-containing fertilizer. Sci Total Environ. 2002;293(1–3):97–105. https://doi.org/10.1016/s0048-9697(01)01150-0.
172. Yabuki K, Haratake J, Tsuda Y, Shiba E, Harada H, Yorita K, Uchihashi K, Matsuyama A, Hirata K, Hisaoka M. Lanthanum-Induced Mucosal Alterations in the Stomach (Lanthanum Gastropathy): a Comparative Study Using an Animal Model. Biol Trace Elem Res. 2018;185(1):36–47. https://doi.org/10.1007/s12011-017-1235-4.
173. Yang J, Liu Q, Zhang L, Wu S, Qi M, Lu S, Xi Q, Cai Y. Lanthanum chloride impairs memory, decreases pCaMK IV, pMAPK and pCREB expression of hippocampus in rats. Toxicol Lett. 2009;190(2):208–14. https://doi.org/10.1016/j.toxlet.2009.07.016.
174. Yang Q, Liu Y, Wang L, Zhou Q, Cheng M, Zhou J, Huang X. Cerium exposure in Lake Taihu water aggravates microcystin pollution via enhancing endocytosis of Microcystis aeruginosa. Environ Pollut. 2022;292(Pt A): 118308. https://doi.org/10.1016/j.envpol.2021.118308.
175. Yao C, Ma Y. Superconducting materials: Challenges and opportunities for large-scale applications. iScience. 2021;24(6): 102541, https://doi.org/10.1016/j.isci.2021.102541.
176. Yu L, Lu Y, Man N, Yu SH, Wen LP. Rare earth oxide nanocrystals induce autophagy in HeLa cells. Small. 2009;5(24):2784–7. https://doi.org/10.1002/smll.200901714.
177. Yuan L, Li Q, Bai D, Shang X, Hu F, Chen Z, An T, Chen Y, Zhang X. La(2)O(3) Nanoparticles Induce Reproductive Toxicity Mediated by the Nrf-2/ARE Signaling Pathway in Kunming Mice. Int J Nanomedicine. 2020;15:3415–31. https://doi.org/10.2147/ijn.S230949.
178. Yuan Z-K, Liu Y, Yu H-Q. Study on relationship between rare earth level in blood and health condition of residents. Chin J Public Health. 2003;19(2):133–5.
179. Zaichick S, Zaichick V, Karandashev V, Nosenko S. Accumulation of rare earth elements in human bone within the lifespan. Metallomics. 2011;3(2):186–94. https://doi.org/10.1039/c0mt00069h.
180. Zhang H, Feng J, Zhu W, Liu C, Xu S, Shao P, Wu D, Yang W, Gu J. Chronic toxicity of rare-earth elements on human beings: implications of blood biochemical indices in REE-high regions, South Jiangxi. Biol Trace Elem Res. 2000;73(1):1–17. https://doi.org/10.1385/bter:73:1:1.
181. Zhang H, Zhang H. Special Issue: Rare earth luminescent materials. Light: Sci Applications 2022;11(1): 260. https://doi.org/10.1038/s41377-022-00956-9.
182. Zhao C, Yang J, Zhang X, Fang X, Zhang N, Su X, Pang H, Li W, Wang F, Pu Y, Xia Y. A human health risk assessment of rare earth elements through daily diet consumption from Bayan Obo Mining Area, China. Ecotoxicol Environ Saf. 2023;266: 115600. https://doi.org/10.1016/j.ecoenv.2023.115600.
183. Zhao H, Cheng J, Cai J, Cheng Z, Cui Y, Gao G, Hu R, Gong X, Wang L, Hong F. Liver injury and its molecular mechanisms in mice caused by exposure to cerium chloride. Arch Environ Contam Toxicol. 2012;62(1):154–64. https://doi.org/10.1007/s00244-011-9672-0.
184. Zhao H, Hong J, Yu X, Zhao X, Sheng L, Ze Y, Sang X, Gui S, Sun Q, Wang L, Hong F. Oxidative stress in the kidney injury of mice following exposure to lanthanides trichloride. Chemosphere. 2013;93(6):875–84. https://doi.org/10.1016/j.chemosphere.2013.05.034.
185. Zhao WH, Gou BD, Zhang TL, Wang K. Lanthanum chloride bidirectionally influences calcification in bovine vascular smooth muscle cells. J Cell Biochem. 2012;113(5):1776–86. https://doi.org/10.1002/jcb.24049.
186. Zhao Y, Liang J, Meng H, Yin Y, Zhen H, Zheng X, Shi H, Wu X, Zu Y, Wang B, Fan L, Zhang K. Rare Earth Elements Lanthanum and Praseodymium Adversely Affect Neural and Cardiovascular Development in Zebrafish (Danio rerio). Environ Sci Technol. 2021;55(2):1155–66. https://doi.org/10.1021/acs.est.0c06632.
187. Zhong H, Geng Y, Chen J, Gao R, Yu C, Yang Z, Chen X, Mu X, Liu X, He J. Maternal exposure to CeO(2)NPs during early pregnancy impairs pregnancy by inducing placental abnormalities. J Hazard Mater. 2020;389: 121830. https://doi.org/10.1016/j.jhazmat.2019.121830.
188. Zhu W, Xu S, Shao P, Zhang H, Wu D, Yang W, Feng J. Bioelectrical activity of the central nervous system among populations in a rare earth

element area. Biol Trace Elem Res. 1997;57(1):71–7. https://doi.org/10.1007/bf02803871.
189. Zhuang M, Xie H, Jiang Y, Xiao P, Wang K, Chu Z, Zhao J, Zhang T. Probabilistic assessment of dietary rare earth elements intake among people living near a rare earth ore. Sci Total Environ 2023;856: 159141, https://doi.org/10.1016/j.scitotenv.2022.159141.
190. Zhuang M, Zhao J, Li S, Liu D, Wang K, Xiao P, Yu L, Jiang Y, Song J, Zhou J, Wang L, Chu Z. Concentrations and health risk assessment of rare earth elements in vegetables from mining area in Shandong, China. Chemosphere. 2017;168:578–82. https://doi.org/10.1016/j.chemosphere.2016.11.023.

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