Ecotoxicology and Environmental Safety 115 (2015) 40–48

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv

# Health effects and toxicity mechanisms of rare earth elements—Knowledge gaps and research prospects

Giovanni Pagano[a,*], Marco Guida[a], Franca Tommasi[b], Rahime Oral[c]

[a] Federico II University of Naples, Environmental Hygiene, I-80126 Naples, Italy
[b] "Aldo Moro" Bari University, Department o f Plant Biology, I-70124 Bari, Italy
[c] Ege University, Faculty of Fisheries, TR-35100 Bornova, Izmir, Turkey

ARTICLE INFO

*Article history:*
Received 16 November 2014
Received in revised form
24 January 2015
Accepted 31 January 2015
Available online 11 February 2015

*Keywords:*
Rare earth elements
Health effects
Oxidative stress
Hormesis
pH

ABSTRACT

In the recent decades, rare earth elements (REE) have undergone a steady spread in several industrial and medical applications, and in agriculture. Relatively scarce information has been acquired to date on REE-associated biological effects, from studies of bioaccumulation and of bioassays on animal, plant and models; a few case reports have focused on human health effects following occupational REE exposures, in the present lack of epidemiological studies of occupationally exposed groups. The literature is mostly confined to reports on few REE, namely cerium and lanthanum, whereas substantial information gaps persist on the health effects of other REE. An established action mechanism in REE-associated health effects relates to modulating oxidative stress, analogous to the recognized redox mechanisms observed for other transition elements. Adverse outcomes of REE exposures include a number of endpoints, such as growth inhibition, cytogenetic effects, and organ-specific toxicity. An apparent controversy regarding REE-associated health effects relates to opposed data pointing to either favorable or adverse effects of REE exposures. Several studies have demonstrated that REE, like a number of other xenobiotics, follow hormetic concentration-related trends, implying stimulatory or protective effects at low levels, then adverse effects at higher concentrations. Another major role for REE-associated effects should be focused on pH-dependent REE speciation and hence toxicity. Few reports have demonstrated that environmental acidification enhances REE toxicity; these data may assume particular relevance in REE-polluted acidic soils and in REE mining areas characterized by concomitant REE and acid pollution. The likely environmental threats arising from REE exposures deserve a new line of research efforts.



**Contents**



* Corresponding author.
*E-mail address:* gbpagano@tin.it (G. Pagano).

http://dx.doi.org/10.1016/j.ecoenv.2015.01.030

## 1. Introduction

The widespread and growing relevance of REE in a number of industrial, agricultural and medical technologies has become evident in the last decades (USEPA, 2012). Established and growing evidence points to REE-related marine, freshwater and soil pollution, along with REE bioaccumulation (Tu et al., 1994; Moermond et al., 2001; Hu et al., 2002; Bustamante and Miramand, 2005; Kulaksız and Bau, 2011; Tranchida et al., 2011; Censi et al., 2013; Fu et al., 2014; Liang et al., 2014). Despite the sharp rise in REE extraction and manufacturing, hence growing environmental and human exposures, the toxicological investigations on REE-associated health effects have been relatively scarce up to recent years. By comparing the toxicologic literature on other inorganic xenobiotics, the PubMed database provides approx. 1200 citations for REE, vs., e.g., some 10,000 citations for cadmium. This state-of-art leaves a number of unsolved questions as to any adverse effects of REE pollution, toxicity mechanisms to biota, as well as occupational or iatrogenic or environmental human exposures.

Previous reviews on REE-associated biological effects have been scanty, since the early paper by Haley (1965) rarely encompassing more than one REE (Hirano and Suzuki, 1996; Cassee et al., 2011; Rim et al., 2013). The present review is aimed at providing a comprehensive survey of the literature focused on REE-associated health effects from studies conducted *in vitro*, in animals, and in plants, along with few case reports or geographic studies from human exposures, in the attempt to highlight the major knowledge gaps, and pointing to the roles of three relevant phenomena involved in REE-related effects, i.e. oxidative stress, hormesis, and medium acidification.

An outstanding limitation of REE-associated health effects shows that the toxicological database is mostly confined to Ce and La, with lesser information available for Gd and Nd, and scanty data available for the other REE, especially for heavy REE. These are, nonetheless, relevant to manufacturing several technological products as, e.g., alloys and magnets, hence with realistic impact related to occupational and environmental exposures.

An apparent controversy between favorable and adverse REE-associated health effects is discussed and attributed to the well-known hormesis phenomenon that has been reported for broad-ranging xenobiotics and physical agents (reviewed by Calabrese, 2013; Mattson, 2008), consisting of a concentration- or dose-related shift from stimulatory to inhibitory effects. Clear-cut REE-induced hormetic effects have been reported for extensive numbers of agents (Calabrese, 2010) and one may envision that hormesis is displayed by several REE, thus recognizing that both stimulatory and inhibitory findings can be recognized in a unified scenario (Jenkins et al., 2011; Wang et al., 2012).

The role for redox imbalance leading to oxidative stress (OS) has been established for several REE in a number of independent studies conducted both in plant and animal models, suggesting that OS may underlie REE-induced toxicity for most, if not all, REE (Tseng et al., 2012; Wang et al., 2012; Zhao et al., 2013). It should be noted that other studies have reported on antioxidant effects of some REE, e.g. Ce oxide ($CeO_2$), suggesting ad hoc clinical applications (Wong and McGinnis, 2014).

Human exposures to REE range from iatrogenic to occupational routes, and likely or suspect environmental exposure routes. A recognized iatrogenic exposure consists of Gd use as a contrast agent in magnetic resonance imaging, up to reports on renal toxicity (nephrogenic systemic fibrosis) in the last decade (Thomsen, 2006; Chien et al., 2011; Bernstein et al., 2012). Occupational exposures to REE dusts have been associated with observations of pneumoconiosis since early case reports (Sabbioni et al., 1982; McDonald et al., 1995), yet no case-control or cohort study has been retrieved in this review. Environmental exposures in populations residing close to REE mining areas showed REE bioaccumulation related to distance from mining sites (Peng et al., 2003; Tong et al., 2004).

Another outcome of REE toxicity relates to the induction of cytogenetic effects that have been detected both in plant and in animal cells, such as inhibition of mitotic activity, mitotic aberrations and induction of micronuclei (Huang et al., 2007; Oral et al., 2010).

A few studies reported on pH-induced modulation of REE toxicity, in some cases referring to "acid rain" (Liang and Wang, 2013), and other reports showed the toxicity modulation of acidic ligands (Ould-Moussa et al., 2014). This limited body of literature may be anticipated to predict a broader and environmentally relevant event, both due to the established notion of pH-modulated toxicity of several metals (Luís et al., 2014; Pardo et al., 2014) and, even more so, due to the concomitant pollution by REE and inorganic acids in the areas surrounding-or downstream-REE mining and manufacturing facilities (Tong et al., 2004; Olías et al., 2005; Grawunder et al., 2014).

Altogether, the present review may offer some insights into the current database on REE-associated health effects and its major gaps, by addressing proper study design aimed at elucidating presently open questions.

## 2. Methods

A MedLine retrieval up to January 2015 was carried out for reports on individual REE or for REE mixtures. The papers reporting on toxicity of each REE were evaluated according to: (a) health effects; (b) OS endpoints; (c) hormetic effects, (d) cytogenetic effects, and (e) pH-related effects. The reports failing to provide clear-cut data for concentrations were not included for evaluation, nor were included self-repeating reports of previous or contemporary studies. The reports on radioactive REE (Pm) or on REE radionuclides (e.g., $^{90}Y$, $^{166}Ho$) were not considered for this review.

## 3. State-of-art in REE-associated health effects

Most of REE technological applications have been developed in the last two decades, thus the early database on REE biological effects has been scarce up to 1990s (Haley, 1965; Hirano and Suzuki, 1996). As shown in Fig. 1a, the reports on REE-induced effects only started to grow in the last decade and at a faster pace since 2010; this trend appears more remarkable in Fig. 1b, showing the number of reports per year that was more than doubled in the last approx. five years (95 papers/yr) vs. the previous 2000–2009 decade (37 papers/yr). This trend witnesses a growing and more focused attention toward REE-associated health effects. These include the opposite outcomes of the published studies, i.e. REE-induced toxicity and a number of stimulatory or favorable effects that raise, altogether, a partly unsolved controversy (see below, Section 6).

Independently of reporting on favorable or adverse effects, the current literature shows dramatic differences as to numbers of papers focusing on individual REE. As shown in Fig. 2, by far most of reviewed publications have focused on Ce (a total of 63 reports, including 55 with toxicity findings and 8 with negative or favorable findings) and La (55 reports), while lesser numbers of reports were published on Gd (21), Nd (16), and Y (15), Pr (10); Tb and Yb (8), and scanty numbers of reports for the other REE. This information frame suggests that a relatively adequate database is confined to two REE, Ce and La, whereas the health effects associated with the other REE (especially heavy REE) are broadly