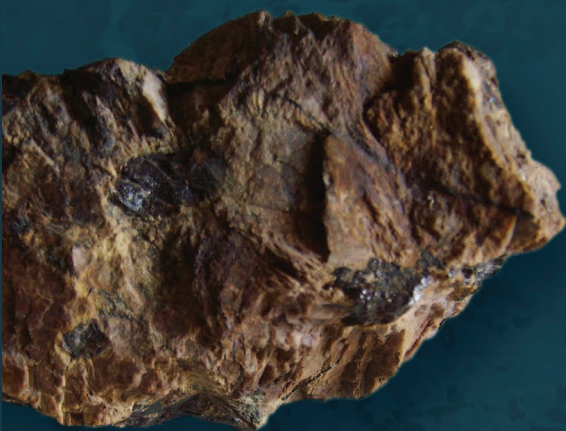


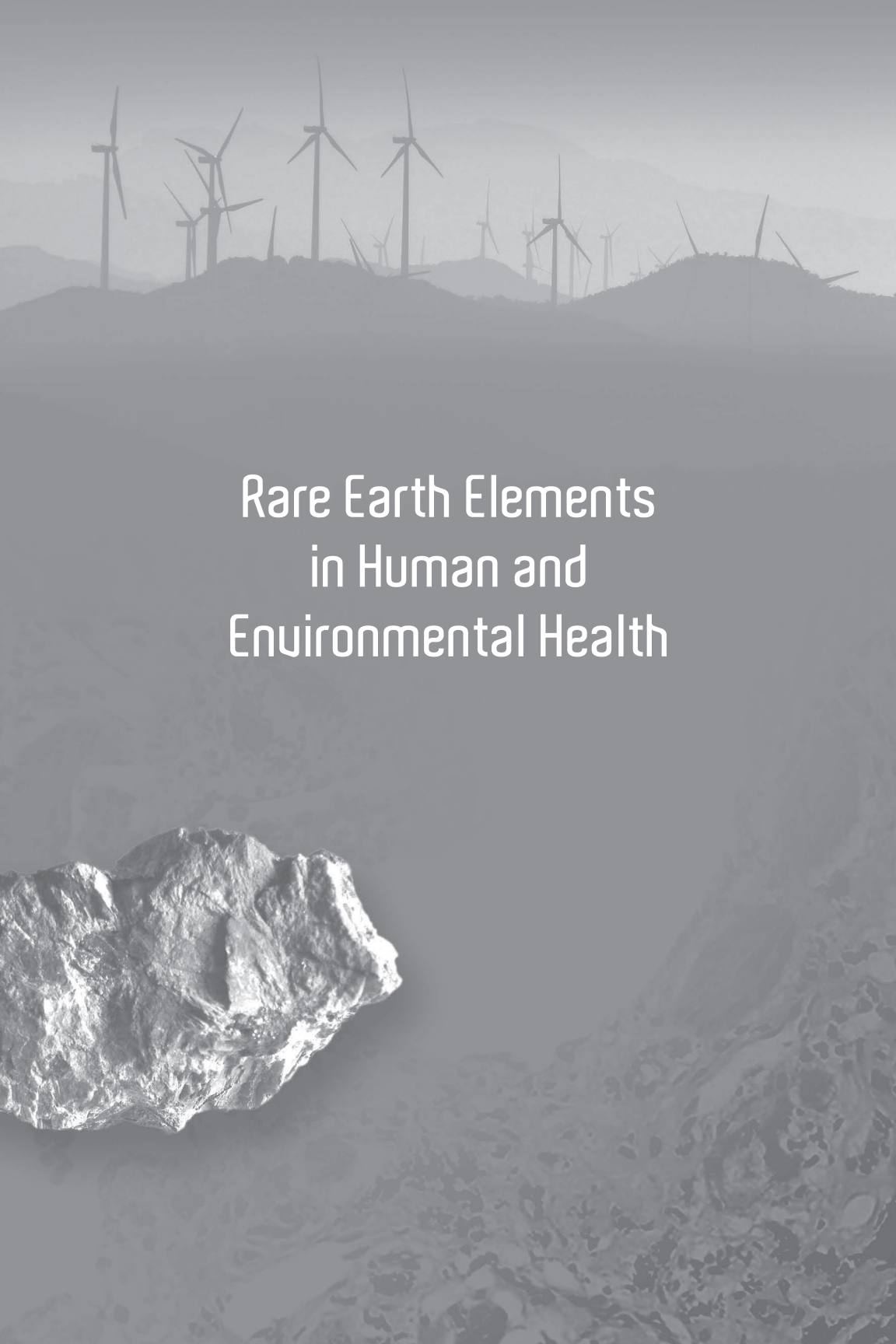


Rare Earth Elements in Human and Environmental Health

At the Crossroads between Toxicity and Safety

edited by Giovanni Pagano





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Preface

A limited number of books have been devoted so far to rare earth elements (REEs), mainly focused on REE-related chemistry, mineralogy, economy, and developing technologies for these elements.

Among the recent developments in the field of REE environmental and human health implications, the present book is aimed at presenting the multi-faceted aspects of REEs both including the potential benefits of REEs in several applications and adverse health effects. Human, animal, and plant exposures, including REE bioaccumulation and REE-induced pathologies, are reported along with other mechanistic issues related to REE environmental spread. The two-fold REE-related environmental and health issues provide this book with an updated and balanced approach to REE research and technology.

The broadly open questions on the impacts of REEs on health effects following environmental and occupational exposures raise a growing concern that is unconfined to academia and is widespread among a number of stakeholders, potentially including students, media workers, and decision-makers.

The recognized and potential benefits arising from REE-related technologies in medical, agronomical, and zootechnical applications are discussed in this book, thus representing prospect avenues in developing further advantages of REE-related technological applications.

As stated in the title, "At the Crossroads between Toxicity and Safety", this book provides novel yet established information with a particular highlight on the hormesis phenomenon.

The chapter authors include renown scientists from Americas, Europe, and Asia, having contributed to crucial studies of REE-associated health effects and having background knowledge in several disciplines, such as environmental, medical, and chemical.

I hope this book will assist present-day and future scientists and technologists to navigate at the crossroads between REE-associated adverse and beneficial effects.

Giovanni Pagano
Summer 2016

Introduction to Rare Earth Elements: Novel Health Hazards or Safe Technological Devices?

Rare earth elements (REEs) have been the subject of a limited number of books or technical reports since the 1980s to present, with a major (or exclusive) focus on REE-related chemistry, mineralogy, economy, and developing technological applications for these elements [1, 9, 14, 16, 17, 20, 44, 49]. Recent research achievements on REE-associated health effects have been reported as sections or chapters of this literature [17, 44] and have been highlighted in a report by the European Agency for Safety and Health at Work [8] in 2013. Thus, one may recognize that REE-associated health effects constitute a thriving area of research in recent years, though confined so far to journal reports based on individual laboratory studies and with a limited number of review papers [26, 27, 35].

In the wake of the recent and pending developments in the field of REE environmental and human health implications, the present book is aimed at presenting the multifaceted aspects of REEs from the potential benefits of REEs in technological, agricultural, and medical applications (Chapter 3) to studies and reviews on adverse health effects (Chapters 2, 4, and 7). Human exposures, including REE bioaccumulation and REE-induced pathologies, are reported in Chapter 1. Other mechanistic issues related to REE environmental spread are discussed in this book, such as the affinity between REEs and other elements (Chapters 9 and 10).

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Given this duality in REE-related environmental and health issues, this book attempts to provide an updated and balanced approach to REE research and technology with an open-minded attitude.

1. REEs in the Environment

Most of the global REE ore extraction and refining is located in China [9, 16, 44], and these activities constitute the majority of REE environmental pollutions in mining sites and in the surrounding areas. This environmental impact of REE ore mining has been associated to bioaccumulation among residents at different distances from mining sites [30, 43]. Further implications of REE extraction and refining activities as relevant environmental issues arise from the use of strong acids at several stages of ore processing and refining [44], with consequent release of acidic effluents affecting downstream waterbodies. Thus, the limited evidence for combined toxicities of REEs and pH decrease [21, 45, 46], along with a long-established notion of multifold acid toxicity [40], altogether raise substantial concern over the environmental impact at downstream mining sites and refining facilities. The current information gap in this subject warrants field investigations and ad hoc experimental studies.

In addition to mining and refining activities, worldwide REE manufacturing activities may also raise environmental concern for REE-polluted wastewater, with consequent bioaccumulation and still scarcely investigated effects on aquatic biota [2, 15].

A third and most widespread source of REE-related air and soil pollution may refer to the global use of cerium oxide nanoparticles ($n\text{CeO}_2$) as a catalytic additive in diesel fuel. The so far limited literature points to $n\text{CeO}_2$ as a component of diesel exhaust particulate matter [5, 6, 23, 39], thus prompting investigations on the relevance and possible health implications of diesel exhaust particulate matter following occupational and environmental exposures.

2. REE-Induced Adverse Effects: Toxicity Mechanisms

Except for scanty reports dating back to the 1960s [12], REEs were broadly neglected as xenobiotics up to recent years despite their

unprecedented boost in technological applications in the last two decades.

Investigations on REE-associated health effects have been thriving in recent years, which include experimental and bioaccumulation studies involving a number of endpoints evaluated in cell, animal, and plant models. This growing database of REE toxicity has been reviewed recently [26, 27, 35]. A number of animal-specific damages, such as organ and system effects, and plant-specific damages, such as growth inhibition and decreased chlorophyll production, have been reported and are reviewed in Chapters 4, 6, and 7. A more general outcome of several toxicity studies consisted of redox imbalances induced by a number of REEs in cell systems, animals, and plants. The current evidence is summarized in Table 1.

Table 1 Summary of REE-induced pro-oxidant effects in animal and plant models reported in Chapters 4 and 7

| Assay Models | Endpoints |
|------------------------------|--|
| Animals | |
| Animal cells | ↑ ROS formation and oxidative damage; ↓ GSH; SOD and CAT modulation; mitochondrial dysfunction |
| Mammals | ↑ ROS and lipid peroxidation; ↓ antioxidant capacity; ↑ proinflammatory cytokines |
| Fish | |
| <i>Carassius auratus</i> | ↑↓ SOD, CAT, and GPx |
| Sea urchins | |
| <i>Paracentrotus lividus</i> | ↑ ROS and nitrite formation |
| Plants | |
| <i>Nymphoides peltata</i> | ↑↓ SOD and GSH |
| <i>Glycine max</i> | ↓ CAT and GPx; H ₂ O ₂ and lipid peroxidation |
| <i>Oryza sativa</i> | ↑ H ₂ O ₂ and lipid peroxidation |
| <i>Armoracia rusticana</i> | ↑ ROS and lipid peroxidation |

ROS: reactive oxygen species; GSH: glutathione; SOD: superoxide dismutase; CAT: catalase; GPx: glutathione peroxidase

Source: Refs. [26–28 and 35]

Altogether, one may recognize a major role of redox imbalance as a relevant feature of REE-associated toxicity, with mechanistic details provided in Chapter 2. Another aspect of REE-associated toxicity relies on the findings of excess ROS and nitrite formation, along with cytogenetic damage and transmissible damage from REE-exposed sperm to their offspring [25, 28]. These data should prompt further investigations on possible REE-induced clastogenicity and/or genotoxicity in other biota, as reported in previous studies that found chromosomal aberrations in bone marrow cells of REE-exposed mice [19].

Beyond the database of REE-associated adverse effects, it should be noted, however, that antioxidant mechanisms have also been reported in the scope of REE-associated effects, as discussed in Chapter 3 and discussed in the following paragraphs.

The available literature on REE-associated toxicity is, so far, confined to a few REEs (mostly Ce, La, and Gd), requiring investigations on comparative toxicities of other, as-yet-neglected REEs. Animal studies are limited to short- to medium-term observation (mostly 1 to 3 months) [27]; thus, studies of long-term REE exposures and life-long observations are as yet lacking.

A few reports on occupational REE exposures have shown adverse health effects on the respiratory tract, along with REE bioaccumulation [11, 24, 36, 48], as discussed in Chapter 1. To the best of present knowledge, this limited body of literature dates back to 1982 up to 2005 and almost invariably consists of case reports [27]. Therefore, a major knowledge gap for the possible long-term effects of occupational REE exposures is due to the current lack of epidemiological studies, which represent an outstanding research priority in industrial medicine.

A last and relevant adverse effect of REEs has been appraised following the observation of severe skin fibrosis (nephrogenic systemic fibrosis) related to the use of gadolinium (Gd) as a contrast agent in magnetic resonance imaging [33, 42], as discussed in Chapters 7 and 10. Adverse effects of Gd-based contrast agents are regarded as a potential threat in dialysis patients undergoing magnetic resonance imaging [33].

Despite the crucial role microorganisms play in the environment, the nature of the interaction between REEs and microorganisms is still an open question. A relatively small amount of data are so far

available about uptake, accumulation, and biochemical effects of REEs on microorganisms and a considerable amount of such data deal with the use of microbial biomass as a biosorbent material for REE recovery from aqueous solutions. Chapter 5 will try to outline the state of the art of this intriguing but still unclear puzzle.

3. REE-Induced Beneficial Effects: A Case for Hormesis

A body of literature points to beneficial or safe effects of REEs that were found to exert antioxidant and neuroprotective action [7, 31, 37, 47], as discussed in Chapter 3. The use of $n\text{CeO}_2$ as antioxidants in biological systems has shown protective effect in reducing oxidative stress in cell culture and in animal disease models that are associated with oxidative stress. Ophthalmic therapeutics by $n\text{CeO}_2$ was reported to slow the progression of retinal degeneration along with anti-angiogenic agents in rodent models. The authors suggested that the radical scavenging activity of $n\text{CeO}_2$ is mainly due to the increase in the surface area-to-volume ratio in these nanocrystalline structures [47]. Another study reported that cerium oxide or yttrium oxide nanoparticles protect nerve cells from oxidative stress and that the neuroprotection is independent of particle size [37].

Altogether, one can recognize that a line of research has found antioxidant and potentially beneficial effects of REE nanoparticles with potential use in therapeutic applications. This promising body of literature awaits further investigations aimed at elucidating action mechanisms and validating this approach.

The application of REEs as feed additives for livestock and in crop improvement has been practiced in China for some time and relevant results were reported in the Chinese literature. Where applicable, these beneficial effects included increase in body weight gains in cattle, pigs, chicken, fish, and rabbits, as well as increases in milk production in dairy cows and egg production in laying hens [13, 29, 34]. However, other studies have extensively investigated REE bioaccumulation and adverse effects to plant growth [4] and to algae, as discussed in Chapters 4 and 6.

Further suggestions for REE-associated stimulating effects have been provided by several studies conducted in mammalian cells, algae, and microorganisms [10, 18, 22, 32]. These reports suggest a role for low-level REEs in substituting essential elements [10] or even suggest the novel concept that REEs may represent essential elements for some biota [32]. It should be noted that there are drugs and other commercial products already on the market, which use the physicochemical characteristics of REEs to produce health or environmental benefits (Chapter 9).

Altogether, the apparently controversial bodies of literature, of REE-associated toxicity and stimulatory action, also termed “dual effects” [44], are not new. Since the earliest report by Hugo Schulz in 1888 [38], a redoubtable body of evidence supports the hormesis concept [3, 41], implying that low levels of chemical or physical agents induce stimulatory effects in a broad number of biological endpoints, which are then inhibited by increasing agent levels. Hormesis is discussed in detail in Chapter 8 of this book.

As an indispensable tool in the interpretation of REE-related hormesis and toxicity, REE speciation is discussed in Chapters 9 to 11. Understanding the different (complementary, or opposite) actions of dissolved species versus nanoparticles, and the roles for nanoparticle size and geometry and of ligands, will allow forthcoming studies to evaluate and/or predict the biological actions of REEs in environmental and human health. This book will be useful in laying out some of these challenges.

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