Rare earth elements are involved in a number of essential technological applications. Their effects raise a number of challenges in environmental sciences and in human health. The present book provides an extensive and balanced survey of the manifold—adverse and favorable—effects associated with rare earth elements.

Prof. Dr. José L. Domingo
Rovira i Virgili University, Spain

The present book is a valuable tool to gain insight into the complex and sometimes surprising health effects of rare earth elements. Especially interesting—due to my field of research—are the chapters addressed to the study of the changes in redox endpoints in a number of organisms and cell systems. This carefully edited book, with a multidisciplinary view of rare earth elements, is really an important scientific contribution.

Prof. Dr. Federico V. Pallardó
University of Valencia, Spain

I congratulate the authors for this timely production of an extensive overview of an important topic in environmental and medical sciences: the risks and challenges that may be connected with increasing use and distribution of rare earth elements. It is essential to increase our knowledge about the environmental fate and biological effects of these technologically so important metals in order to prevent unforeseen long-term consequences of our doing. This book will surely become an important resource for scientists, engineers, and decision makers who understand the need of a sensible exploitation of this resource.

Prof. Dr. Susanne Heise
Hamburg University of Applied Sciences, Germany

This book presents the multifaceted aspects of rare earth elements (REEs), focusing on both their potential benefits and adverse health effects. The adverse impacts of REEs on human and environmental health raise a growing concern not only in the scientific community but also among a number of stakeholders, potentially including students, media workers, and decision makers. The recognized and potential benefits arising from REE-related technological applications may envisage their further advantages.

A limited number of books have been devoted so far to REEs, and they mainly focus on REE-related chemistry, mineralogy, economy, and developing technologies for these elements. This book presents recent research achievements in REE-associated health effects, which have been mostly confined to journal reports on individual laboratory studies so far. It is an updated and balanced approach to REE research and technology. It provides novel yet established information as stated in the title “At the Crossroads between Toxicity and Safety,” with particular emphasis on the hormesis phenomenon.

Giovanni Pagano has 40 years’ experience in environmental research, including projects supported by grants from the European Commission and the North Atlantic Treaty Organization. He has been a senior scientist at the Italian National Cancer Institute in Naples, Italy, and a contractor scientist at the University of Naples Federico II, Italy. He is a visiting professor in various universities of France, Greece, and Croatia. Prof. Pagano has published 105 journal articles and 22 book chapters, with 1900 ResearchGate citations.
Rare Earth Elements in Human and Environmental Health
Rare Earth Elements in Human and Environmental Health
At the Crossroads between Toxicity and Safety

edited by
Giovanni Pagano
Contents

Preface xi

Introduction to Rare Earth Elements: Novel Health Hazards or Safe Technological Devices? 1

1. Trends in Occupational Toxicology of Rare Earth Elements 11
   Kyung-Taek Rim
   1.1 Industrial Use of REEs 12
   1.2 Evaluation of Workers’ Health for REE-Related Hazards 20
   1.3 Recent Trends in Occupational Toxicology of REEs 28
   1.4 Additional Efforts to Promote REE Occupational Health 34
   1.5 Conclusions and Prospects 37

2. Rare Earth Elements, Oxidative Stress, and Disease 47
   Paola Manini
   2.1 Introduction 48
   2.2 Redox Chemistry of REEs 49
      2.2.1 Case of Cerium Oxide Nanoparticles 52
   2.3 Oxidative Stress and Diseases: Roles of REEs 54
      2.3.1 REE Adverse Effects 58
      2.3.2 REE Favorable Effects 60
   2.4 Conclusion 61

3. Cerium Oxide Nanoparticles–Associated Oxidant and Antioxidant Effects and Mechanisms 69
   Lily L. Wong
   3.1 Introduction 70
   3.2 Physicochemical Properties and Catalytic Activities of Nanoceria Are Dictated by Their Synthesis Methods 74
3.2.1 Additional Catalytic Activity and Effects of Buffers on CeNPs' Activities 80

3.2.2 Synthesis Method and Characterization of CeNPs that Showed Beneficial Effects in Blinding Retinal Disease Models 81

3.3 Biological Effects of Nanoceria: Antioxidative, Oxidative, and Modulation of Oxygen Level 82

3.3.1 In Cell Culture Systems 82

- 3.3.1.1 Study 1: Antioxidative Effect 82
- 3.3.1.2 Study 2: Oxidative Effect 83
- 3.3.1.3 Study 3: Neutral or Oxidative Effect Depending on Cell Types Used 84
- 3.3.1.4 Study 4: Antioxidative Effect 85
- 3.3.1.5 Limitations of Current Methodologies 85
- 3.3.1.6 Study 5: Modulation of Oxygen Level 86

3.3.2 In Animal Models 87

- 3.3.2.1 Studies 1 and 2: Antioxidative Effect 87
- 3.3.2.2 Study 3: Antioxidative Effect 89
- 3.3.2.3 Studies 4–6: Antioxidative Effect and Nontoxic Effect in Normal Retinas 89
- 3.3.2.4 Study 7: Oxidative Effect in Cancer Cells and Nontoxic to Normal Cells 92

3.4 Catalytic Activity of Nanoceria in Biological Tissues 93

3.5 Molecular Mechanisms of Nanoceria in Biological Systems 96

3.6 Conclusion 100

3.7 Acknowledgments 100

4. Rare Earth Elements and Plants 107

Franca Tommasi and Luigi d' Aquino

4.1 Introduction 108
4.2 REEs in Mosses and Lichens 109
4.3 REEs and Ferns 110
4.4 REEs in Seed Plants 111
4.4.1 REEs and Seeds 111
4.4.2 REEs and Seedling Growth 112
4.4.3 REEs and Wild Plants 112
4.4.4 REEs and Crops 114
4.4.5 REEs and Aquatic Plants 117
4.5 Mechanisms of REE Effects 118
4.6 Critical Remarks and Research Perspectives 118

5. Rare Earth Elements and Microorganisms 127
   Luigi d’Aquino and Franca Tommasi
   5.1 Introduction 128
   5.2 REEs and Microorganisms 129
   5.3 Conclusion 135

6. Rare Earth Element Toxicity to Marine and Freshwater Algae 143
   Marco Guida, Antonietta Siciliano, and Giovanni Pagano
   6.1 Introduction 144
   6.2 REE-Associated Toxicity Database in Algae 144
   6.3 REE Uptake and Bioaccumulation in Algae 147
   6.4 Critical Remarks and Research Prospects 149

7. Exposure to Rare Earth Elements in Animals: A Systematic Review of Biological Effects in Mammals, Fish, and Invertebrates 155
   Philippe J. Thomas, Giovanni Pagano, and Rahime Oral
   7.1 Rare Earth Elements: An Overview 156
   7.2 Methods 159
   7.2.1 Study Selection 159
   7.2.2 Evaluation and Inclusion Criteria 159
   7.2.3 Data Extraction 160
   7.2.4 Sources of Bias and Data Comparability 161
   7.3 Results 162
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.3.1</td>
<td>Studies</td>
<td>162</td>
</tr>
<tr>
<td>7.3.2</td>
<td>Endpoints</td>
<td>170</td>
</tr>
<tr>
<td>7.3.3</td>
<td>Effects</td>
<td>170</td>
</tr>
<tr>
<td>7.4</td>
<td>Discussion</td>
<td>171</td>
</tr>
<tr>
<td>7.4.1</td>
<td>Assessment of Common Themes in Extracted Studies</td>
<td>171</td>
</tr>
<tr>
<td>7.4.2</td>
<td>Pathways of Effect in Mammals</td>
<td>172</td>
</tr>
<tr>
<td>7.4.3</td>
<td>Effects on Fish and Invertebrates</td>
<td>174</td>
</tr>
<tr>
<td>7.5</td>
<td>Conclusion and Future Directions</td>
<td>174</td>
</tr>
<tr>
<td>8.</td>
<td>Hazard Assessment and the Evaluation of Rare Earth Element Dose–Response Relationships</td>
<td>183</td>
</tr>
<tr>
<td>8.1</td>
<td>Risk-Based Standards and Dose–Response Assessment</td>
<td>184</td>
</tr>
<tr>
<td>8.2</td>
<td>Features of the Hormetic Response</td>
<td>185</td>
</tr>
<tr>
<td>8.3</td>
<td>REE Dose–Response</td>
<td>188</td>
</tr>
<tr>
<td>8.4</td>
<td>Implications for REE Assessments</td>
<td>190</td>
</tr>
<tr>
<td>9.</td>
<td>Rare Earth Elements as Phosphate Binders: From Kidneys to Lakes</td>
<td>195</td>
</tr>
<tr>
<td>9.1</td>
<td>Introduction</td>
<td>195</td>
</tr>
<tr>
<td>9.1.1</td>
<td>The Essential Phosphorus</td>
<td>196</td>
</tr>
<tr>
<td>9.1.2</td>
<td>Phosphorus as a Toxic Element</td>
<td>198</td>
</tr>
<tr>
<td>9.1.2.1</td>
<td>For human health</td>
<td>198</td>
</tr>
<tr>
<td>9.1.2.2</td>
<td>For the environment</td>
<td>200</td>
</tr>
<tr>
<td>9.1.3</td>
<td>Biogeochemical Cycle of Phosphorus</td>
<td>201</td>
</tr>
<tr>
<td>9.2</td>
<td>The P-REE Relationship</td>
<td>202</td>
</tr>
<tr>
<td>9.2.1</td>
<td>Oral Phosphate Binders: Uses in Medicine</td>
<td>202</td>
</tr>
<tr>
<td>9.2.2</td>
<td>REE-Modified Clays: Uses in the Environment</td>
<td>204</td>
</tr>
<tr>
<td>9.2.3</td>
<td>Logistical Considerations for Lanthanum-Modified Clays</td>
<td>208</td>
</tr>
<tr>
<td>9.2.4</td>
<td>Economic Considerations of the Use of Lanthanum Oral Phosphate Binders and Chemically Modified Clays</td>
<td>209</td>
</tr>
</tbody>
</table>
9.2.5 Environmental Considerations of the Use of La-Based Oral Phosphate Binders and La-Modified Clays 210

9.3 Conclusion 211

10. Rare Earth Elements: Modulation of Calcium-Driven Processes in Epithelium and Stroma 219
   James Varani
   10.1 Introduction 219
   10.2 Growth Control in Epithelium and Stroma: Role(s) of Calcium 220
       10.2.1 Structure of Skin and Its Relationship to Calcium Levels 220
       10.2.2 Calcium Requirements for Keratinocyte and Fibroblast Function 221
       10.2.3 Cellular and Molecular Events Responsive to Calcium 222
       10.2.4 Calcium: Growth Control in Other Tissues 224
   10.3 REE: Modulation of Epithelial Cell Biology 224
       10.3.1 Cellular Molecules Responsive to REEs 224
       10.3.2 Modulation of Proliferation and Differentiation in Epithelial Cells by REEs 225
       10.3.3 REE Modulation of Epithelial Proliferation and Differentiation: Potential Impact on Calcium Chemopreventive Activity in Colon 228
   10.4 REE and Stromal Cell Biology 229
       10.4.1 Fibroblast Proliferation in Response to REE Exposure 229
       10.4.2 REE Effects on Collagen Metabolism 234
       10.4.3 Intracellular Events in REE-Stimulated Fibroblasts 237
   10.5 Summary and Conclusion 240

11. Rare Earth Elements Equilibria in Aqueous Media 251
   Marco Trifuoggi, Ermanno Vasca, and Carla Manfredi
   11.1 Hints to Chemical Speciation 251
<table>
<thead>
<tr>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.2 Equilibrium Analysis at a Glance</td>
</tr>
<tr>
<td>11.3 Aspects of Cerium Oxides Nanoparticles Speciation in Biological Systems</td>
</tr>
</tbody>
</table>

*Conclusion: Identifying Main Research Priorities* 267

*Index* 273
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
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).
Introduction to Rare Earth Elements

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 (nCeO₂) as a catalytic additive in diesel fuel. The so far limited literature points to nCeO₂ 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

<table>
<thead>
<tr>
<th>Assay Models</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Animals</strong></td>
<td></td>
</tr>
<tr>
<td>Animal cells</td>
<td>↑ ROS formation and oxidative damage; ↓ GSH; SOD and CAT modulation; mitochondrial dysfunction</td>
</tr>
<tr>
<td>Mammals</td>
<td>↑ ROS and lipid peroxidation; ↓ antioxidant capacity; ↑ proinflammatory cytokines</td>
</tr>
<tr>
<td>Fish</td>
<td></td>
</tr>
<tr>
<td><em>Carassius auratus</em></td>
<td>↑↓ SOD, CAT, and GPx</td>
</tr>
<tr>
<td>Sea urchins</td>
<td></td>
</tr>
<tr>
<td><em>Paracentrotus lividus</em></td>
<td>↑ ROS and nitrite formation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Nymphoides peltata</em></td>
<td>↑↓ SOD and GSH</td>
</tr>
<tr>
<td><em>Glycine max</em></td>
<td>↓ CAT and GPx; H₂O₂ and lipid peroxidation</td>
</tr>
<tr>
<td><em>Oryza sativa</em></td>
<td>↑ H₂O₂ and lipid peroxidation</td>
</tr>
<tr>
<td><em>Armoracia rusticana</em></td>
<td>↑ ROS and lipid peroxidation</td>
</tr>
</tbody>
</table>

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 nCeO₂ 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 nCeO₂ 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 nCeO₂ 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.

References


