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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)