

# Human Exposures to Rare Earth Elements: Present Knowledge and Research Prospects

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**Abstract:** The extensive use of rare earth elements (REEs) in a number of technologies is expected to impact on human health, including occupational REE exposures. A body of experimental evidence on REE-associated toxicity has been accumulated in recent decades. Unlike experimental studies, the consequences of REE exposures to human health have been subjected to relatively fewer investigations. Geographical studies have been conducted on residents in the Chinese REE mining districts, reporting on REE bioaccumulation, and associations between REE residential exposures and adverse health effects. A more limited series of studies has been focused on occupational REE exposures, such as movie operator (with occurrence of cerium aerosol) with the observation of pneumoconiosis and lung fibrosis. Similar effects have been reported in case reports for other workers, such as a lens grinder and a printer exposed to carbon-arc lamp emission. As for the occupations related to REE mining and processing, REE bioaccumulation in scalp hair and excess REE urine levels were reported. A study was devoted to workers employed in e-waste separation, showing alterations of several plasma markers. As for other REE occupational exposures, mention should be made of: a) mechanical workshops, with exposures to diesel exhaust microparticulate (containing nanoCeO<sub>2</sub> as a catalytic additive) and, b) production and manufacture of REE supermagnets for hybrid engines and wind turbines. Diesel exhaust microparticulate has been studied in animal models, leading to evidence of several pathological effects in animals exposed by respiratory or systemic routes. As for supermagnet production and manufacture, a body of literature is reviewed of experimental studies, and of human exposure studies showing several pathological effects of static magnetic fields, warranting further investigations.

**Keywords:** rare earth elements; toxicity; occupation; diesel exhaust; supermagnet

## 1. Introduction

Rare earth elements (REEs) have become an essential component of present-day life due to their pervasive applications in a number of technologies [1-3]. A body of experimental evidence, mostly obtained since the 2000s has established the multiple REE-associated adverse effects in a number of biota, including mammals (both *in vivo* and *in vitro* models) [4-16], other vertebrates [17-18], invertebrates [19-28], plant and microbial models [29-37], as shown in Tables 1A-1B. The array of REE-induced toxicity includes extensive adverse events, such as organ pathologies in mammals [4-12], cytogenetic and embryologic damage [14,19-21], and growth inhibition [22-31]. Individual REEs were found to exert different toxicities in comparative studies that suggested toxicity gradients according atomic mass and magnetic properties [21,35]. It is worth noting, however, that a line of studies pointed to beneficial (hormetic) effects of REEs [38-40], which are also utilized as fertilizers in agronomy and or feed additives zootechny [41-45].

Altogether, the current experimental evidence for REE-associated toxicity raises environmental health concern on the possible adverse effects in areas affected by excess REE pollution, such as close to mining districts or related to REE manufacturing. Unlike experimental evidence, human REE exposures have been focused to date in a lesser number of investigations. The present review attempts to evaluate the available literature on human REE exposures, both including environmental/residential and occupational exposures, trying to raise working hypotheses on currently unexplored fields in human REE exposures. The literature concerning iatrogenic or occupational REE exposures in radiologic or nephrologic practice is not evaluated herein.

## 2. Human Environmental REE Exposures

The residents in Chinese regions involved in REE mining and processing have been investigated in a set of studies assessing scalp hair REE accumulation as a function of distance from mining sites and with different accumulation extent according to gender and age, raising health concern for highly REE-exposed children [46-52]. A possible association between environmental REE exposures and specific pathologies was investigated. Two studies by Wang *et al.* [50-51] reported on excess hypertension risk among housewives residing in Shanxi Province, as a function of REE hair levels, or to REE-containing indoor air pollution (Table 2). Excess REE levels were reported in vegetables, soil and street dust in REE mining levels, suggesting exposure routes *via* dietary or respiratory REE exposures [53-55].

As an additional component of environmental concern, REE ores are associated with naturally occurring radioactive materials (NORM) that have been quantified and both include thorium and uranium, with concentrations of ThO<sub>2</sub> up to 0.05% and of U<sub>3</sub>O<sub>8</sub> up to 0.002%. [56-59]. Moreover, Wang *et al.* [59] reported that activity levels of airborne <sup>232</sup>Th in total suspended particulate (TSP) ranged from three to five orders of magnitude in a mining area and in a smelting area, above the world reference of 0.5 μBqm<sup>-3</sup>. Thus, one can speculate that REE ores and their by-products may both affect exposed populations due to REE-specific and to NORM-associated adverse effects.

One may be tempted to consider environmental REE exposures as a prerogative of residents in REE mining and processing areas, with exceedingly high environmental REE levels. However, the existence of areas featuring REE pollution, such as e-waste dumping sites [60,61] or heavy traffic urban areas [62] (see below) makes these subjects unexplored to date and should prompt *ad hoc* investigations.

### 3. Occupational REE Exposures

#### 3a. REE mining and processing

Based on the as yet limited literature on REE environmental exposures in REE mining and processing areas, one might infer that occupational exposures should imply health risks to miners and workers employed in REE manufacturing. At least three reports – to the best of our knowledge – suggest the occurrence of occupational-related health damage to REE-exposed workers. An indirect association to occupational REE exposure was suggested by Chen *et al.* [63], who investigated the rates of respiratory tract diseases in groups of miners exposed in high-dust and low-dust workshops employed in REE mining and iron mining. Unfortunately, this report was only focused on «thorium lung burden» and no mention was provided regarding analytical data of REE levels either in dust or in term of REE uptake. Though with such limitation, that report may provide grounds for studies of possible links between occupational exposures to REE dust and respiratory tract diseases.

Urinary REE levels were measured by Li *et al.* [63] in workers manufacturing cerium and lanthanum oxide and nanoparticles, and excess levels of La, Ce, Nd and Gd were found in exposed workers *vs.* controls.

Liu *et al.* [64] measured scalp hair levels of REEs and other eight metals in REE miners and controls, and performed proteomic analysis for a set of plasma proteins. These authors found excess REE and Fe levels in miners *vs.* controls, and dysregulation of 29 differentially expressed proteins. Thus, further investigations are warranted on the grounds of this report (Table 3).

#### 3b. Exposures to REE Aerosols and Dusts

Starting from the early paper by Sabbioni *et al.* in 1982 [65], a series of case reports associated the occurrence of pneumoconiosis or of lung fibrosis in workers exposed to REE aerosols produced by carbon-arc lamps, such as movie operator [67-69] or lithography printer [70], or to REE dust as lens grinder [71,72]. Thus, the term was adopted of "rare earth pneumoconiosis" [69,73]. Subsequently, Yoon *et al.* [71] described the microscopic features of dendriform pulmonary ossification in a worker exposed to REE dust.

A recent study by Henríquez-Hernández *et al.* [60] focused on the occupational exposures to REEs and other metals in workers employed in e-waste processing. In this study, the concentrations of 48 elements (including REE and other metals) were determined by ICP-MS in whole blood samples of anemic and non-anemic workers. The levels of several REEs (Ce, La, Nd, Sm, Eu, Er) were higher in anemic *vs.* non-anemic workers; the same was found for other elements (Ag, As, Ba, Bi, Ga, Pb, Sn, Ta), and for Th and U. The authors concluded that the higher levels of Pb, REEs and other metals in anemic participants suggested the possibility that these elements could play a role in the development of anemia (Table 3).

#### **4. Beyond the Present Knowledge: Need for Research**

##### *4a. REEs in Diesel Exhaust*

The addition of Ce- and La-based catalytic additives in oil refining and diesel oil formulation has become a current practice in the last three decades [73-75], thus the presence of CeO<sub>2</sub> nanoparticulate (nano-ceria) can be regarded as a pervasive event in diesel exhaust [1-3]. As summarized in Table 4, an established body of evidence has assessed a number of adverse effects in animals exposed to nano-ceria by different administration routes and resulting in several damages in various organs, such as liver and brain, or affecting inflammatory endpoints [7-12,76-82]. To date, human exposures to

nano-ceria have been recognized [reviewed in 3,78,83] but, to the best of our knowledge, no report has been published relating human exposures to nano-ceria *vs.* any health effects, such as REE bioaccumulation or the onset of pathological changes. The current lack of information may include the likely events of occupational REE exposures among mechanics, necessarily exposed to diesel exhaust emissions and, possibly, among residents in urban areas affected by heavy traffic concentrations. In order to solve this information gap, an on-going study is investigating the REE levels both in ground dust in mechanic workshops and in surface crusts of urban tunnels in Naples, Italy, as well as REE uptake among mechanics, by both measuring urine and scalp hair REE levels. The preliminary results found excess REE levels in workshop ground dust, and evidence for excess urine REE levels in mechanics *vs.* unexposed control workers [Trifuoggi *et al.*, unpublished]. The further steps of this investigation will ascertain whether, and to what extent, excess REE bioaccumulation might result in any pathological outcome(s).

#### *4b. REE Supermagnets: A New Challenge?*

The primary paramagnetic properties of some REEs as Nd, Sm and, even more, Dy and Ho [84] have caused their pervasive use in producing supermagnetic devices for hybrid engines and wind turbines [85,86].

As summarized in Table 5, the biological effects of magnetic fields (MF) have been investigated since early studies [87] and a body of literature is available on the adverse outcomes of MF exposures in animal, plant and *in vitro* studies [88-104]. These effects were observed also independently of reactive oxygen species (ROS) formation [94], a well-established feature of iron toxicity and also detected for REEs [21]. The available information on the effects of magnetic fields is mainly focused on extremely low frequency

magnetic fields [98], whereas static magnetic fields have been focused with relatively lesser investigations [99-104].

No published reports, to the best of our knowledge, have been focused on the occupational exposures associated with producing and manufacturing REE-based supermagnets. It is worth noting that the workshop areas committed to these procedures as melting, molding and polishing REE supermagnets are expected to be characterized by definite static magnetic fields, whose intensity is currently unknown. Also unknown are possible health effects of these magnetic fields to the workforce involved in these manufactures.

Altogether, one may assume that the whole technology involved in the production and manufacture of REE-based supermagnets may represent an unexplored field that warrants *ad hoc* investigations.

## **5. Conclusions**

Unlike an extensive body of experimental evidence pointing to REE-associated toxicity, the available information on human REE exposures points to a series of adverse effects including bioaccumulation and only partly known pathological outcomes. The present review attempted to evaluate the state-of-art for other two technologies expected to lead to occupational REE exposures and deserving *ad hoc* investigations.



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Table 1A.

Background information on REE-associated toxicity by in vivo (mammals, other vertebrates) and in vitro models.

Species/Model	Main effects/Endpoints	References
Rats	Yttrium-induced renal damage	4
	Neurotoxicological effects following LaCl <sub>3</sub> oral administration	5
	CeO <sub>2</sub> fine particles, by intratracheal instillation, induce:	
	Multiple respiratory damage	7
	Liver toxicity	8; 11
	Lung, liver, kidney, spleen and brain accumulation	9
	Lung fibrosis	10; 80
	CeO <sub>2</sub> intravenous infusion results in multiple oxidative stress	12
Mice	CeCl <sub>3</sub> oral administration induces lung and liver toxicity	6
Rat lung alveolar macrophages	LaCl <sub>3</sub> -, CeCl <sub>3</sub> - and Nd <sub>2</sub> O <sub>3</sub> -induced cytotoxicity	13
Mouse bone marrow cells	Intraperitoneal Pr <sub>6</sub> O <sub>11</sub> and Nd <sub>2</sub> O <sub>3</sub> induce chromosomal aberrations	14
BEAS-2B cells	nCeO <sub>2</sub> -induced oxidative stress	15
HepG2 and HT-29 cell lines	CeCl <sub>3</sub> and LaCl <sub>3</sub> affect gene regulation detected by RT-PCR based arrays	16
<i>Carassius auratus</i>	CeO <sub>2</sub> -induced changes of enzymatic activities (AChE, SOD, and CAT)	17
Zebrafish embryos	La and Yb affect the development of zebrafish embryos	18

Table 1B.

Background information on REE-associated toxicity by means of invertebrates and microbial models.

Species/Model	Main effects/Endpoints	References
Sea urchin embryos and sperm	Comparative toxicities of several REEs to early development, fertilization success, offspring damage, cytogenetic damage and oxidative stress	19-21
<i>Daphnia pulex</i>	CeO <sub>2</sub> uptake in gut content, independent on feeding conditions	22
<i>Caenorhabditis elegans</i>	Reproduction and growth inhibition	23
<i>Gammarus roeseli</i> and <i>Dreissena polymorpha</i>	nCeO <sub>2</sub> decreased size of the lysosomal system, catalase activity and lipoperoxidation in <i>D. polymorpha</i>	24
<i>Nitzschia palea</i> , <i>Chironomus riparius</i> , <i>Xenopus laevis</i> and <i>Pleurodeles waltl</i>	nCeO <sub>2</sub> -associated comparative toxicities	27
<i>Caenorhabditis elegans</i>	PrCl <sub>3</sub> , NdCl <sub>3</sub> and ScCl <sub>3</sub> induce behavioral deficits and neural damage	28
Various invertebrates and microbiota	Comparative toxicities of REEs in four invertebrates and in two bacteria species	25
Ames test (5 strains) and Bhas 42 cells	Nano-sized Dy <sub>2</sub> O <sub>3</sub> showed strong mutagenesis both in Ames test and in Bhas 42 cell transformation	37



Table 2.

Human environmental REE exposures - geographic studies.

Exposed populations	Main Endpoints	References
Children and mothers living in a REE mining area (Jiangxi, China)	The REE hair level of young children in mining area was significantly higher than that in their mothers	46-48
Residents in South Jiangxi Province	Significantly lower serum total protein and globulin from both HREE and LREE areas, and albumin from the LREE area	49
Housewives exposed to indoor air pollution	Excess REE levels were found in scalp hair as related to indoor air pollution and associated with hypertension risk	50,51
Residents in Baiyun Obo mining area	Excess scalp hair levels of REEs, heavy metals and uranium	52
Fujian and Shandong Provinces	Excess REE accumulation in soil and vegetables	53,54
Zhuzhou (industrial city in central China)	Excess REE levels in street dust and associated health risk	55

Table 3.

Human occupational REE exposures – case reports and case-control studies.

Occupation	Main Endpoints	References
Movie projectionist	Pneumoconiosis; interstitial lung disease	65-69
Exposure to carbon arc lamps in photoengraving laboratory	Pneumoconiosis; comparison of REE lung levels with 11 non-exposed workers	70
Glass polisher	Dendriform pulmonary ossification	71
Manufacturing Ce and La oxide	Excess Ce and La urine levels	72
e-waste processing	Decreased hemoglobin concentration in REE-exposed	60

Table 4.

Another REE exposure – Diesel exhaust: experimental data.

Species/Model	Main Endpoints	References
Cell cultures	nCeO <sub>2</sub> + diesel exhaust (DE) increase tumor necrosis factor- $\alpha$ and the oxidative stress marker HMOX-1	77
Rats	CeO <sub>2</sub> -induced granulomas in the liver; oxidative stress changes in liver and spleen. Nanoscale ceria was persistently retained by mononuclear phagocyte system, associated with adverse changes. nCeO <sub>2</sub> added to diesel fuel (DECe) induces more adverse pulmonary effects vs. DE. Lung accumulation of Ce, translocation to liver, and delayed clearance are concerns to health effects of DECe particle clumps in DEP + CeO <sub>2</sub> were significantly larger than CeO <sub>2</sub> or DEP; CeO <sub>2</sub> induced lung phospholipidosis and fibrosis CeO <sub>2</sub> -induced inflammatory reaction by neutrophil increases in the lung	78-81
Mice	CeO <sub>2</sub> -induced oxidative stress and DNA damage	82
	CeO <sub>2</sub> -induced lung inflammation	83

Table 5.

Background information on the adverse effects of static magnetic fields.

Species/Model	Main effects/Endpoints	References
Human neuroblastoma SHSY5Y and glioblastoma A172 cells	Magnetite decreases cell viability	88
Human brain cell cultures		89
Human blood mononuclear cells	Cytotoxic effects of moderate static magnetic field (SMF)	90
Rats (Huntington disease model)	Exposure to static magnetic field and apomorphine induce behavioral changes	91
Mouse hepatocytes	SMF reduced cell viability, caused apoptosis, and cell cycle aberrations on hepatocytes in vitro and in vivo	92
<i>Caenorhabditis elegans</i>	Developmental abnormalities	93
<i>Saccharomyces cerevisiae</i>	ROS-independent toxicity of Fe <sub>3</sub> O <sub>4</sub> nanoparticles and mitochondrial dysfunction	94
Green Alga <i>Chlorella vulgaris</i>	Inhibition of photosynthesis, induction of oxidative stress, and the inhibition of cell division rate	95
<i>Vicia faba</i>	Static magnetic field + radioactivity induce modification of catalase and mitogen-activated protein kinase (MAPK)	96