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Review

Rare Earth Elements (REEs) in veterinary medicine: practical applications and tissue distribution in terrestrial vertebrate animals

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Abstract

Rare earth elements (REEs) have shown promising potential in veterinary medicine, particularly as feed additives and diagnostic and therapeutic tools. Moreover, the increasing industrial use of REEs has raised concerns about their potential environmental contamination and bioaccumulation in animal tissues. While numerous studies have focused on the distribution of REEs in marine and freshwater ecosystems, information regarding their presence in terrestrial environments remains fragmented. This narrative review aims to describe the practical applications of REEs in veterinary medicine, with a specific focus on studies evaluating the potential accumulation of these elements in the tissues of terrestrial vertebrate animals. Additionally, the review addresses research on the intentional residual presence of REEs and in-field studies evaluating the contamination burden from REE exposure in domestic and wild animals. In conclusion, this review identifies critical scientific gaps and provides future research directions to advance understanding of the long-term effects, mechanisms of action, and environmental impacts of REEs in veterinary practices.

Keywords

domestic animals, emerging contaminants, environment, lanthanides

Introduction

Rare Earth Elements (REEs) are a group of 17 chemical elements that include the 15 lanthanides and due to their chemical similarity, encompasses also two transition metals namely scandium and yttrium 1. The 15 lanthanides are a series of elements located in the sixth period of group IIIB on the periodic table, known for their similar properties, particularly their magnetic and optical characteristics. They include the following elements: lanthanum (La), cerium (Ce), praseodymium (Pr), neodymium (Nd), promethium (Pm), samarium (Sm), europium (Eu), gadolinium (Gd), terbium (Tb), dysprosium (Dy), holmium (Ho), erbium (Er), thulium (Tm), ytterbium (Yb) and lutetium (Lu).

The term "rare earth" is a historical artifact reflecting the initial challenges in discovering and extracting these elements rather than their actual abundance in nature. Despite their name, many REEs are quite common in the Earth's crust, but their economic extraction remains complex and resource-intensive 2. The adjective "rare” is a bit of a misnomer and has historical roots rather than accurately reflecting the actual abundance of these elements. The term "earth", indeed, refers to the fact that these elements were initially discovered in oxide forms, which were historically referred to as "earths" by chemists. Although termed "rare," most rare earth elements are relatively abundant in the Earth's crust. However, they are rarely found concentrated in pure deposits. Instead, they tend to be dispersed and mixed with other minerals, making extraction and purification challenging. Moreover, the difficulty in extracting and refining REEs contributed to their reputation as "rare." These processes often involve complex, time-consuming, and costly methods due to the chemical similarity of the elements to each other, which makes them hard to separate 2.

REEs are increasingly used in nowadays technologies, from the production of electronic devices to industrial catalysts.

However, the growing use of rare earths has raised concerns about their potential toxicity and environmental impact, including their effects on domestic mammals and terrestrial and aquatic ecosystems. The economic importance of rare earth elements lies in their multiple and critical applications across high-tech industries, green technology, defense, healthcare, and agriculture. The high-tech applications of REEs include their use in the manufacturing of electronic devices such as smartphones, computers, and televisions 3. Elements like neodymium, praseodymium, and dysprosium are crucial for producing powerful magnets used in hard drives and loudspeakers. In the field of green technology neodymium and dysprosium are essential for making permanent magnets used in wind turbines and electric vehicle motors. Lanthanum and cerium are also important for catalytic converters and battery technologies 1. The global supply chain of REEs is highly concentrated and restricted, with China dominating over 80% of the world's production and processing capacity 4. This evidence poses strategic vulnerabilities for other nations reliant on these materials. Diversifying supply sources and developing recycling technologies are therefore crucial for ensuring stable supplies of these critical materials.

Recent experimental and epidemiological studies indicate that REEs can have both positive and negative health effects on domestic terrestrial animals. For instance, in China, REEs have been successfully used as feed additives to improve growth and feed conversion in different farm animals, including chickens, pigs, ducks, and cattle 5. These additives have been associated with increased body weight and improvements in milk production in dairy cows and egg production in laying hens. However, data from these studies should be interpreted cautiously, as they often lack methodological details and long-term health monitoring. Despite their potential benefits, there are also potential harmful risks associated with exposure to REEs. These elements can be toxic if ingested in large quantities and can accumulate in animal tissues, leading to potential negative health consequences. Studies on animals suggest that rare earths can cause specific organ damage, negatively affect growth and embryonic development, and cause cytotoxicity.

Research on the effects of rare earths on domestic animals is still limited, and further studies are needed to fully understand their impacts. To date, most studies have focused on aquatic organisms, which are considered good ecotoxicological indicators, but it is essential to expand this research to terrestrial mammals to obtain more comprehensive and reliable data.

The aim of the present narrative literature review is to describe the applications of REEs in veterinary medicine highlighting also studies evaluating their potential accumulation in tissue of terrestrial animal vertebrates.

Applications of REEs in veterinary medicine

Rare earth elements (REEs) due to their unique properties find practical applications in various medical fields. In veterinary medicine, although not extensively studied, these elements are potentially used as feed additives to improve growth performance of farm animals 6. In rabbits, cerium oxide (CeO) administration improved average daily feed intake, body weight gain, feed conversion rate and blood mean corpuscular haemoglobin, differential leukocyte counts, and urea 7 8. In pregnant rabbits, REEs diet administration improved litter weight and embryo survival rate enhancing animal reproductive performance 9. In pigs REE-enrich yeast administration increased average daily gain, feed conversion rate, blood lymphocyte counts and total tract digestibility 10. In laying hens dietary CeO improved feed conversation rate, increase egg production and shell breaking strength decreasing also SOD and MDA levels 11 12. Moreover, in the same animal species, La and Ce increased Ca and P plasma levels in first and second month 13, improved laying rate, enhanced egg embryo development and embryo survival rate 14. In 10-day-old broilers the administration of rare earth nitrate improved the body weight gain 15. In sheep, a linear increase in nutrients digestibility with a significant decrease in ruminal pH (6.72 to 6.53) and ruminal ammonia content and an improve of ruminal microbial protein synthesis was observed with increasing REE supplementation 16. In Simmental steers a linear and quadratic increase of total volatile fatty acids and propionate with increasing La supplementation 17. Despite REEs are widely used as feed additives, the potential mechanism of action in animal growth performance modulation is still less clarified.18 suggested four potential mechanisms through which rare earth elements (REEs) could benefit animal health: enhancing enzyme activity, improving protein metabolism, suppressing bacterial growth, and promoting the secretion of digestive fluids in the stomach. Additionally, 19 proposed that REEs have anti-inflammatory and immunostimulating effects that could promote animal growth. 20 considered effects on hormone activity and cell proliferation as further mechanisms for the beneficial impact of REEs. These elements have been shown to possess antibacterial properties by selectively inhibiting the growth of certain bacterial species in the gastrointestinal tract. Research by 21 and 22 found that REEs suppressed the growth of several bacteria in a dose-dependent manner.

In Europe, the use of REEs as feed additives is a relatively new area of interest, and thus, specific regulations directly targeting REEs in animal feed are still under development. However, the general principles of food safety, environmental protection, and animal health apply to their use, and any new feed additive, including those containing REEs, must undergo rigorous safety assessments by the European Food Safety Authority (EFSA) before being approved for use. This ensures that any potential health risks to animals and humans, as well as environmental impacts, are thoroughly evaluated. The Directive 2002/32/EC on undesirable substances in animal feed establishes maximum permissible levels for contaminants, including certain metals, dioxins, and pesticides, but does not currently include specific limits for REEs 23. This directive is regularly updated based on scientific and technical advancements to ensure the continued safety of animal feed. Recently, the European Commission just enacted the law No. 2020/1370 on October 1, 2020 approving the use of REE citrate “Lancer” feed additive for weaned piglets 24.

Rare earth elements (REEs) are also gaining attention in veterinary medicine for their diagnostic and therapeutic potential. Gadolinium-based contrast agents are widely used in Magnetic Resonance Imaging (MRI) to enhance the visibility of internal structures. They improve the accuracy of diagnoses in animals by highlighting abnormalities in tissues such as the brain, spine, and joints modifying longitudinal and transverse magnetic relaxation, shortening the T1 and T2 of the tissues where it concentrates 25. Unbound gadolinium is highly toxic and so is chelated to reduce toxicity. Gadolinium chelates do not cross the normal blood–brain barrier due to their large molecular size 26. Several gadolinium-chelates are used for MRI contrast studies. However, none of them is authorized for veterinary use and all are for only medicine prescription 27. Cerium oxide nanoparticles (CNPs) have attracted great attention in the field of nanotechnology due to their self-regenerating antioxidant properties. Cerium oxide nanoparticles have been shown to exhibit significant antioxidant activity against various reactive species, including superoxide radicals, hydrogen peroxide, hydroxyl radicals, peroxynitrite, and nitric oxide. This has been demonstrated in both *in vitro* and *in vivo* studies, where CNPs mimic antioxidant enzymes and exhibit anti-inflammatory properties 28. Given that oxidative stress caused by excessive reactive oxygen species (ROS) is linked to numerous pathological conditions, CNPs present a promising therapeutic potential for treating a variety of acute and chronic diseases also in domestic animals due to their bio-mimetic antioxidant capabilities.

Concentrations of REEs in terrestrial vertebrate animals

The residual impacts of REEs in animal carcasses are a topic of growing interest due to the potential implications for food safety and environmental health. REEs can accumulate in various tissues of animals, but the extent and distribution vary depending on the specific element and animal species. Commonly studied REEs include La, Ce, and Gd. Studies have shown that REEs tend to accumulate more in the liver, bones, and kidneys of animals, with lower concentrations in muscle tissues 24. 29 reported high concentrations of REEs in pig bones, suggesting a high affinity for bone tissue. Additionally, rapid elimination of REEs from liver tissue and preserved meat quality were observed after supplementation of chickens with REEs, with no significant accumulation in either chicken liver or muscle 30. Similarly, in meat-breed ducks, REE residues in meat and liver tissues ranged from 0.1 to 0.2 mg/kg, with only trace amounts detected in eggs 31. 32 concluded that REEs were detected in low, safe concentrations in chickens, pigs, and fish, with the highest concentrations found in bone, gill, and fin tissues; however, this accumulation went to rapid elimination. In a recent study the content of rare earth elements (REEs) and other elements were evaluated in hen eggs sold in Italy aiming to compare the differences among various farming methods and assess the associated health risks for consumers 33. The results of the study showed as REE concentrations were generally low in hen eggs, irrespective of the farming method. However, certain elements such as La and Ce were detected at varying levels. Moreover, eggs from different farming methods (organic, free-range, barn, and cage) showed some variation in REE concentrations. Organic eggs tended to have slightly higher levels of certain elements, possibly due to the natural soil and feed variations in organic farming. However, these levels were still within safe limits for human consumption. The findings indicated that the consumption of hen eggs from all farming methods posed no significant health risk to consumers, as the levels of REEs and other potentially toxic elements were well below harmful thresholds 33. Several regulatory and monitoring efforts are underway to develop guidelines and regulations for the permissible levels of REEs in animal feed and food products. Regulatory bodies are working to establish maximum residue levels (MRLs) for REEs in food products to ensure consumer safety. Moreover, increased surveillance and monitoring of REE levels in animal tissues and food products should be guaranteed to assess potential risks and implement mitigation strategies.

In relation to the diagnostic use of REEs as contrast agents in MRI, gadolinium was detectable at a level of 1.5 to 2.5 µg gadolinium/g tissue in dog cerebellum 35 months after last MRI examination 26. In another experimental study on Swiss-Alpine sheep, at 10 weeks after injection, gadolinium-based contrast agents resulted in highest mean concentrations in the kidney (502 ng/g) and liver (445 ng/g) while low concentrations were found in the deep cerebellar nuclei (30 ng/g). No histopathologic alterations were observed irrespective of tissue concentrations within any examined organ 34.

Despite the intentional use of rare earth elements (REEs) in veterinary medicine as feed additives and diagnostic/therapeutic agents, there is growing evidence of potential contamination in various ecosystems due to their widespread industrial applications.

REE concentrations have been detected in the feathers of various bird species, including Sandwich terns (*Thalasseussandvicensis*), Kentish plovers (*Charadriusalexandrinus*), and Humboldt penguins (*Spheniscushumboldti*) 35 36 37. Specifically, the concentrations of REEs in the feathers of young Sandwich terns, aged 16-20 days, were the highest reported in the literature for bird feathers, measuring 940.9 ± 223.0 ng/g 36. Additionally, REE concentrations in the feathers of Kentish plovers indicated significant exposure to these elements, with considerable variation depending on the geographical location 35. Just few studies have examined the concentrations of rare earth elements (REEs) in the tissues of terrestrial vertebrate animals, highlighting their environmental and biological impacts. A study focusing on terrestrial ecosystems in the eastern Canadian Arctic revealed that REEs generally follow a coherent bioaccumulation pattern in different tissues of animals. The research showed that vertebrates from all ecosystems, including marine, freshwater and terrestrial, had REE muscle concentrations that were orders of magnitude lower than REE concentrations in biota near the base of the food web 38. The authors evaluated muscle and liver REE concentrations in three terrestrial herbivores: snowshoe hare (*Lepus americanus*), willow ptarmigan (*Lagopuslagopus*), and caribou (*Rangifer tarandus*). All animals had low mean REE muscle concentrations, less than 0.01 mg/kg and REE concentrations in liver were consistently higher (approx. 4 - 200 times) than in muscle for all vertebrates with statistically significant differences were statistically significant for willow ptarmigan 38. Overall, the study highlights the presence of REEs in terrestrial ecosystems of the eastern Canadian Arctic, primarily from natural geological sources with some anthropogenic contributions. While current levels are generally low, the potential for bioaccumulation and long-term ecological impacts necessitates ongoing monitoring and regulatory attention. One significant study analyzed the concentrations of REEs in the marine and terrestrial matrices of Northern Italy 37. This research highlighted that the highest REE values were found in plant feed within terrestrial environments, due to the lithophilic nature of these elements. However, the study also noted lower concentrations in animal tissues compared to plants and soils, suggesting limited bioaccumulation potential within higher trophic levels of terrestrial vertebrates. In fact, the highest REE concentrations were found in plant feed (mean value 1.8 mg/kg), followed by wildlife livers (0.043 mg/kg), fruit (0.0088 mg/kg), and honey (0.0078 mg/kg) 37. Liver samples from different wild species (n = 15, wild boar, roe deer, deer, sparrow hawk, tawny owl, crow) were collected in Aosta valley (Italy) from animals found dead by local veterinarian services. REE contents in animal tissues were related to the geochemical characteristics of the regions where animals live. In fact, the same authors in a previous investigation found a REE concentrations of 3.0 mg/kg in forage from the same geographical area, values that were consistent with those recorded in wildlife livers 39. Another recent Italian study aimed to evaluate the liver concentrations of REEs in domestic dogs (*Canis lupus familiaris*) and Apennine wolves (*Canis lupus italicus*) living in the Abruzzo region, Italy, considering also biological, nutritional, and lifestyle factors 33. The study found that wolves had statistically significantly higher concentrations of rare earth elements (REEs) in their livers compared to domestic dogs. Additionally, genetic differences influenced REE levels, with purebred wolves exhibiting higher liver concentrations of REEs than wolf-dog hybrids. Among dogs, females and adults showed elevated REE levels compared to males and juveniles, while diet and lifestyle factors did not result in significant differences in REE concentrations 33. In another study, the same researchers examined REE concentrations with regard to the pathological condition of the animals 40. Specifically, they measured REE levels in healthy and neoplastic Formalin-Fixed Paraffin-Embedded (FFPE) mammary gland tissues of dogs. They found that healthy mammary tissues had higher REE concentrations compared to neoplastic mammary glands. These findings confirmed that there are differences in inorganic element concentrations between healthy and neoplastic tissues, underscoring the potential importance of these variations in toxicologic pathology 40.

Potential toxicological effects of REEs

Rare earth elements (REEs) can accumulate in human and animal bodies after prolonged exposure . Various studies have reported the presence of REEs in different human matrices, such as hair 41, nails 42, placenta , serum 43, and breast milk . Human exposure to REEs can occur through iatrogenic, occupational, and likely environmental routes. A well-known iatrogenic exposure is the use of gadolinium (Gd) as a contrast agent in magnetic resonance imaging, with reports in recent years linking it to renal toxicity, specifically nephrogenic systemic fibrosis 44. Occupational exposure to REE dust has been associated with pneumoconiosis 45, while environmental exposures among populations living near REE mining sites have shown bioaccumulation correlated with proximity to these sites 46 47. However, recent studies highlight that the global increase in waste electrical and electronic equipment, which is rich in REEs, has intensified environmental pollution and posed new health risks due to REE exposure 48. The persistence and long half-lives of these pollutants facilitate their spread through air and other pathways, extending REE exposure beyond mining areas 49.

The adverse health effects linked to REE exposure include cardiotoxicity, neurotoxicity, and reproductive toxicity 50. Several epidemiological studies have also examined the impact of prenatal REE exposure on neonatal health. A recent study investigating the association between REE levels and thyroid hormone levels, as well as birth outcomes in 109 newborns in Beijing, China, detected 14 REEs in umbilical cord serum. Higher concentrations of terbium (Tb) and lutetium (Lu) were inversely correlated with birth length, while a positive association was found between exposure to a mixture of 14 REEs and levels of free thyroxine (FT4), triiodothyronine (T3), and birth length 51.

The apparent contradiction between favorable and adverse health effects related to REEs is often attributed to the well-known phenomenon of hormesis, which has been reported for various xenobiotics and physical agents 52. Hormesis is a biphasic dose–response phenomenon characterized by a low-dose stimulation and a high-dose inhibition 53. The available data on REE-related effects suggest hormetic trends in several studies involving different REEs. Interestingly, endocrine-disrupting chemicals, such as xenoestrogens, often show an inverted U-shaped dose-response curve, similar to the low-dose stimulation seen in hormesis 54.

Among the key events associated with adverse outcomes from REE exposure, oxidative stress and cytotoxicity are frequently discussed. Redox imbalance leading to oxidative stress has been demonstrated for several REEs in numerous experimental studies using both plant and animal models, suggesting that oxidative stress may underlie the toxicity of many REEs 55. However, it is important to note that some studies have reported antioxidant effects for certain REEs, such as cerium oxide (CeO2), indicating potential clinical applications 56. Cytogenetic effects, including the inhibition of mitotic activity, mitotic aberrations, and micronuclei induction, have been observed in both plant and animal cells 57. Additionally, recent studies have identified epigenetic changes, such as alterations in non-coding RNA expression profiles and DNA methylation, as potential toxicological events related to REE exposure 58 59.

Conclusions

Rare earth elements (REEs) hold significant potential in veterinary medicine, particularly as feed additives and diagnostic tools. Their ability to enhance growth, improve nutrient absorption, and boost immune responses in animals positions them as valuable assets in animal health management. However, to fully harness these benefits while mitigating risks, careful regulation and extensive research are necessary.Addressing the long-term effects of REE supplementation on animal health and productivity is crucial. More studies are needed to understand these impacts over extended periods. Additionally, elucidating the precise biological mechanisms by which REEs exert their effects will help optimize their use and improve their efficacy.Assessing the environmental impact of widespread REE use in agriculture and animal husbandry is also essential to ensure sustainable practices. The widespread industrial use of REEs has led to detectable concentrations in various ecosystems, including terrestrial environments. With the anticipated increase in REE industrial applications, it is plausible to expect a scenario of increased environmental contamination by these elements.Given the interrelated nature of human, animal, and environmental health within the One Health framework, it is imperative to conduct further field studies to monitor the environmental background levels of REEs and assess both animal and human exposure. Establishing the real scenario of REE exposure is essential for building effective risk assessment strategies. In conclusion, while REEs offer significant benefits in veterinary medicine, comprehensive research and careful regulatory oversight are necessary to fully realize their potential while ensuring safety for animals, humans, and the environment.

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