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
0147-6513/

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

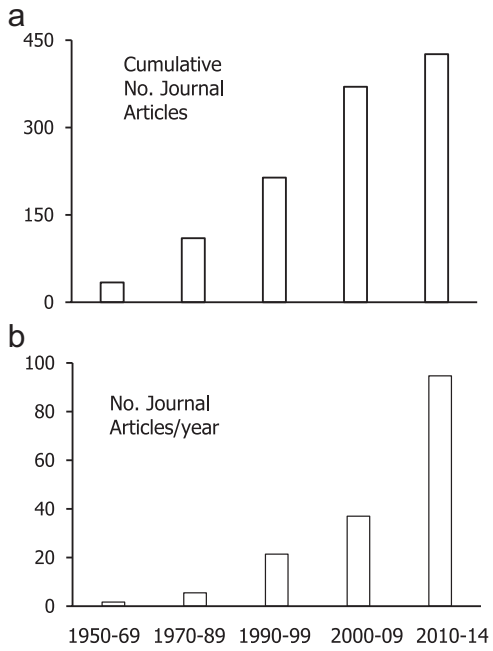

Fig. 1. (a) Cumulative publication of journal articles on REE-associated health effects. (b) Rates of published articles per decade and in the present half-decade (2010 to mid-2014).

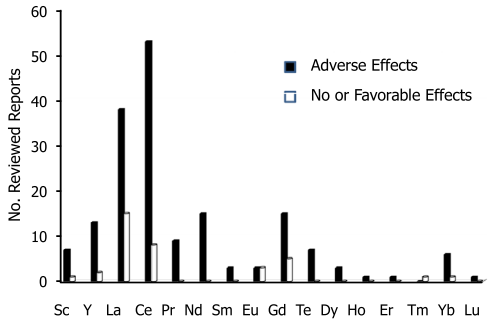

Fig. 2. Published articles reporting on either toxic (■) or stimulatory (□) effects of individual REE.

unexplored. This information gap is in contrast with the on-going- and growing-use of the other REE in several industries, both implying concern for human occupational exposures and for environmental spread in mining areas and in manufacturing facilities. This is case, e.g., for the production of magnetic alloys used for hybrid engines and utilizing Nd, Dy and Sm (Haley et al., 1961; Weilin et al., 2006; USEPA, 2009; Alonso et al., 2012). Altogether, the current state-of-art prompts substantial efforts to elucidate the health effects associated with a number of as yet underscored REE.

4. Redox mechanisms in REE-associated health effects

The role for redox mechanisms in the toxicity of several transition elements (primarily, yet not confined to iron and copper) has been long recognized since early reports dating back to 1980s (reviewed by Stohs and Bagchi, 1995; Toyokuni, 1996). The occurrence of redox mechanisms in the biological effects of REE has been reported by few papers on Tb and Yb toxicity (Shimada et al., 1996; Hongyan et al., 2002), and found to result in either antioxidant or prooxidant activity (Kawagoe et al., 2005; Schubert et al., 2006; Lin et al., 2006; Wong and McGinnis, 2014).

As shown in Table 1, oxidative stress (OS)-related effects have been reported for seven REE, namely Y (Marubashi et al., 1998; Fu et al., 2014), La (Huang et al., 2011; Liang and Wang, 2013; Wu et al., 2013), Ce (Li et al., 2010a; Zhao et al., 2011; Rico et al., 2013; Hong et al., 2014), Nd (Li et al., 2010b; Huang et al., 2011; Zhao et al., 2011), Gd (Xia et al., 2011; Ghio et al., 2011; Pereira et al., 2012; Cho et al., 2014), Tb (Shimada et al., 1996; Jiang et al., 2011) and Yb (Hongyan et al., 2002).

The most frequently investigated OS endpoints were reactive oxygen species (ROS) formation, lipid peroxidation, and modulation of antioxidant activities, such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). This database was obtained from studies conducted in plants and in fish, rats and mice, or animal cells (Table 1), and altogether points to REE-induced prooxidant states. Nevertheless, opposite-antioxidant-action was reported in several studies (Kawagoe et al., 2005; Schubert et al., 2006; Wong and McGinnis, 2014; Li et al., 2014), and this apparent controversy will be discussed below (Section 6).

5. REE human exposures

5.1. Gadolinium iatrogenic exposure

Gadolinium is routinely utilized as a magnetic resonance imaging contrast agent (CA). Favorable safety profiles of Gd-based CA had been reported in previous studies (reviewed by Kirchin and Runge, 2003). However, a severe reaction known as nephrogenic systemic fibrosis was reported in patients (Thomsen, 2006; Chien et al., 2011; Bernstein et al., 2012; Chang et al., 2013). Darrah et al. (2009) found excess Gd concentrations in the femoral head bones of patients exposed to chelated Gd used as a CA for medical imaging. This finding was related to an increased risk of endogenous Gd release for patients with increased rates of bone resorption. Thus, the diagnostic use of Gd-based CA is currently managed with the caution of preventing severe renal complications.

5.2. Occupational exposures

An early study by Palmer et al. (1987) tested the cytotoxicity of some REE vs. Cd in rat pulmonary alveolar macrophages, and found significant cytotoxicity of Ce, La and Nd; the authors predicted that “REE metal fumes should be considered as cytotoxic to lung tissue and therefore potentially fibrogenic”.

The current database on REE occupational exposures is confined to anecdotal information from case report studies, pointing to observations of pneumoconiosis and interstitial lung disease in REE-exposed workers (Sabbioni et al., 1982; Waring and Watling, 1990; Gong, 1996). McDonald et al. (1995) found Ce particles in the lungs of a Ce-exposed worker by means of scanning electron microscopy with energy-dispersive X-ray analysis. Electron microscopy evidence for Ce and La lung particles was provided in a patient with an occupational history of REE exposure and affected by dendriform pulmonary ossification and pneumoconiosis (Yoon et al., 2005).

In the present lack both of adequate epidemiological studies (such as cohort or case-control studies), and of animal evidence for long-term effects of REE exposures, one may raise the question as to other late effects of these exposures beyond pneumoconiosis, such as other respiratory damage (or possible oncogenic outcomes?), warranting ad hoc studies. A possible hint for the working hypothesis of an involvement, if any, of REE in carcinogenesis was provided by Zhuang et al. (1996), who found excess levels of La, Ce, Gd, and Lu in brain tumor tissues from patients with astrocytomas vs. normal human brain tissues. Finally, one should reason that the most recognized agents both inducing pneumoconiosis and respiratory cancer display OS-related action

Table 1
Oxidative stress-related findings in REE-associated toxicity.

Elements	Test models	Findings	References
Yttrium	*Nymphoides peltata*	↑↓ Superoxide dismutase (SOD) and glutathione (GSH)	Fu et al. (2014)
	Rats	↑ MnSOD activity	Marubashi et al. (1998)
Lanthanum	Soybean (*Glycine max*)	↓ Catalase (CAT) and glutathione peroxidase (GPx); ↑ H_2O_2 accumulation and lipid peroxidation	Liang and Wang (2013)
	Cerebral cortical neurons	↑ ROS formation; mitochondrial dysfunction	Wu et al. (2013)
	Rat liver	↓ SOD and CAT; ↑ GPx, GSH and malondialdehyde (MDA)	Huang et al. (2011)
Cerium	Mice	↑ ROS and lipid peroxidation; ↓ antioxidant capacity;	Hong et al. (2014)
		↑ Proinflammatory cytokines, cyclooxygenase-2	Zhao et al. (2011)
		↑ Lipid peroxidation; ↓ antioxidant capacity;	Li et al. (2010)
		↓ SOD and CAT	
	Oryza sativa	↑ H_2O_2 and lipid peroxidation	Rico et al. (2013)
	Human lung epithelial cells	(↑) ROS, (↓) GSH and induction of OS-related genes	Park et al. (2008)
Neodymium	Rat liver	↓ SOD and CAT; ↑ GPx, GSH and MDA	Huang et al. (2011)
	Mice	↑ Lipid peroxidation; ↓ antioxidant capacity;	Zhao et al. (2011)
		↓ SOD and CAT	Li et al. (2010)
Gadolinium	Human lymphocytes	↑ ROS formation	Cho et al. (2014)
	Rats	↑ Ferritin, transferrin oversaturation; and lipid peroxidation	Pereira et al. (2012)
		N-acetylcysteine (NAC) protection	
	Rat cortical neurons	↑ ROS formation; NAC protection	Xia et al. (2011)
	Four cell lines	↑ Ferritin increased iron import	Ghio et al. (2011)
Terbium	Horseradish (*Armoracia rusticana*)	↑ ROS and lipid peroxidation	Jiang et al. (2011)
	Mice	↓ SOD, CAT and GPx; ↑ lipid peroxidation	Shimada et al. (1996)
Ytterbium	*Carassius auratus*	↑↓ SOD, CAT and GPx	Hongyan et al. (2002)

mechanisms (reviewed by Liu et al., 2013) that, indeed, are exerted by REE as above discussed in Section 4.

5.3. Environmental exposures

Cerium compounds are currently used as diesel fuel additives and as abrasives in printed circuit manufacture (Ma et al., 2011; USEPA, 2012; Yokel et al., 2012), thus resulting in the emission of CeO_2 nanoparticles in the exhaust and/or in dust or fume. An animal inhalation study reported an increased IL-12 production by alveolar macrophages (AM) and increased AM apoptosis, and increased suppressor of cytokine signaling-1 (Ma et al., 2011). A recent report of this group found that CeO_2 induces a sustained inflammatory response, along with activated AM and lymphocyte secretion of the proinflammatory cytokines IL-12 and IFN-γ, respectively. Lymph nodes from rats exposed to diesel exhaust particles (DEP)+CeO_2 showed significantly larger particle clumps than in animals exposed to CeO_2 or DEP alone, and with dense clumps spreading throughout the lymph nodes (Ma et al., 2014). The authors concluded that CeO_2 as diesel fuel catalyst may cause health concerns. A study by Cassee et al. (2012) investigated the effects of DEP vs. CeO_2-containing DEP (Ce-DEP) in atherosclerosis-prone mice, and found controversial outcomes, i.e. an increased size and complexity of the atherosclerotic plaques following DEP exposure, not evident in the Ce-DEP group. However, Ce-DEP exposure resulted in increased levels of proinflammatory cytokines in a brain region and in liver. A specific liver toxicity was reported by Yokel et al. (2012), who tested the effects of an i.v. infusion of 5% aqueous dispersion of citrate-stabilized 30 nm CeO_2 nanoparticles to rats, and found liver granulomas and time-dependent OS changes both in liver and in spleen. Nanoscale ceria was persistently retained by organs of the mononuclear phagocyte system, associated with adverse changes. Similar results were observed by Tseng et al. (2012), who found acute ceria nanoparticle sequestration by Kupffer cells with subsequent bioretention in parenchymal cells.

Altogether these data may raise concern about the possible health effects of environmental exposures to CeO_2 nanoparticles and should prompt ad hoc, as yet lacking studies of CeO_2 air levels in heavy traffic areas and of possible bioaccumulation and health effects of Ce-contaminated diesel exhaust particulate. The possible effects of prolonged occupational exposures to heavy concentrations of CeO_2 nanoparticles, e.g. for workers at truck depots or for municipal guards might raise unsolved questions as to possible Ce bioaccumulation and health effects, warranting adequate investigations. Our unpublished analyses of diesel exhaust particulate collected on the ground of a bus depot confirm the presence of CeO_2 nanoparticles, thus supporting the need for ad hoc studies of possible health effects in exposed workers.

Human environmental exposures to REE have been investigated in a number of biomonitoring studies mostly focused on REE mixtures, or on Ce, and as function of distance from REE mining areas. Two studies performed biomonitoring of REE levels in scalp hair from a total of 71 children and 62 of their mothers as a function of distance from mining and surrounding areas in Southern China, and found a significant correlation between Ce levels and distances from mining sites (Peng et al., 2003; Tong et al., 2004).

6. Hormesis in REE-associated health effects

The literature on REE-associated health effects displays apparently controversial findings of stimulatory and beneficial effects as well as of inhibitory and adverse effects. The current state-of-art has led to opposite views and strategies, ranging from the agricultural use of REE mixtures as fertilizers-mainly in China – (reviewed by Pang et al., 2002; USEPA, 2012) up to concern for REE-associated threats to environmental health (see below).

The observation of such opposite effects is not new in toxicology and pharmacology, as far as non-monotonic concentration- or dose-related trends have been known since ancient science and medicine (e.g. Paracelsus) (Jonas and Ives, 2008), and currently recognized as hormesis (reviewed by Mattson, 2008; Calabrese, 2013). A hormetic trend displays concentration-related effects, by increases or improvements in biological events (e.g. growth) at low levels of an agent, followed by inhibitory or toxic effects at increasing doses/concentrations. In order to detect hormetic trends, extensive dose/concentration ranges should be evaluated (e.g., four to five concentration orders of magnitude), thus enabling the observation both of stimulatory and of inhibitory effects.

Table 2
Hormesis-related REE toxicity reports.

Elements	Concentration	Test models	Findings	References
Multiple (14) REE	1–10 μM (↑) 50–100 μM (↓)	Human keratinocytes	Matrix metalloproteinase-1 (MMP-1) Cell proliferation	Jenkins et al. (2011)
Y(III)	11–56 μM	*Nymphoides peltata*	Photosynthetic pigments, nutrient contents, enzymatic and non-enzymatic antioxidants, and ultrastructure	Fu et al. (2014)
La(III)	2–480 μM	*Vicia faba* seedlings	(↑↓) Catalase (CAT), guaiacol peroxidase (GPX), and ascorbate peroxidase (APX)	Wang et al. (2011)
	0.1–50 μM	Bovine vascular smooth muscle cells	Calcium deposition; β-glycerophosphate-induced alkaline phosphatase; apoptosis	Zhao et al. (2012)
	0.1 nM–0.1 μM (↑) 1 mM (↓)	Murine preosteoblast MC3T3-E1 cell line	Proliferation; osteogenic differentiation, and mineralization	Liu et al. (2012)
La(III) + pH decrease	82 μM+pH 4.5 (↑) 82 μM+pH 3.5 (↓) 2.45 mM+pH 2.5 (↓↓)	*Oryza sativa* seedlings	Net photosynthetic rate, stomatic Conductance, intercellular CO_2 Concentration and Hill reaction activity	Wang et al. (2014)
CeO_2 nanoparticles ($nCeO_2$)	0.3–3 mM	*Oryza sativa*	(↑↓) Lipid peroxidation; fatty acid and lignin content; electrolyte leakage	Rico et al. (2013)
	0.1–1.6 mM	*Carassius auratus*	(↑↓) Na+/K+-ATPase induction	Xia et al. (2013)
	1.7×10^{-7}–1.7×10^{-5} M	*Anabaena* CPB4337 and *P. subcapitata*	(↑↓) photosynthesis; ROS formation	Rodea-Palomares et al. (2012)
Ce(III)	10–80 μM	*Armoracia rusticana*	(↑↓) Membrane proteins; plasma membrane	Yang et al. (2012)
Ce(IV)	10^{-8}–10^{-5} M	*Paracentrotus lividus* (embryos and sperm)	Hormetic trends in fertilization rate, mitotic abnormalities and developmental defects in offspring of exposed sperm	Oral et al. (2010)
Pr(III)	20–80 mg/kg	Rats (i.v.)	(↑↓) Lecithin:cholesterol acyltransferase and erythrocyte osmotic fragility	Godin and Frohlich (1981)
Gd(III) (insoluble vs. solubilized with organic chelators)	12.5–125 μM	Human dermal fibroblasts	(↑↓) Proliferation vs. toxicity	Bleavins et al. (2012)
Gd-based contrast agents	10^{-5}–10^{-3} M	Human dermal fibroblasts	(↑↓) Proliferation vs. toxicity	Edward et al. (2010)
Ho(III)	$< 10^{-5}$–10^{-3} M	*Vicia faba*	(↑↓) Micronuclei; chromosomal aberrations and mitotic index	Qu et al. (2004)

The available database of REE-associated effects appear to follow hormetic trends in a number of studies having tested several REE. As shown in Table 2, REE mixtures and individual REE have been tested for a number of endpoints resulting in hormetic trends.

An extensive study by Jenkins et al. (2011) evaluated the effects of fourteen REE (La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, and Lu) on human keratinocytes by testing the expression of matrix metalloproteinase-1 and cell proliferation. REE concentrations ranged from 1 to 100 μM and both of tested endpoints showed clear-cut hormetic effects that were exerted, to different extents, by all assayed REE with stimulatory effects at 1–10 μM followed by inhibition at 50–100 μM (Jenkins et al., 2011).

The aquatic plant *Nymphoides peltata* was exposed to Y(III) at concentrations ranging from 1 to 5 mg/l (≈ 11–56 μM). Despite this quite narrow concentration range, peroxidase activity was induced, while initial rises in SOD activity and glutathione content were followed by subsequent declines; some of the tested endpoints, such as ascorbate levels and catalase activity decreased significantly for all Y(III) concentrations (Fu et al., 2014).

More extensive studies have been carried out by testing La(III) and reporting on hormetic trends, in concentration ranges encompassing three (or more) orders of magnitude. Wang et al. (2011) tested La(III) at concentrations ranging from 2 to 480 μM in *Vicia faba* seedlings, and found concentration-related hormetic trends for catalase, guaiacol peroxidase and ascorbate peroxidase activities. Bovine vascular smooth muscle cells were exposed to La (III) (0.1–50 μM) and tested for calcium deposition, β-glycerophosphate-induced alkaline phosphatase activity and apoptosis, finding concentration-related hormetic trends (Zhao et al., 2012). Liu et al. (2012) exposed a murine preosteoblast cell line to La(III) at concentrations ranging from 0.1 nM to 1 mM by testing cell proliferation and osteogenic differentiation, and found stimulatory effects by 0.1 nM–0.1 μM La(III) concentrations with a progressive endpoint suppression at higher La(III) concentrations up to 1 mM. In a recent report Wang et al. (2014) tested La(III) at concentrations ranging from 82 μM to 2.45 mM and at three pH values (4.5, 3.5 and 2.5) in rice seedlings, and found that low-level La(III) at pH 4.5 enhanced photosynthetic activity, which was depressed by higher La(III) levels and pH decrease.

Data on Ce-associated hormetic trends have been reported for $nCeO_2$, Ce(III) and Ce(IV). Rico et al. (2013) tested $nCeO_2$ in rice seedlings (*Oryza sativa*) at nominal concentrations ranging from 0.3 to 3 mM for lipid peroxidation, fatty acid and lignin content, and electrolyte leakage, and found hormetic trends for all endpoints. The same effects were reported by testing $nCeO_2$ (0.1 to 1.6 mM) in *Carassius auratus* for Na+/K+-ATPase induction (Xia et al., 2013), and in algae *(Anabaena* CPB4337 and *Pseudokirchneriella subcapitata)* exposed to $nCeO_2$ (0.17–17 μM) tested for photosynthesis and ROS formation (Rodea-Palomares et al., 2012).

Horseradish (*Armoracia rusticana*) seedlings were exposed to Ce(III) at concentrations ranging from 10 to 80 μM and hormetic trends were observed for membrane proteins and plasma membrane structure (Yang et al., 2012). We tested Ce(IV) (0.01–10 μM) in sea urchin *(Paracentrotus lividus)* embryos and sperm and found hormetic trends in sperm fertilization rate, mitotic abnormalities, and developmental defects in the offspring of exposed sperm. Exposure to La(III) in the same study resulted in lesser toxicity than Ce(IV), however with non-monotonic concentration-related trends (Oral et al., 2010).

An early study by Godin and Frohlich (1981), conducted an i.v. administration of Pr nitrate (PrN) to rats reported on "*paradoxical pathophysiological effects*", since low PrN doses (20 and 40 mg/kg) decreased plasma lecithin:cholesterol acyltransferase activity and erythrocyte osmotic fragility, while a higher PrN dose (80 mg/kg) increased both.

Different Gd compounds, i.e. insoluble or solubilized salts with organic chelators, or ionic and nonionic linear and macrocyclic contrast agents, at concentrations ranging from 10 μM to 1 mM, were tested in human dermal fibroblasts; two independent studies

found cell proliferation at low Gd levels, turning to toxicity and cell lysis at high Gd concentrations (Edward et al., 2010; Bleavins et al., 2012).

A hormetic trend for Ho(III) was suggested by Qu et al. (2004), who treated *V. faba* root tips with Ho nitrate at concentrations from $<10\,\mu M$ to 1 mM, and reported an increase in root tip growth-hence suggesting an increase in mitotic activity at Ho(III) levels $<10\,\mu M$, whereas higher Ho(III) levels both induced cytogenetic anomalies and decreased mitotic index.

Altogether, the available database provides substantial evidence of hormetic trends for most of REE, as per the above cited literature and, especially, based on the systematic investigation by Jenkins et al. (2011), who found hormetic trends for fourteen REE. The occurrence of this phenomenon, otherwise broadly recognized for a number of xenobiotics (Calabrese, 2010), accounts for the only apparent controversy between beneficial and adverse effects of REE. On the other hand, this database should raise warnings about the use of REE in agriculture, that might possibly conceal long-term adverse effects due to bioaccumulation and/or excess soil REE concentration. Finally, one should recognize that a consistent body of literature points to antioxidant roles of REE both in plants and in animals (Liang and Wang, 2013; Ciofani et al., 2013; Wong and McGinnis, 2014). Thus, future studies should both consider health concern and prospect beneficial use of REE based on appropriate evaluation of beneficial and adverse effects of REE exposures in plants, animals and humans.

7. REE-induced cytogenetic effects

One of the adverse effects of REE consists of changes in mitotic activity or cytogenetic anomalies. As shown in Table 3, few independent reports have focused on these outcomes following REE exposures. Cerium was tested as Ce(III) or Ce(IV) salts in two independent studies utilizing maize and sea urchin embryos and gametes, respectively (Huang et al., 2007; Oral et al., 2010); cytogenetic anomalies included increased micronuclei formation in maize root tips (Huang et al., 2007) and excess mitotic aberrations both in Ce-exposed embryos and in the offspring of Ce-pretreated sea urchin sperm (Oral et al., 2010). No cytogenetic effects were observed by exposing sea urchin embryos or sperm to La(III) (0.1 to 10 μM). No adverse effects were reported by Pierscionek et al. (2010) who tested $nCeO_2$ in human lens epithelial cells; however, the narrow concentration range utilized in this study (5 and 10 μg/ml) may have prevented the observation of possible adverse effects by testing a more extensive concentration range that might display adverse trends.

The study by Huang et al. (2007) provided evidence for excess micronuclei formation by testing Ce(III), Er(III), Sm(III), Y(III), and Eu(III) in maize root tips, finding different effective concentrations from 1 to 10 μM. Also this study failed to find any significant excess micronuclei formation by La(III) exposure.

The effects of Pr(III) and Nd(III) were tested for cytogenetic abnormalities by Jha and Singh (1994) in *V. faba* root tips reared in Pr(III) and Nd(III) in a millimolar range (0.1–0.5%); in a subsequent study (Jha and Singh, 1995) Pr(III) and Nd(III) were tested in mouse bone marrow cells following in vivo administration at dosages ranging from ≈ 5 to ≈ 40 mg/100 g b.w. Both studies found Pr(III)- and Nd(III)-induced cytogenetic abnormalities, including micronuclei and chromosomal aberrations. The same results were reported by Qu et al. (2004) who tested Ho(III) in *V. faba* root tips for growth and cytogenetic abnormalities. This study also found a growth increase at Ho(III) concentrations below 4 mg/l, followed by growth inhibition and increase in cytogenetic abnormalities at higher Ho(III) levels.

Though so far limited to few reports, one may consider cytogenetic effects as a shared property of REE, awaiting ad hoc studies both in experimental sets and, desirably, among occupationally REE-exposed groups.

8. pH-dependent modulation of REE toxicity

A pH-dependent toxicity modulation of several metals has long been established as related to environmental acidification including, yet not confined to, acid rain (reviewed by Goyer et al., 1985; Soskolne et al., 1989; Singh and Agrawal, 2008). Likewise, REE toxicity has been found to be modulated by medium acidification, and a few studies reported on pH-induced modulation of REE toxicity, as reported in Table 4.

Combined exposures to La(III) (from 6 μM to 0.85 mM) and pH decrease (4.5–3) were tested in soybean and rice leaves and roots, with combined effect of La(III) and pH decrease on photosyntetic activity (Liang et al., 2010; Wang et al., 2014), chloroplast ultrastructure (Wen et al., 2011), and in decreased catalase and peroxidase activities, along with increased H_2O_2 production and lipid peroxidation (Liang and Wang, 2013). Wang et al. (2014) reported that combined treatment of high-level La(III) and low pH had more severe effects on photosynthesis in rice than La(III) or acid exposure alone.

A study by Ma et al. (2011) reported on dissolution of La_2O_3 nanoparticles (NP) by acetic acid resulting in increased toxicity in cucumber plants (*Cucumis sativus*), suggesting that organic acids extruded from root cells played an important role in the phytotoxicity of La_2O_3 NPs.

A recent study (Thomas et al., 2014) tested the effects of three REE [La(III), Ce(III) and Y(III)] in five plant species (*Asclepias syriaca* L., *Desmodium canadense* L. DC, *Panicum virgatum* L., *Raphanus sativus* L., and *Solanum lycopersicum* L.). REE were dissolved in soil in an extensive range at seven to eight concentrations, within two orders of magnitude [e.g., La(III) from 7 to 700 mg/kg]. Ce(III) was also tested by comparing the effects of soil acidification (pH 4 vs. pH 7). The most severe damage to germination was observed with Ce(III) at low pH. The effects on growth inhibition showed

Table 3
Selected cytogenetic effects findings for REE.

Elements	Test models	Findings	References
Multiple	*Zea mais*	(↑) Micronuclei by Ce(III) ≤ 25 mg/l, Er(III) ≤ 5 mg/l, Y(III) ≤ 5 mg/l, Sm(III) ≤ 125 mg/l, and Eu(III) ≤ 125 mg/l; no significant effect by La(III)	Huang et al. (2007)
Ce(IV) & La(III)	Sea urchin *(Paracentrotus lividus)*	Ce(IV)-induced mitotic aberrations; no significant effect by La(III) exposure	Oral et al. (2010)
Pr(III) & Nd(III)	*Vicia faba*	(↑) Micronuclei; mitotic & chromosomal aberrations	Jha and Singh (1994)
	Mouse bone marrow cells	(↑) Chromosomal aberrations	Jha and Singh (1995)
Ho(III)	*Vicia faba*	(↑↓) Micronuclei; chromosomal aberrations and mitotic index	Qu et al. (2004)
Tb(III)	Human telomeric DNA	htel21 Quadruplex is stabilized by low Tb(III) levels (8 μM); Tb(III) $>10\,\mu M$ destabilizes quadruplex	Galezowska et al. (2007)

Table 4
pH-related REE toxicity.

Elements	Test models	Findings	References
La(III)	Soybean *(Glycine max)*	(↓) Photosynthetic parameters and chloroplast Ultrasturcture by increasing La(III) and decreasing pH	Liang et al. (2010) Wen et al. (2011)
		(↓) Catalase and peroxidase, (↑) H_2O_2 accumulation and lipid peroxidation by 0.1 mM La (III) at pH 4.5 and 3.0	Liang and Wang (2013)
nLa_2O_2	*Cucumis sativus*	(↑) Dissolution and toxicity of La_2O_3 NPs by organic acids	Ma et al. (2011)
La(III) + pH decrease	Rice (*Oryza sativa*)	Photosyntetic activity from (↑) La(III) 82 μM + pH 4.5 to (↓↓) La(III) 2450 μM + pH 2.5	Wang et al. (2014)
La(III), Ce(III) and Y(III)	Five plant species	(↓) Germination at pH 4 vs.(↑) at pH 6.7	Thomas et al. (2014)
$nCeO_2$	*Raphanus sativus*	Citric acid coating decreases CeO_2 NPs toxicity	Trujillo-Reyes et al. (2013)
	Mouse fibroblasts		Ould-Moussa et al. (2014)

different species sensitivity, with reductions in biomass for the two Canadian native forb species (*A. syriaca* and *D. canadense*). Root bioaccumulation followed a dose-response trend. The authors concluded that REE are of limited toxicity, although they raised the concern about soil accumulation of these elements that can result in plant toxicity (Thomas et al., 2014). One should consider that agricultural activities may turn in relevant inputs of REE in soil. Turra et al. (2011) reported that REE-containing fertilizers may result in substantial increase in the REE content of the soil and could cause harmful effects to the environment and humans. These adverse impacts may involve other trophic levels, as reported by Li et al. (2010b) who found that a large input of REE into the environment reduced soil macrofauna community diversity.

Acid coating of nanoceria ($nCeO_2$) was tested in two independent studies conducted in radish (*Raphanus sativus*) and in mouse fibroblasts, with opposite results in plant *vs.* animal cells. Citric acid (CAc)-coated $nCeO_2$ was tested at concentrations ranging from 50 to 200 mg/l resulting in improved radish seed germination (at 200 mg/l, or 1.16 mM) compared to bare nanoparticles with a significant increase in root biomass, increased water content and reduced Ce uptake (Trujillo-Reyes et al., 2013). The authors suggested that CAc coating decreases $nCeO_2$ toxicity to plants. One might note that a 1:4 (50–200) concentration range might prevent these authors from observing any response shift from stimulatory to inhibitory effects, which might be detected at higher $nCeO_2$ concentrations. Opposite to the above report, Ould-Moussa et al. (2014) found that CAc-coated $nCeO_2$ particles, but not particles coated with poly(acrylic acid), enhanced Ce cell absorption and caused toxicity and moderate genotoxicity in mouse fibroblasts at concentrations above 1 mM. As discussed in Section 6, opposite results may conceal the lack of suitably extensive concentration ranges, which could allow observations of hormetic trends both including stimulatory and inhibitory effects.

Altogether, the combined environmental spread of REE and acidic pollution should be regarded-and possibly regulated-as a serious environmental concern, especially in REE mining areas where the occurrence both of mining by-products and of acid pollution are well-established (Grawunder et al., 2014; Olías et al., 2005).

9. Overview and conclusions

Broadly neglected as xenobiotics up to recent years, REE have undergone an unprecedented boost of technological utilization in the last two decades that implies the current-and growing-spread of REE in environmental and occupational exposures. REE-associated action mechanisms have been associated with redox reactivity, involving ROS formation, lipid peroxidation and modulation of antioxidant activities. In turn, REE exposures involve a number of endpoints such as cell growth and differentiation, membrane structure and stability, or some specific functions as e.g. photosynthetic activity and cell division. The literature from animal studies and limited data from human occupational exposures suggests REE-induced tissue-specific bioaccumulation and damage to lungs, liver and brain. An enhanced adverse action has been found following combined exposures to REE and acidic pollutants.

A controversy between stimulatory *vs.* inhibitory REE-associated health effects has arisen in the literature, involving environmental, medical and agricultural sciences. Far from reaching a dispute matter, this controversy may find substantial reconciliation in view of the hormesis phenomenon. This interpretation both relies on some studies of REE-associated effects and on an extensive body of literature dating back to the 19th century that established the stimulatory effects of low-level toxicants (Schulz, 1888; reviewed by Stebbing, 1982).

The currently thriving literature on REE-associated health effects is mostly confined to three REE (Ce, La and Gd), thus the information for several REE remains relatively scarce, notwithstanding their growing industrial utilization and, hence, environmental spread and human exposures. This gap, along with several open questions in REE health effects, shall be filled in the forthcoming investigations.

References

Alonso, E., Sherman, A.M., Wallington, T.J., Everson, M.P., Field, F.R., Roth, R., Kirchain, R.E., 2012. Evaluating rare earth element availability: a case with revolutionary demand from clean technologies. Environ. Sci. Technol. 46, 3406–3414.

Bernstein, E.J., Schmidt-Lauber, C., Kay, J., 2012. Nephrogenic systemic fibrosis: a systemic fibrosing disease resulting from gadolinium exposure. Best Pract. Res. Clin. Rheumatol. 26, 489–503.

Bleavins, K., Peron, P., Naik, M., Rehman, M., Aslam, M.N., Dame, M.K., Meshinchi, S., Bhagavathula, N., Varani, J., 2012. Stimulation of fibroblast proliferation by insoluble gadolinium salts. Biol. Trace Elem. Res. 145, 257–267.

Bustamante, P., Miramand, P., 2005. Subcellular and body distributions of 17 trace elements in the variegated scallop *Chlamys varia* from the French coast of the Bay of Biscay. Sci. Total Environ. 337, 59–73.

Calabrese, E.J., 2010. Hormesis is central to toxicology, pharmacology and risk assessment. Hum. Exp. Toxicol. 29, 249–261.

Calabrese, E.J., 2013. Hormetic mechanisms. Crit. Rev. Toxicol. 43, 580–606.

Cassee, F.R., van Balen, E.C., Singh, C., Green, D., Muijser, H., Weinstein, J., Dreher, K., 2011. Exposure, health and ecological effects review of engineered nanoscale cerium and cerium oxide associated with its use as a fuel additive. Crit. Rev. Toxicol. 41, 213–229.

Cassee, F.R., Campbell, A., Boere, A.J., McLean, S.G., Duffin, R., Krystek, P., Gosens, I., Miller, M.R., 2012. The biological effects of subacute inhalation of diesel exhaust following addition of cerium oxide nanoparticles in atherosclerosis-prone mice. Environ. Res. 115, 1–10.

Censi, P., Randazzo, L.A., D'Angelo, S., Saiano, F., Zuddas, P., Mazzola, S., Cuttitta, A., 2013. Relationship between lanthanide contents in aquatic turtles and environmental exposures. Chemosphere 91, 1130–1135.

Chang, Y., Lee, G.H., Kim, T.J., Chae, K.S., 2013. Toxicity of magnetic resonance imaging agents: small molecule and nanoparticle. Curr. Top. Med. Chem. 13, 434–445.

Chien, C.C., Wang, H.Y., Wang, J.J., Kan, W.C., Chien, T.W., Lin, C.Y., Su, S.B., 2011. Risk of acute kidney injury after exposure to gadolinium-based contrast in patients

with renal impairment. Ren. Fail. 33, 758–764.
Darrah, T.H., Prutsman-Pfeiffer, J.J., Poreda, R.J., Ellen Campbell, M., Hauschka, P.V., Hannigan, R.E., 2009. Incorporation of excess gadolinium into human bone from medical contrast agents. Metallomics 1, 479–488.
Cho, S., Lee, Y., Lee, S., Choi, Y.J., Chung, H.W., 2014. Enhanced cytotoxic and genotoxic effects of gadolinium following ELF-EMF irradiation in human lymphocytes. Drug Chem. Toxicol. 37, 440–447.
Ciofani, G., Genchi, G.G., Liakos, I., Cappello, V., Gemmi, M., Athanassiou, A., Mazzolai, B., Mattoli, V., 2013. Effects of cerium oxide nanoparticles on PC12 neuronal-like cells: proliferation, differentiation, and dopamine secretion. Pharm. Res. 30, 2133–2145.
Edward, M., Quinn, J.A., Burden, A.D., Newton, B.B., Jardine, A.G., 2010. Effect of different classes of gadolinium-based contrast agents on control and nephrogenic systemic fibrosis-derived fibroblast proliferation. Radiology 256, 735–743.
Fu, Y., Li, F., Xu, T., Cai, S., Chu, W., Qiu, H., Sha, S., Cheng, G., Xu, Q., 2014. Bioaccumulation, subcellular, and molecular localization and damage to physiology and ultrastructure in *Nymphoides peltata* (Gmel.) O. Kuntze exposed to yttrium. Environ. Sci. Pollut. Res. Int. 21, 2935–2942.
Galezowska, E., Gluszynska, A., Juskowiak, B., 2007. Luminescence study of G-quadruplex formation in the presence of Tb3+ ion. J. Inorg. Biochem. 101, 678–685.
Ghio, A.J., Soukup, J.M., Dailey, L.A., Richards, J., Deng, Z., Abraham, J.L., 2011. Gadolinium exposure disrupts iron homeostasis in cultured cells. J. Biol. Inorg. Chem. 16, 567–575.
Godin, D.V., Frohlich, J., 1981. Erythrocyte alterations in praseodymium-induced lecithin:cholesterol acyltransferase (LCAT) deficiency in the rat: comparison with familial LCAT deficiency in man. Res. Commun. Chem. Pathol. Pharmacol. 31, 555–566.
Gong Jr., H., 1996. Uncommon causes of occupational interstitial lung diseases. Curr. Opin. Pulm. Med. 2, 405–411.
Goyer, R.A., John Bachmann, J., Clarkson, T.W., Ferris Jr., B.G., Graham, J., Mushak, P., Perl, D.P., Rall, D.P., Schlesinger, R., William Sharpe, W., John, M., Wood, J.M., 1985. Potential human health effects of acid rain: report of a workshop. Environ. Health Perspect. 60, 355–368.
Grawunder, A., Merten, D., Büchel, G., 2014. Origin of middle rare earth element enrichment in acid mine drainage-impacted areas. Environ. Sci. Pollut. Res. Int. 21, 6812–6823.
Haley, T.J., Raymond, K., Komesu, N., Upham, H.C., 1961. Toxicological and pharmacological effects of gadolinium and samarium chlorides. Brit. J. Pharmacol. 17, 526–532.
Haley, T.J., 1965. Pharmacology and toxicology of the rare earth elements. J. Pharm. Sci. 54, 663–670.
Hirano, S., Suzuki, K.T., 1996. Exposure, metabolism, and toxicity of rare earths and related compounds. Environ. Health Perspect. 104 (Suppl. 1), 85–95.
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., 2014. Pulmonary toxicity in mice following exposure to cerium chloride. Biol. Trace Elem. Res. 159, 269–277.
Hongyan, G., Liang, C., Xiaorong, W., Ying, C., 2002. Physiological responses of Carassius auratus to ytterbium exposure. Ecotoxicol. Environ. Saf. 53, 312–316.
Hu, X., Ding, Z., Chen, Y., Wang, X., Dai, L., 2002. Bioaccumulation of lanthanum and cerium and their effects on the growth of wheat (*Triticum aestivum* L.) seedlings. Chemosphere 48, 621–629.
Huang, S.F., Li, Z.Y., Fu, M.L., Hu, F.F., Xu, H.J., Xie, Y., 2007. Detection of genotoxicity of 6 kinds of rare earth nitrates using orthogonal experimental design. J. Agro-Environ. Sci. 1, 351–356.
Huang, P., Li, J., Zhang, S., Chen, C., Han, Y., Liu, N., Xiao, Y., Wang, H., Zhang, M., Yu, Q., Liu, Y., Wang, W., 2011. Effects of lanthanum, cerium, and neodymium on the nuclei and mitochondria of hepatocytes: accumulation and oxidative damage. Environ. Toxicol. Pharmacol. 31, 25–32.
Jiang, N., Wang, L., Lu, T., Huang, X., 2011. Toxic effect of terbium ion on horseradish cell. Biol. Trace Elem. Res. 143, 1722–1728.
Jenkins, W., Perone, P., Walker, K., Bhagavathula, N., Aslam, M.N., DaSilva, M., Dame, M.K., Varani, J., 2011. Fibroblast response to lanthanoid metal ion stimulation: potential contribution to fibrotic tissue injury. Biol. Trace Elem. Res. 144, 621–635.
Jha, A.M., Singh, A.C., 1994. Clastogenicity of lanthanides–induction of micronuclei in root tips of *Vicia faba*. Mutat. Res. 322, 169–172.
Jha, A.M., Singh, A.C., 1995. Clastogenicity of lanthanides: induction of chromosomal aberration in bone marrow cells of mice in vivo. Mutat. Res. 341, 193–197.
Jonas, W.B., Ives, J.A., 2008. Should we explore the clinical utility of hormesis? Hum. Exp. Toxicol. 27, 123–127.
Kawagoe, M., Hirasawa, F., Cun Wang, S., Liu, Y., Ueno, Y., Sugiyama, T., 2005. Orally administrated rare earth element cerium induces metallothionein synthesis and increases glutathione in the mouse liver. Life Sci. 77, 922–937.
Kirchin, M.A., Runge, V.M., 2003. Contrast agents for magnetic resonance imaging: safety update. Top Magn. Reson. Imaging 14, 426–435.
Kulaksız, S., Bau, M., 2011. Rare earth elements in the Rhine River, Germany: first case of anthropogenic lanthanum as a dissolved microcontaminant in the hydrosphere. Environ. Int. 37, 973–979.
Li, N., Wang, S., Liu, J., Ma, L., Duan, Y., Hong, F., 2010a. The oxidative damage in lung of mice caused by lanthanoide. Biol. Trace Elem. Res. 134, 68–78.
Li, J., Hong, M., Yin, X., Liu, J., 2010b. Effects of the accumulation of the rare earth elements on soil macrofauna community. J. Rare Earths 28, 957–964.
Li, B., Sun, Q., Yu, X., Xie, Y., Hong, J., Zhao, X., Sang, X., Shen, W., Hong, F., 2014. Molecular mechanisms of silk gland damage caused by phoxim exposure and protection of phoxim-induced damage by cerium chloride in Bombyx mori. Environ. Toxicol. . http://dx.doi.org/10.1002/tox.21983
Liang, C.J., Pan, D.Y., Xu, Q.R., Zhou, Q., 2010. Combined injured effects of acid rain and lanthanum on growth of soybean seedling. Huan Jing Ke Xue 31, 1652–1656.
Liang, C., Wang, W., 2013. Antioxidant response of soybean seedlings to joint stress of lanthanum and acid rain. Environ. Sci. Pollut. Res. Int. 20, 8182–8191.
Liang, T., Li, K., Wang, L., 2014. State of rare earth elements in different environmental components in mining areas of China. Environ. Monit. Assess. 186, 1499–1513.
Lin, W., Huang, Y.W., Zhou, X.D., Ma, Y., 2006. Toxicity of cerium oxide nanoparticles in human lung cancer cells. Int. J. Toxicol. 25, 451–457.
Liu, D., Zhang, J., Wang, G., Liu, X., Wang, S., Yang, M., 2012. The dual-effects of $LaCl_3$ on the proliferation, osteogenic differentiation, and mineralization of MC3T3-E1 cells. Biol. Trace Elem. Res. 150, 433–440.
Liu, G., Cheresh, P., Kamp, D.W., 2013. Molecular basis of asbestos-induced lung disease. Annu. Rev. Pathol. 8, 161–187.
Luís, A.T., Bonet, B., Corcoll, N., Almeida, S.F., da Silva, E.F., Figueira, E., Guasch, H., 2014. Experimental evaluation of the contribution of acidic pH and Fe concentration to the structure, function and tolerance to metals (Cu and Zn) exposure in fluvial biofilms. Ecotoxicology 23, 1270–1282.
Ma, J.Y., Zhao, H., Mercer, R.R., Barger, M., Rao, M., Meighan, T., Schwegler-Berry, D., Castranova, V., Ma, J.K., 2011. Cerium oxide nanoparticle-induced pulmonary inflammation and alveolar macrophage functional change in rats. Nanotoxicology 5, 312–325.
Ma, J.Y., Young, S.H., Mercer, R.R., Barger, M., Schwegler-Berry, D., Ma, J.K., Castranova, V., 2014. Interactive effects of cerium oxide and diesel exhaust nanoparticles on inducing pulmonary fibrosis. Toxicol. Appl. Pharmacol. 278, 135–147.
Marubashi, K., Hirano, S., Suzuki, K.T., 1998. Effects of intratracheal pretreatment with yttrium chloride (YCl3) on inflammatory responses of the rat lung following intratracheal instillation of YCl3. Toxicol. Lett. 99, 43–51.
Mattson, M.P., 2008. Hormesis defined. Ageing Res. Rev. 7, 1–7.
McDonald, J.W., Ghio, A.J., Sheehan, C.E., Bernhardt, P.F., Roggli, V.L., 1995. Rare earth (cerium oxide) pneumoconiosis: analytical scanning electron microscopy and literature review. Mod. Pathol. 8, 859–865.
Moermond, C.T., Tijink, J., van Wezel, A.P., Koelmans, A.A., 2001. Distribution, speciation, and bioavailability of lanthanides in the Rhine-Meuse estuary, The Netherlands. Environ. Toxicol. Chem. 20, 1916–1926.
Li, N., Wang, S., Liu, J., Ma, L., Duan, Y., Hong, F., 2010. The oxidative damage in lung of mice caused by lanthanoide. Biol. Trace Elem. Res. 134, 68–78.
Olías, M., Cerón, J.C., Fernández, I., De la Rosa, J., 2005. Distribution of rare earth elements in an alluvial aquifer affected by acid mine drainage: the *Guadiamar aquifer* (SW Spain). Environ. Pollut. 135, 53–64.
Ould-Moussa, N., Safi, M., Guedeau-Boudeville, M.A., Montero, D., Conjeaud, H., Berret, J.F., 2014. In vitro toxicity of nanoceria: effect of coating and stability in biofluids. Nanotoxicology 8, 799–811.
Oral, R., Bustamante, P., Warnau, M., D'Ambra, A., Guida, M., Pagano, G., 2010. Cytogenetic and developmental toxicity of cerium and lanthanum to sea urchin embryos. Chemosphere 81, 194–198.
Palmer, R.J., Butenhoff, J.L., Stevens, J.B., 1987. Cytotoxicity of the rare earth metals cerium, lanthanum, and neodymium in vitro: comparisons with cadmium in a pulmonary macrophage primary culture system. Environ. Res. 43, 142–156.
Pang, X., Li, D., Peng, A., 2002. Application of rare-earth elements in the agriculture of China and its environmental behavior in soil. Environ. Sci. Pollut. Res. Int. 9, 143–148.
Pardo, T., Bernal, M.P., Clemente, R., 2014. Efficiency of soil organic and inorganic amendments on the remediation of a contaminated mine soil: I. Effects on trace elements and nutrients solubility and leaching risk. Chemosphere 107, 121–128.
Park, E.J., Choi, J., Park, Y.K., Park, K., 2008. Oxidative stress induced by cerium oxide nanoparticles in cultured BEAS-2B cells. Toxicology 245, 90–100.
Peng, R.L., Pan, X.C., Xie, Q., 2003. Relationship of the hair content of rare earth elements in young children aged 0–3 years to that in their mothers living in a rare earth mining area of Jiangxi. Zhonghua Yu Fang Yi Xue Za Zhi 37, 20–22.
Pereira, L.V., Shimizu, M.H., Rodrigues, L.P., Leite, C.C., Andrade, L., Seguro, A.C., 2012. N-acetylcysteine protects rats with chronic renal failure from gadolinium-chelate nephrotoxicity. PLoS One 7, e39528.
Pierscionek, B.K., Li, Y., Yasseen, A.A., Colhoun, L.M., Schachar, R.A., Chen, W., 2010. Nanoceria have no genotoxic effect on human lens epithelial cells. Nanotechnology 21, 035102.
Qu, A., Wang, C.R., Bo, J., 2004. Research on the cytotoxic and genotoxic effects of rare-earth element holmium to *Vicia faba*. Yi Chuan 26, 195–201.
Rico, C.M., Morales, M.I., McCreary, R., Castillo-Michel, H., Barrios, A.C., Hong, J., Tafoya, A., Lee, W.Y., Varela-Ramirez, A., Peralta-Videa, J.R., Gardea-Torresdey, J. L., 2013. Cerium oxide nanoparticles modify the antioxidative stress enzyme activities and macromolecule composition in rice seedlings. Environ. Sci. Technol. 47, 14110–14118.
Rim, K.T., Koo, K.H., Park, J.S., 2013. Toxicological evaluations of rare earths and their health impacts to workers: a literature review. Saf. Health Work 4, 12–26.
Rodea-Palomares, I., Gonzalo, S., Santiago-Morales, J., Leganés, F., García-Calvo, E., Rosal, R., Fernández-Piñas, F., 2012. An insight into the mechanisms of nanoceria toxicity in aquatic photosynthetic organisms. Aquat. Toxicol. 122–123, 133–143.
Sabbioni, E., Pietra, R., Gaglione, P., Vocaturo, G., Colombo, F., Zanoni, M., Rodi, F., 1982. Long-term occupational risk of rare-earth pneumoconiosis. A case report

as investigated by neutron activation analysis. Sci. Total Environ. 26, 19–32.
Schubert, D., Dargusch, R., Raitano, J., Chan, S.W., 2006. Cerium and yttrium oxide nanoparticles are neuroprotective. Biochem. Biophys. Res. Commun. 342, 86–91.
Schulz, H., 1888. über Hefegifte. Pflüg. Arch. gesamte Physiol. Menschen Tiere 42, 517–541.
Shimada, H., Nagano, M., Funakoshi, T., Kojima, S., 1996. Pulmonary toxicity of systemic terbium chloride in mice. J. Toxicol. Environ. Health 48, 81–92.
Singh, A., Agrawal, M., 2008. Acid rain and its ecological consequences. J. Environ. Biol. 29, 15–24.
Soskolne, C.L., Pagano, G., Cipollaro, M., Beaumont, J.J., Giordano, G.G., 1989. Epidemiologic and toxicologic evidence for chronic health effects and the underlying biologic mechanisms involved in sub-lethal exposures to acidic pollutants. Arch. Environ. Health 44, 180–191.
Stebbing, A.R., 1982. Hormesis—the stimulation of growth by low levels of inhibitors. Sci. Total Environ. 22, 213–234.
Stohs, S.J., Bagchi, D., 1995. Oxidative mechanisms in the toxicity of metal ions. Free Radic. Biol. Med. 18, 321–336.
Thomas, P.J., Carpenter, D., Boutin, C., Allison, J.E., 2014. Rare earth elements (REEs): effects on germination and growth of selected crop and native plant species. Chemosphere 96, 57–66.
Thomsen, H.S., 2006. Nephrogenic systemic fibrosis: a serious late adverse reaction to gadodiamide. Eur. Radiol. 16, 2619–2621.
Tong, S.L., Zhu, W.Z., Gao, Z.H., Meng, Y.X., Peng, R.L., Lu, G.C., 2004. Distribution characteristics of rare earth elements in children's scalp hair from a rare earths mining area in southern China. J. Environ. Sci. Health A Tox. Hazard. Subst. Environ. Eng. 39, 2517–2532.
Toyokuni, S., 1996. Iron-induced carcinogenesis: the role of redox regulation. Free Radic. Biol. Med. 20, 553–566.
Tranchida, G., Oliveri, E., Angelone, M., Bellanca, A., Censi, P., D'Elia, M., Neri, R., Placenti, F., Sprovieri, M., Mazzola, S., 2011. Distribution of rare earth elements in marine sediments from the Strait of Sicily (western Mediterranean Sea): evidence of phosphogypsum waste contamination. Mar. Pollut. Bull. 62, 182–191.
Trujillo-Reyes, J., Vilchis-Nestor, A.R., Majumdar, S., Peralta-Videa, J.R., Gardea-Torresdey, J.L., 2013. Citric acid modifies surface properties of commercial CeO_2 nanoparticles reducing their toxicity and cerium uptake in radish (*Raphanus sativus*) seedlings. J. Hazard. Mater. 263 (2), 677–684.
Tseng, M.T., Lu, X., Duan, X., Hardas, S.S., Sultana, R., Wu, P., Unrine, J.M., Graham, U., Butterfield, D.A., Grulke, E.A., Yokel, R.A., 2012. Alteration of hepatic structure and oxidative stress induced by intravenous nanoceria. Toxicol. Appl. Pharmacol. 260, 173–182.
Tu, Q., Wang, X.R., Tian, L.Q., Dai, L.M., 1994. Bioaccumulation of the rare earth elements lanthanum, gadolinium and yttrium in carp (*Cyprinus carpio*). Environ. Pollut. 85, 345–350.
Turra, C., Fernandes, E.A.N., Bacchi, M.A., 2011. Evaluation on rare earth elements of Brazilian agricultural supplies. J. Environ. Chem. Ecotoxicol 3, 86–92.
US Environmental Protection Agency, 2009. Provisional peer-reviewed toxicity values for stable (nonradioactive) samarium chloride (CASRN 10361-82-7) and stable (nonradioactive) samarium nitrate (CASRN 10361-83-8). National Center for Environmental Assessment. Superfund Health Risk Technical Support Center, Cincinnati, OH.
US Environmental Protection Agency, 2012. Rare Earth Elements: A Review of Production, Processing, Recycling, and Associated Environmental Issues. EPA 600/R-12/572. ⟨www.epa.gov/ord⟩.
Wang, C., He, M., Shi, W., Wong, J., Cheng, T., Wang, X., Hu, L., Chen, F., 2011. Toxicological effects involved in risk assessment of rare earth lanthanum on roots of *Vicia faba* L. seedlings. J. Environ. Sci. (China) 23, 1721–1728.
Wang, C., Luo, X., Tian, Y., Xie, Y., Wang, S., Li, Y., Tian, L., Wang, X., 2012. Biphasic effects of lanthanum on *Vicia faba* L. seedlings under cadmium stress, implicating finite antioxidation and potential ecological risk. Chemosphere 86, 530–537.
Wang, L., Wang, W., Zhou, Q., Huang, X., 2014. Combined effects of lanthanum (III) chloride and acid rain on photosynthetic parameters in rice. Chemosphere 112, 355–361.
Waring, P.M., Watling, R.J., 1990. Rare earth deposits in a deceased movie projectionist. A new case of rare earth pneumoconiosis? Med. J. Aust. 153, 726–730.
Weilin, S., Xiuying, S., Xiying, M., 2006. Effects of samarium on liver and kidney of rats. J. Rare Earths 24, 415–418.
Wen, K., Liang, C., Wang, L., Hu, G., Zhou, Q., 2011. Combined effects of lanthanum ion and acid rain on growth, photosynthesis and chloroplast ultrastructure in soybean seedlings. Chemosphere 84, 601–608.
Wong, L.L., McGinnis, J.F., 2014. Nanoceria as bona fide catalytic antioxidants in medicine: what we know and what we want to know. Adv. Exp. Med. Biol. 801, 821–828.
Wu, J., Yang, J., Liu, Q., Wu, S., Ma, H., Cai, Y., 2013. Lanthanum induced primary neuronal apoptosis through mitochondrial dysfunction modulated by Ca^{2+} and Bcl-2 family. Biol. Trace Elem. Res. 152, 125–134.
Xia, Q., Feng, X., Huang, H., Du, L., Yang, X., Wang, K., 2011. Gadolinium-induced oxidative stress triggers endoplasmic reticulum stress in rat cortical neurons. J. Neurochem. 117, 38–47.
Xia, J., Zhao, H.Z., Lu, G.H., 2013. Effects of selected metal oxide nanoparticles on multiple biomarkers in *Carassius auratus*. Biomed. Environ. Sci. 26, 742–749.
Yang, G., Sun, Z., Lv, X., Deng, Y., Zhou, Q., Huang, X., 2012. Living target of Ce(III) action on horseradish cells: proteins on/in cell membrane. Biol. Trace Elem. Res. 150, 396–402.
Yokel, R.A., Au, T.C., MacPhail, R., Hardas, S.S., Butterfield, D.A., Sultana, R., Goodman, M., Tseng, M.T., Dan, M., Haghnazar, H., Unrine, J.M., Graham, U.M., Wu, P., Grulke, E.A., 2012. Distribution, elimination, and biopersistence to 90 days of a systemically introduced 30 nm ceria-engineered nanomaterial in rats. Toxicol. Sci. 127, 256–268.
Yoon, H.K., Moon, H.S., Park, S.H., Song, J.S., Lim, Y., Kohyama, N., 2005. Dendriform pulmonary ossification in patient with rare earth pneumoconiosis. Thorax 60, 701–703.
Zhao, H., Cheng, Z., Hu, R., Chen, J., Hong, M., Zhou, M., Gong, X., Wang, L., Hong, F., 2011. Oxidative injury in the brain of mice caused by lanthanid. Biol. Trace Elem. Res. 142, 174–189.
Zhao, W.H., Gou, B.D., Zhang, T.L., Wang, K., 2012. Lanthanum chloride bidirectionally influences calcification in bovine vascular smooth muscle cells. J. Cell Biochem. 113, 1776–1786.
Zhao, H., Hong, J., Yu, X., Zhao, X., Sheng, L., Ze, Y., Sang, X., Gui, S., Sun, Q., Wang, L., Hong, F., 2013. Oxidative stress in the kidney injury of mice following exposure to lanthanides trichloride. Chemosphere 93, 875–884. http://dx.doi.org/10.1016/j.chemosphere.2013.05.034.
Zhuang, G., Zhou, Y., Lu, H., Lu, W., Zhou, M., Wang, Y., Tan, M., 1996. Concentration of rare earth elements, As, and Th in human brain and brain tumors, determined by neutron activation analysis. Biol. Trace Elem. Res. 53, 45–49.