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Review article

Rare earth elements in human and animal health: State of art and research priorities

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ABSTRACT

Background: A number of applications have been developed using rare earth elements (REE), implying several human exposures and raising unsolved questions as to REE-associated health effects.
Methods: A MedLine survey was retrieved from early reports (1980s) up to June 2015, focused on human and animal exposures to REE. Literature from animal models was selected focusing on REE-associated health effects.
Results: Some REE occupational exposures, in jobs such as glass polishers, photoengravers and movie projectionists showed a few case reports on health effects affecting the respiratory system. No case-control or cohort studies of occupational REE exposures were retrieved. Environmental exposures have been biomonitored in populations residing in REE mining areas, showing REE accumulation. The case for a iatrogenic REE exposure was raised by the use of gadolinium-based contrast agents for nuclear magnetic resonance. Animal toxicity studies have shown REE toxicity, affecting a number of endpoints in liver, lungs and blood. On the other hand, the use of REE as feed additives in livestock is referred as a safe and promising device in zootechnical activities, possibly suggesting a hormetic effect both known for REE and for other xenobiotics. Thus, investigations on long-term exposures and observations are warranted.
Conclusion: The state of art provides a limited definition of the health effects in occupationally or environmentally REE-exposed human populations. Research priorities should be addressed to case-control or cohort studies of REE-exposed humans and to life-long animal experiments.

1. Introduction

Rare earth elements have been utilized in a number of industrial, medical, and agricultural or zootechnical applications (Du and Graedel, 2011; USEPA, 2012). The growing increase in REE extraction and manufacturing have led to a number of human exposures, included among "New and Emerging Risks to Occupational Safety and Health" by the European Agency for Safety and Health at Work (EU-OSHA, 2013). Some selected technologies involved in REE production, processing and utilization are summarized in Table 1.

Human exposures to REE range from occupational to environmental and to iatrogenic routes. Occupational exposures to REE dusts have been associated with observations of pneumoconiosis since early case reports (Sabbioni et al., 1982). Non-occupational, environmental REE exposures have been reported by a few studies of populations residing in REE mining areas that reported REE accumulation as related to distance from mining areas (Peng et al., 2003; Tong et al., 2004), or associated REE exposure with changes in serologic endpoints (Zhu et al., 2005). A recognized iatrogenic exposure consists of gadolinium (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).

Toxicological investigations on REE-associated health effects have been relatively scarce up to recent years, and a number of questions are pending as to any adverse effects of REE occupational and/or environmental exposures (Cassee et al., 2011; Pagano et al., 2012; 2015).

Animal studies are as yet confined to few REE (mostly Ce and La), and to short- to medium-term observation (mostly 1–3 months), and have provided multiple evidence for adverse effects in terms of inflammation endpoints, oxidative stress (OS), and tissue damage (liver, lungs and kidneys) (reviewed by Pagano

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Table 1
Current technologies associated with occupational REE exposures (summarized from USEPA, 2012; Gambogi and Cordier, 2013).

REE-related activities	Primary Pollutants of Concern
Mining and processing	REE dust; radionuclides; mine influenced waters/ acid minedrainage/alkaline or neutral mine drainage; tailings
Production and utilization	
Alloys	Ce, Gd, Nd, Sc, Tb, Yb
Petroleum-cracking catalysts	nanoCeO_2
Permanent magnets	Nd, Sm
Optical lens grinding	CeO_2 dust
Photoengraving	REE mist
Lighter sparking flints	CeO_2 dust
Nuclear reactors	Eu, Ho
TV and PC screens	Y
Ceramics, colored glass	Nd, Pr
Computer chips	Gd

Note: with the exception of the few jobs referred to in Table 2, no published investigations were retrieved on potential health risks in REE-exposed workers.

et al., 2012, 2015). However, studies of long-term REE exposures and life-long observations are as yet lacking.

REE are currently used in zootechnical practice as feed additives s, with reported safety and improvements in animal growth, egg laying, and crop productivity (He and Rambeck, 2000; Igbusan and Adebayo, 2012). This apparent contradiction between favorable and adverse REE-associated effects is discussed below.

Altogether, the current database on REE-associated health effects and its major gaps raise presently open questions that should be elucidated in forthcoming investigations.

2. Methods

A MedLine retrieval up to June 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 health effects in humans, and to organ and tissue toxicity in animal studies. 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.

3. REE human exposures

3.1. Occupational exposures

A number of industrial activities imply occupational exposures to REE dusts or mists, such as REE extraction or refining,, and production of a number of REE-containing products, such as alloys, petroleum catalysts, permanent magnets, glass and ceramics (Du and Graedel, 2011; USEPA, 2012; Rim et al., 2013; Gambogi and Cordier, 2013) (Table 1).

The current database on REE occupational exposures is confined to early case reports, pointing to observations of pneumoconiosis and interstitial lung disease mostly in individual REE-exposed workers, as reported in Table 2. Photoengravers were reported to be affected by pneumoconiosis in individual case reports (Sabbioni et al., 1982; Vocaturo et al., 1983; Sulotto et al., 1986), and in five REE-exposed photoengravers (Vogt et al., 1986). Clinical cases of movie projectionists, also occupationally exposed to REE, were characterized by pneumoconiosis (Waring and Watling, 1990; Pairon et al., 1995; Porru et al., 2001). McDonald et al. (1995) found cerium (Ce) particles in the lungs of a Ce-exposed optical lens polisher 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 (as crystal polisher) and affected by dendriform pulmonary ossification and pneumoconiosis (Yoon et al., 2005).

Epidemiological data, from case-control or cohort studies of REE occupationally exposed workers relating work history with specific pathologies are currently lacking for most of REE-related occupations. Thus one may raise the question as to other late effects of REE exposures beyond pneumoconiosis, such as further damage to the respiratory system, and/or to other organs and systems, as suggested by some geographic studies of environmental exposures, and by animal studies.

3.2. Environmental exposures

Human environmental exposures to REE have been investigated in a number of biomonitoring studies mostly focused on REE mixtures, or on Ce, related to distance from REE mining areas. Three studies measured REE levels in scalp hair from children and their mothers residing at different distances from mining sites in Southern China, and found a significant correlation between Ce scalp accumulation and distances from mining sites (Peng et al., 2003; Tong et al., 2004; Wei et al., 2013). A study by Zhu et al. (2005), also conducted on residents at different distances from REE mining sites, showed that residents in contaminated areas with heavy (HREE) or light (LREE) REE had significantly lower serum total protein and globulin levels compared to controls, and residents in the HREE area had significantly elevated IgM levels *vs*. LREE residents.

Beyond the so far scanty literature on environmental REE exposures, one should consider that REE and, in particular, Ce compounds are used, among many other applications, as diesel fuel additives (Park et al., 2008) and as abrasives in glass and in printed circuit manufacture (Du and Graedel, 2011; USEPA, 2012), thus

Table 2
Case report studies of REE-occupationally exposed workers.

Job	No. cases	Disease/other findings	References
Photoengraver	1	Interstitial pneumoconiosis	Sabbioni et al. (1982)
	1	Pulmonary fibrosis/excess REE levels in lung biopsies	Vocaturo et al. (1983)
	1	Pneumoconiosis/excess REE levels in lungs and in nails	Sulotto et al. (1986)
	5	Pneumoconiosis/excess REE levels in lungs	Vogt et al. (1986)
Movie projectionist	1	Pneumoconiosis	Waring and Watling (1990)
Movie projectionist	1	Pneumoconiosis	Porru et al. (2001)
Optical lens polisher	1	Pneumoconiosis/Ce particulate deposits in the lungs	McDonald et al. (1995)
Crystal smelter and Movie projectionist	1	Pleural plaque and interstitial lung disease	Pairon et al. (1995)
Crystal polisher	1	Dendriform pulmonary ossification	Yoon et al. (2005)

resulting in the emission of Ce oxide (CeO_2) nanoparticles in the exhaust and/or in dust that might involve both environmental and occupational human exposures. These open questions should prompt new research efforts.

3.3. REE iatrogenic exposures

Gadolinium is routinely utilized in magnetic resonance imaging contrast agents (CAs) since 1980s (Carr et al., 1984), and Gd-based CAs (GDBCAs) have been regarded as safe for several decades (reviewed by Kirchin and Runge, 2003). In the last decade, however, a severe reaction known as nephrogenic systemic fibrosis was reported in patients treated with GDBCAs (Thomsen, 2006; Thomsen et al., 2007; Chien et al., 2011; Bernstein et al., 2012; Chang et al., 2013). Thus, the diagnostic use of GDBCAs is currently managed with the caution of preventing severe renal complications (Edwards et al., 2014).

Lanthanum carbonate has been used as a phosphate binder in patients with chronic kidney disease, showing effective and safe performance (Takahara et al., 2014).

4. Animal REE toxicity studies

A substantial body of literature has reported on REE toxicity in animals, as reviewed by us (Pagano et al., 2012; 2015), and summarized in Table 3.

CeO_2 nanoparticulate ($nCeO_2$) inhalation in rats was found to increase IL-12 and IFN-γ production by alveolar macrophages (Ma et al., 2011, 2014). The authors concluded that $nCeO_2$ as diesel fuel catalyst may cause health concerns. A study by Cassee et al. (2012) investigated the effects of DEP *vs*. $nCeO_2$-containing DEP (Ce-DEP) in atherosclerosis-prone mice, and found that Ce-DEP exposure resulted in increased levels of proinflammatory cytokines in a brain region and in liver.

Aalapati et al. (2014) exposed CD1 mice to $nCeO_2$ by nose inhalation, and found markers of lung injury, along with pro-inflammatory cytokines in bronchoalveolar lavage fluid (BALF), OS in lungs, bioaccumulation, and histopathology of pulmonary and extrapulmonary tissues.

Kawagoe et al. (2008) treated adult mice with $CeCl_3$ by gavage (200 or 500 mg/kg BW), or neonatal mice via milk and fetal mice transplacentally. Adult mice showed pulmonary hemorrhage, pulmonary venous congestion, thickened alveolar septae, hepatic necrosis and neutrophil infiltrations. Damage in fetal mice consisted of pulmonary and hepatic congestion. This study showed that gavage $CeCl_3$ administration resulted in respiratory and liver damage. These changes were less severe in neonatal and fetal mice. When $CeCl_3$ was injected into adult mice through the tail vein, cerium was distributed mainly to the liver, spleen and lung dose-dependently. Anticoagulation in mouse plasma showed that clotting time was significantly prolonged when $CeCl_3$ was added to plasma (Kawagoe et al., 2008).

Cheng et al. (2014) administered $CeCl_3$ to mice by gavage 90 d, and found decreased WBC and % neutrophils, along with increased alkaline phosphatase, lactate dehydrogenase, cholinesterase, triglycerides and cholesterol. Moreover, differential expression was observed of 675 genes involved in a number of endpoints (Cheng et al., 2014).

Two independent studies tested gavage administration of $LaCl_3$ (40 mg/kg BW) to rats, providing evidence both for behavioral changes, with increased Ca^{2+}-ATPase activity in hippocampal cells, and for OS endpoints including decreased superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), and excess malondialdehyde (MDA) (Feng et al., 2006; He et al., 2008). Other studies confirmed the induction of OS-related damage following gavage administration of La(III), Ce(III) and Nd(III) (Huang et al., 2011; Zhao et al., 2013).

It should be noticed that no recent animal studies, to the best of our knowledge, were focused on late effects of life-long REE

Table 3
Some selected data of organ- and tissue-related toxicity in REE-treated animals.

Element	Species	Treatment (dose)	Post-exposure observation	Findings	References
Ce(III)	Mice	Gavageor i.v. injection	7 d	Pulmonary hemorrhage and hepatic congestion, thickenedalveolar septa, liver necrosis, neutrophil infiltrations;	Kawagoe et al. (2008)
		Gavage	90 d	↓ WBC, lymphocyte, and platelet, reticulocyte count and %neutrophils; ↑ alkaline phosphatase, lactate dehydrogenase,cholinesterase, triglycerides and cholesterol; differentialexpression of genes involved in immune/ inflammation response,apoptosis,cell cycle, cell proliferation, cytoskeleton, oxidativestress, signal transduction, transcription, and translation	Cheng et al. (2014)
$nCeO_2$	Rats	Intratracheal Instillation	28 d	↓ Liver weight, hepatocyte enlargement, sinusoidal dilatation;↑ ALT, ↓ albumin levels, Na:K ratio, and triglyceride levels	Nalabotu et al. (2011)
	Mice		28 d	↑ Numbers of neutrophils and lymphocytes in bronchoalveolarlavage fluid (BALF); ↑ lactate dehydrogenase activity;pathological changes in the lung tissues	Xue et al. (2013)
	Mice	Nose inhalation		Pulmonary inflammation with secretion of pro-inflammatorycytokines, with lipid peroxidation, GSH depletion and ↑ BALFlactate dehydrogenase	Aalapati et al. (2014)
La(III)	Rats	Oral Administration	6 mo	Impaired behavioral performance; ↑ [Ca^{2+}](i)/Ca^{2+}-ATPase↓ SOD, CAT and GPx; ↑ MDA	Feng et al. (2006) and He et al. (2008)
La(III), Ce(III) and Nd(III)	Mice	Gavage	42 d	Accumulation in hepatocyte nuclei and mitochondria;↓ SOD, CAT, ↑ GPx activity, GSH and MDA in mitochondria,↓↓ SOD, CAT, GPx and GSH; ↑↑ MDA	Huang et al. (2011)
			90 d	Histopathological changes in the kidney;and peroxidation levels of lipid, ↑ ROS production and↓ SOD, CAT, GST and GR; ↓ GSH, ascorbic acid and thiols	Zhao et al. (2013)

exposures. An early-and pioneering-study by Schroeder and Mitchener (1971) was carried out in long-term effects of exposures to several inorganics, including yttrium, which was found to cause excess cancer mortality. Whether this relevant effect might be confirmed by up-to-date methods and/or ascertained for other REE warrants *ad hoc* studies.

5. REE as animal feed additives and as crop fertilizers

The application of REE as feed additives for livestock has been practiced in China for long time and relevant results were reported in the Chinese literature (reviewed by He and Rambeck, 2000; Redling, 2006), assuming that small amounts of REE in the food can increase body weight gain in cattle, pigs, chicken, fish and rabbits, as well as milk production in dairy cows and egg production in laying hens (He and Rambeck, 2000).

He et al. (2001) reported an increase of body weight and health in piglets, and no variations in the meat quality and product safety, suggesting that REE could be a safe and inexpensive alternative as a performance enhancer for pig production, without any significant REE accumulation in muscles, liver and kidneys of REE-fed pigs.

Other studies showed that REE-supplemented diet improved performance and blood characteristics in rabbits (Adu et al., 2009), broiler chickens (Igbusan and Adebayo, 2012), and ruminants (Yang et al., 2009).

On the other hand, Kraatz et al. (2006) found no significant effects on growth performance of REE-treated piglets, while alterations in the predominant fecal microbiota were observed. A recent study by Cai et al. (2015) evaluated the effects of REE-enriched yeast (RY) on growth performance, nutrient digestibility, meat quality, relative organ weight, and excreta microflora in broiler chickens. The digestibility of gross energy was increased when broiler chickens were fed RY (1500 mg/kg) diet compared with those fed control diet. However, there was no significant influence on growth performance, relative organ weight, and excreta microflora (Cai et al., 2015).

The use of REE mixtures as fertilizers is currently performed in China and a body of literature reported that REE-based fertilizers are successful in improving crop yeld (Pang et al., 2002; Hu et al., 2002; USEPA, 2012).

Altogether, the information both pointing to favorable and to adverse effects of REE may be interpreted in view of the established hormesis phenomenon, i.e. dual dose/concentration trend, displaying the stimulation of a number of biological events induced by low levels of agents that induce inhibition/toxicity at increasing agent levels (Calabrese, 2010). This phenomenon, broadly recognized for a number of agents, has been also recognized for REE (Jenkins et al., 2011; reviewed by Pagano et al., 2015).

In an attempt to relate this database to human and environmental health, this subject warrants *ad hoc* research aimed at verifying any long-term adverse effects.

6. REE speciation and bioavailability

Analogous to several other transition metals, REE display different species related to their oxidation state, coordination with ligand anions, and pH, implying the sharp differences in solubility for compounds of a given REE; as an example, oxides and carbonates are insoluble, whereas chlorides, nitrates and acetates are soluble, and others form chelated compounds. A separate case may be considered for REE nanomaterials, which may be regarded as other effectors compared to more or less soluble salts. These parameters influence significantly the toxicokinetics and bioavailability of REE. In a current study, we have found that Ce(III) choride (10–100 μM) caused larval malformations in sea urchin embryos, whereas Ce(IV) sulfate, in the same concentration range, either resulted in no effects or in hormetic effects; as for CeO_2 and nano-CeO_2, they were insoluble and lacking any effect (Pagano et al., unpublished).

Relevant differences were reported for Gd(III)-induced nephrotoxicity by Thomsen et al. (2007). Gd(III) interferes with cell functions by the process of transmetallation, whereby Gd(III) replaces metals such as zinc and copper. Thus, Gd(III) is bound to chelates that have different physico-chemical properties, including bonds between Gd atoms and the ligands with different stability and strength (Thomsen et al., 2007).

A third, and most relevant case should be made for pH-related modulation in REE toxicity. A body of literature supports the notion of a low pH-enhanced REE toxicity (Wen et al., 2011; Liang and Wang, 2013; Wang et al. 2014). These reports, however, limit their observation scope to “acid rain”, by neglecting that REE-associated acid pollution is inherent with key steps in REE ore processing, metallurgy, and wastewater disposal. Thus, the role(s) of acidic pollution in REE-associated toxicity deserves *ad hoc* investigations.

Altogether, one may anticipate that REE-associated health effects should foster multi-faceted tasks according to appropriate study design and, even more so, in complex data evaluation according to element speciation and to choice of test systems.

7. Overview and conclusions

REE have undergone an unprecedented boost of environmental spread and human exposures. REE-associated action mechanisms have been associated with redox reactivity, proinflammatory cytokine production, involving ROS formation, lipid peroxidation and modulation of antioxidant activities. The literature from animal studies and limited data from human occupational exposures suggests REE-induced tissue-specific bioaccumulation and damage to several organs and to immune response. An enhanced adverse action may be related to combined exposures to REE and acidic pollutants.

The current literature on REE-associated health effects is mostly confined to three REE (Ce, La and Gd), thus the information for several REE remains definitely scarce, notwithstanding their growing utilization and, hence, environmental spread and human exposures. Further investigations are warranted in elucidating a number of broadly unexplored subjects in REE-associated health effects following occupational and environmental exposures. First, the health effects of REE other than Ce, La and Gd should be investigated appropriately, in order to verify the comparative toxicities of individual REE, especially some heavy lanthanoids, *vs*. the more established database on Ce, La and Gd toxicities. Two most relevant subjects of investigation shall focus on case control and/or on cohort studies of REE occupationally exposed workers in the present, unfortunate lack of information of long-lasting health effects or of mortality. Environmental, non-occupational REE exposures should not be confined to residents in mining areas, as in the scarce available literature, but should be extended to biomonitoring and to ascertaining health effects, if any, among populations exposed to potential damage from REE contamination, e.g. diesel engine exhaust.

Relevant research demand reside on design and implementation of life-long animal exposures to REE, unconfined to the presently available short-term observations in animal studies. The use of REE as feed additives and as fertilizers should be evaluated in order to verify the long-term safety of these zootechnical and

agricultural practices.

These tasks are extensive and multi-faceted, yet the "REE challenge" deserves thorough research efforts.

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