Stand Alone Report 14

A Literature Review of the Health and Ecological Effects of the Rare Earth Elements

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List of Acronyms

ACGIH	American Conference of Governmental Industrial Hygienists
BCF	bioconcentration factor
FEL	Frank Effect Level
g	gram
im	intramuscular
ip	intraperitoneal
IRIS	Integrated Risk Information System
kg	kilogram
L	liter
m^3	cubic meters
mg	milligram
mg/kg	milligram per kilogram
mg/L	milligram per liter
NIOSH	National Institute of Occupational Safety and Health
NSF	nephrogenic systemic fibrosis
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
REE	Rare earth element
RfC	Reference Concentration
RfD	Reference Dose
RSL	Regional Screening Level
µmol	micromole
USEPA	United States Environmental Protection Agency

1. Introduction

The rare earth elements (REE) consist of seventeen elements (Table 1), 15 of which are referred to as lanthanides. Two additional elements, scandium (Sc) and yttrium (Y), are included as REE due to their similar chemical and toxicological properties, and because they are often found in the same ore deposits as other REE (Connelly et al., 2005; Thomas et al., 2014). The term "rare" does not refer to the relative abundance of the REE in soil but rather to the fact that the REE are not typically found in concentrated ore deposits like gold or other common metals (Olmez et al., 1991).

The REE play an increasingly important role in modern society through their use in numerous "high technology" applications. Some of these applications include cellphones, optical lenses, digital cameras, high-performance magnets, batteries, automotive catalytic converters, metal alloys, lasers, medical imaging, green energy devices, and aerospace weapons systems (Harbison, 1998; Rim et al., 2013).

Historically, the primary worldwide source of REE has been China. However, due to limitations in the supply of REE from China, REE mines in the United States are increasingly being developed (Mayfield and Fairbrother, 2015). Along with the development of these mines is an increased interest in the environmental health aspects of REE exposure. Such information is needed to facilitate the evaluation of potential health and ecological effects related to REE mine development. This toxicity literature review was prepared to address this need for the Bear Lodge Project in northeastern Wyoming, specifically, the Bull Hill Mine and Upton Hydrometallurgical Plant components of this project.

This toxicity literature review, which addresses both human health and ecological effects, focused on the following REE, which are considered to have the greatest potential for release as part of the Bear Lodge Project:

- Cerium
- Dysprosium
- Erbium
- Europium
- Gadolinium
- Holmium
- Lanthanum
- Lutetium
- Neodymium
- Praseodymium
- Samarium
- Terbium
- Thulium
- Ytterbium
- Yttrium

The primary method used to search the published scientific literature for REE toxicity information was the National Library of Medicine *PubMed* online database (www.ncbi.nlm.nih.gov/pubmed/). This database provides access to over 24 million citations from the biomedical literature in both journals and online books. For the widest possible retrieval, this online search was initially conducted using simply

each individual REE name, for example, “cerium”. This initial search was only narrowed with the additional term “toxic” if an excess (e.g. thousands) of citations were retrieved based on the REE element name alone. These individual element searches were then supplemented with additional searches using the general search terms “rare earth” and “lanthanide”.

In addition, a general Internet search was conducted to obtain related documents that are not likely to have been referenced in the *PubMed* database references (such as government or regulatory agency reports). A third key step in the search included a review of the United States Environmental Protection Agency (USEPA) *Integrated Risk Information System* (IRIS) database (USEPA, 2014a). The IRIS database is the most up-to-date source of key toxicity data used to support quantitative health risk assessments of chemicals. The latest version of the USEPA Regional Screening Levels (RSLs) was also reviewed to determine whether any health risk-based toxicity criteria or environmental benchmarks (i.e. air, water or soil screening levels) have been published for these chemicals (USEPA, 2014b). Finally, the main compilations of national occupational exposure limits (OELs) in the United States developed by the Occupational Safety and Health Administration (OSHA), the National Institute of Occupational Safety and Health (NIOSH), and the American Conference of Governmental Industrial Hygienists (ACGIH) were reviewed to obtain any available OELs for the REE (OSHA, 2014).

It should be noted that the REE, as a group, are among the least studied chemicals with respect to both human health and, especially, ecological toxicity. Thus, for several REE, for example holmium, lutetium, and thulium, very little toxicity information could be located. The information included in this review reflects what is available following a very comprehensive review of the extant literature, including both the published scientific literature and government agency reports. Finally, note that the scope of this review does not include radioactive forms of the REE.

In the following sections, the general chemical and toxicological characteristics of REE are discussed first, followed by discussions of the health and ecological effects of each REE.

2. General Chemical, Physical and Toxicological Properties of the Rare Earth Elements

The REE have very similar physical and chemical properties (USEPA, 2009a; Avalon Rare Metals, Inc., 2014). Some of these properties include:

- Silvery-white, soft metals that tarnish when exposed to air
- Solubility increases with increasing atomic number
- High melting and boiling points
- React with water and dilute acids to form hydrogen gas
- Include both stable and radioactive forms
- Strongly paramagnetic
- Active reducing agents
- Ignite in air
- Soluble forms include chlorides, nitrates, and sulfates
- Insoluble forms include carbonates, phosphates, and hydroxides
- Fluoresce strongly under ultraviolet light
- Dusts of these compounds may present fire and explosion hazards

Health Effects

The REE have no known role or requirement in living systems (Rim et al., 2013).The REE are grouped into "light" REE (Ce, Eu, Gd, La, Nd, Pr, and Sm) and "heavy" REE (Dy, Er, Ho, Lu, Tb, Tm, Y and Yb) based on atomic weight (www.reehandbook.com/intro.html). The light REE deposit mainly in the liver, while the heavy REE tend to mimic calcium and deposit in the bone (Durbin et al., 1956). In addition, the light REE tend to be excreted primarily via the feces whereas the heavy REE tend to be excreted mainly via the urine (Durbin et al., 1956). The toxicity of REE generally decreases with increasing atomic weight (USEPA, 2009a).

The REE as a group have oral LD50s often well above 3000 mg/kg (Table 2). Per Doull et al. (1980), this level of acute toxicity would be classified as "moderately" or "slightly" toxic. The REE oral LD50s are in most cases higher (less toxic) than the LD50 of table salt (4000 mg/kg) (Doull et al., 1980).

The primary target organ of REE via the oral route of exposure is the liver. The lung is the primary target organ via inhalation exposure. In addition, the REE have well-known anticoagulative effects (Harbison, 1998).

Inhalation exposure to the REE, primarily via occupational exposure, is associated in the short-term with acute irritative bronchitis, and in the long-term by pneumoconiosis and progressive pulmonary fibrosis (Vocaturo et al., 1983; Haley, 1991; Harbison, 1998; USEPA, 2009a). Most cases of pneumoconiosis and pulmonary fibrosis have been observed in photoengravers or film projectionists as a consequence of long-term exposure to REE oxide fumes or smoke related to the use of carbon arc lamps (Sabbioni et al., 1982; Vocaturo et al., 1983; Sulotto et al., 1986; Palmer et al., 1987; Porru et al., 2001). These cases are often

associated with high REE concentrations in the lungs and not necessarily related to the presence of any radioactive component (Vocaturo et al., 1983; Sabbioni et al., 1982). However, the evaluation of such cases is often confounded by simultaneous exposure to radioactive elements and/or silica dust (Vocaturo et al., 1983; Haley et al., 1991). Despite the well-documented effects of REE on the lung, no occupational exposure limits (OELs) have been established for any of the REE except yttrium (see Section 17). Inhalation exposure to REE has been shown to result in elevated levels of REE in the fingernails (Sulotto et al., 1986).

A key toxicological characteristic of the REE is their common ability to displace calcium from calcium binding sites (e.g. enzymes) in living systems, resulting in enzyme inhibition or other biochemical dysfunction (Pałasz and Czekaj, 2000; Thomas et al., 2014). This displacement occurs in both plants and animals. For example, REE have been shown to compete for calcium binding sites within photosystem II in plants (Burda et al., 1995). The ability of the REE to displace calcium is believed to be due to their trivalent oxidation state and small ionic radius, resulting in a higher charge density than calcium.

Populations living in high REE regions of South Jiangxi, China showed abnormalities in various blood parameters, including decreased levels of total serum protein, albumin, β-globulin, glutamate pyruvate transaminase, serum triglycerides, and immunoglobulin. These populations also showed an increase in blood cholesterol (Zhang et al, 1999a).

Zhang et al. (1999b) evaluated the effects of REE exposure on the central nervous system, the immune system and cardiovascular system in individuals from regions of high REE concentrations in South Jiangxi, China. Region A was an area of high “heavy” REE, Region B was an area of high “light” REE, and Region C was a background or control area. The intelligence quotients of children were significantly lower in the high REE areas than in the background area. The incidence of arteriosclerosis was also higher in the high REE areas. The average daily intakes of REE in Regions A, B, and C were 6.67, 5.98 and 3.33 mg. The investigators concluded that populations whose intake of REE from food is 6-6.7 mg/day may experience subchronic toxicity. The investigators recommended 4.2 mg/day as a maximum daily allowance to REE in food.

REE are poorly absorbed from the gastrointestinal tract (Durbin et al., 1956). Although poorly absorbed from the skin, the REE are strong skin irritants, progressing from irritation to ulceration and granulomas after prolonged contact. REE are also poorly absorbed from the lungs (Harbison, 1998).

Exposure of the eyes to REE may cause irritation, leading to conjunctivitis, corneal damage and scarring (Harbison, 1998).

Zhu et al. (2005) evaluated liver function in Chinese farmers living in areas of high REE concentrations. The investigators suspected that the common symptoms of indigestion and malabsorption in this population were indicative of high exposure to REE and impairment of digestive enzymes. Serum total protein, globulin and albumin were significantly lower in farmers from high REE areas than in control areas, while IgM levels were higher. However, levels of serum glutamate pyruvate transaminase (SGPT), a sensitive indicator of liver damage, were not significantly different between the control and high REE areas. The investigators concluded there was no significant evidence of liver damage in farmers from areas of high REE concentration.

Currently available toxicity criteria either derived by USEPA or derived using USEPA methods for the REE are summarized in Table 3. These toxicity criteria, which are used extensively in quantitative health risk assessment, include Reference Doses (RfDs) for the oral and inhalation route of exposure, and Reference Concentrations (RfCs) for the inhalation route of exposure. RfDs and RfCs are benchmarks of safe levels of long-term chemical exposure via the ingestion and inhalation routes of exposure, respectively. No inhalation route RfDs currently exist for any of the REE. In addition, none of the REE have been classified as carcinogens by USEPA at this time, so cancer potency slopes (used in health risk assessment to calculate cancer risk) have not been developed for any of the REE (USEPA, 2014a).

Ecological Effects

Very little information exists regarding the ecotoxicity of REE.

The EC50 for growth inhibition of a marine algae was virtually identical (about 30 µmol/L) across all lanthanides, indicating the close chemical and toxicological properties of these elements (Tai et al., 2010).

REE are taken up by plants. Li et al. (2013) measured elevated concentrations of REE in vegetables in an area near a large-scale rare earth mine in southeast China. Concentrations of REE in vegetables grown near the mine were higher relative to areas unimpacted by rare earth mining activities. The highest concentrations were found in leafy vegetables relative to non-leafy vegetables. The mean concentration of total REE in soil in China was determined to be 176.8 mg/kg (Liang et al., 2005). Ce accounted for 42% of the total REE. The REE content in ryegrass was highly correlated to the concentration in soil. Concentrations of REE in mature spring wheat were greatest in the order root>leaf>stem and crust.

3. Cerium

Cerium (Ce) (atomic number 58) is the most abundant REE in the environment (Thomas et al., 2014). It exists commonly in both the 3+ (cerous) and 4+ (ceric) oxidation states, the latter of which results in a higher charge density than the other REE, resulting in a greater potential for toxicity mediated through calcium displacement (as discussed previously in Section 2). Ce is used in automotive catalytic converters, optical glasses, polishing abrasives, various metal alloys and carbon arc lamps (Harbison, 1998; Nalabotu, 2011; Rim et al., 2013). Ce is the most widely studied of the REE.

Health Effects

Ce has low acute toxicity via the ingestion route of exposure. Bruce et al. (1963) determined an oral LD50 in female rats of 4200 mg/kg for Ce nitrate. Oral doses of the corresponding oxide form of 1000 mg/kg were well tolerated.

The acute inhalation toxicity of Ce oxide nanoparticles was investigated in rats (Srinivas et al., 2011). Rats were exposed to a nominal concentration of 641 mg/m^3 for 4 hours. Rats were subject to bronchoalveolar lavage and parameters indicative of an inflammatory response were measured. Exposure resulted in a significant decrease in cell viability, and increases in lactate dehydrogenase, total protein, and alkaline phosphatase. Total leukocyte counts, the percentage of neutrophils, and concentrations of proinflammatory cytokines were also elevated. The investigators concluded that inhalation exposure to Ce oxide nanoparticles induces cytotoxicity via oxidative stress. Ce chloride was highly toxic to pulmonary alveolar macrophages *in vitro* (LC50 of 29 µM), whereas Ce oxide was only minimally toxic (LC50 of 4740 µM) (Palmer et al., 1987). The authors concluded that Ce is cytotoxic to lung tissue and potentially fibrogenic.

Nalabotu (2011) found that a single intratracheal instillation of Ce oxide nanoparticles (1.0, 3.5 or 7.0 mg/kg) in rats resulted in increased concentrations of Ce in the liver and evidence of liver damage, including: decreased liver weight, dose-dependent hydropic degeneration, hepatocyte enlargement, sinusoidal dilation, and nuclear enlargement. This was further evidenced by changes in biochemical parameters. Serum alanine transaminase was increased, while albumin, the sodium-potassium ratio, and triglyceride levels were decreased. Histopathological effects were not observed in the kidney, spleen or heart.

Dogs were administered an intravenous (iv) dose of 10 mg/kg Ce as the chloride, citrate complex, or ethylenediaminetetraacetic acid (EDTA) every 10 minutes for a total of 10 doses. Prothrombin levels and blood coagulation time were significantly increased (Graca et al., 1964).

The effect of Ce chloride on immune system and liver function in mice was investigated (Cheng et al., 2014). Mice were orally administered 2, 10, or 20 mg/kg doses of Ce chloride for 30 days and immune and liver function parameters monitored. Ce caused a significant decrease in white blood cell counts and platelet counts at a dose of 20 mg/kg. The percentage of reticulocytes was also reduced. CD3 lymphocytes were decreased at 10 mg/kg and CD8 lymphocytes were decreased at all Ce doses. IgM was also significantly decreased at all doses. Histopathologic examination of the liver showed fatty degeneration, mild cloudy

swelling, congestion and disruption of liver cytoarchitecture at doses of 10 and 20 mg/kg. The liver function parameter, alanine aminotransferase, was also significantly elevated at these doses.

Ce chloride orally administered to mice via the diet at 20 and 200 ppm for 6 or 12 weeks produced an increase in liver metallothionein and glutathione (Kawagoe et al., 2005).

Occupational exposure of workers to Ce compounds may cause itching, heat sensitivity and skin lesions (Rim et al., 2013).

A higher incidence of endomyocardial fibrosis was observed in a population consuming vegetables grown in high Ce soil in India (Eapen, 1998). Higher levels of Ce in toenails were associated with a greater risk of acute myocardial infarction in subjects from Israel and Europe (Gómez-Aracena et al., 2006).

Durbin et al. (1956) found that less than 0.1% of an orally administered (gavage) dose of Ce nitrate was absorbed from the gastrointestinal tract.

When mice were fed radiolabeled Ce at 200 and 800 mg/kg Ce was detected in virtually all tissues (Rim et al., 2013). However, concentrations were highest in the eye, bone, testis, brain, heart and adipose tissue. Concentrations in the eye were much higher than all other tissues.

Limited information regarding the mutagenicity of Ce is available. Ce was not mutagenic in an Ames test using five strains of *S. typhimurium* (Shimizu et al., 1985), or in a rec-assay using two strains of *B. subtilis* (Nishioka, 1975). However, Ce nitrate was found to induce chromosomal aberrations and reduce the mitotic index in rat bone marrow *in vivo* (Sharma and Talukder, 1987).

No data regarding the carcinogenicity of Ce were located in the available literature.

The USEPA IRIS database contains an inhalation Reference Concentration (RfC) for cerium oxide and cerium compounds of 9E-04 mg/m^3 (USEPA, 2014a). The RfC is defined by USEPA as:

> An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure of a chemical to the human population through inhalation (including sensitive subpopulations), that is likely to be without risk of deleterious noncancer effects during a lifetime (USEPA, 2014c).

The USEPA Regional Screening Levels (RSLs) are health risk-based screening or "safe" levels of a chemical in soil, air and water (USEPA, 2014b). USEPA reports the following RSLs for ceric oxide: 1.3E06 mg/kg (residential soil), 5.4E06 mg/kg (industrial soil), 9.4E-01 µg/m^3 (residential air), and 3.9 µg/m^3 (industrial air).

No OELs have been established for Ce by OSHA, NIOSH, or ACGIH (OSHA, 2014).

Ecological Effects

Broiler chickens were fed a REE-chloride diet containing up to 11 mg/kg La and 15 mg/kg Ce for 35 days. No toxic effects were observed and hematological parameters were not significantly affected. Concentrations of Ce in the liver and muscles were less than 1 mg/kg (He et al., 2008).

Exposure of sea urchin embryos (*Paracentrotus lividus*) to 10^{-5} M Ce^{4+} resulted in 100 percent mortality with an EC50 of 1.9E-06 M (Oral et al., 2010). Mitotic aberrations and developmental arrest were observed at concentrations ranging from 10^{-6}-10^{-5} M Ce^{4+}. Exposure of sea urchin sperm to 10^{-5} M Ce^{4+} resulted in a significant reduction of fertilization success and developmental abnormalities in 100% of offspring. An EC50 of 2.8E-06 M was identified for these latter effects.

Exposure of a variety of crop and Canadian native plants to Ce in soil (at concentrations of 45 to 2128 mg/kg) under high pH conditions did not inhibit germination but did result in a reduction of biomass. Germination was reduced under low pH conditions (Thomas et al., 2014).

Tai et al. (2010) determined a 72 hour EC50 of 29.7 μmol/L for growth inhibition of the marine algae, *Skeletonema costatum*, by Ce nitrate.

The mean background concentration of Ce in fish collected from an unimpacted reservoir in Washington state was 0.083 mg/kg dry weight (whole body basis) (Mayfield and Fairbrother, 2015). Concentrations in fillet (with skin) were much lower than in whole body or carcass. Geometric mean bioaccumulation factors were 263, 1227, and 994 for fillet, carcass, and whole body, respectively.

4. Dysprosium

Dysprosium (Dy) (atomic number 66) is a lanthanide REE used primarily in nuclear reactor control rods (Harbison, 1998). Very limited information regarding the health effects and ecotoxicity of Dy is available. Virtually all of the basic mammalian toxicology information available to date has been developed by Haley et al. (1966). This information is discussed in detail below.

Health Effects

Dy has low acute toxicity. Haley et al. (1966) determined the acute LD50 of Dy chloride in mice to be 7650 mg/kg via the oral route and 585 mg/kg via the intraperitoneal (ip) route. The symptoms of acute toxicity included writhing, ataxia (loss of muscular coordination), labored breathing, stretching of limbs while walking, and lacrimation (excessive tearing). Bruce et al. (1963) determined an oral LD50 in female rats of 3100 mg/kg for Dy nitrate. Oral doses of the corresponding oxide form of 1000 mg/kg were well tolerated.

Rats fed up to 1.0% Dy chloride in the diet for 12 weeks showed no adverse effects on growth or hematological parameters (total erythrocyte counts, differential cell count, thrombocyte count, hemoglobin or hematocrit). All organs appeared normal based on gross appearance and histopathological examination (Haley et al., 1966). Hutcheson et al. (1975) fed mice a combination REE diet that contained up to 1200 ppm Dy (as the oxide). Mice were fed for three generations. No adverse effects on mortality, morbidity, growth rate, hematology, morphological development, maturation, reproduction, litter size or lactational performance were observed.

The Draize test was used to evaluate skin and eye irritation in rabbits (Haley et al., 1966). Administration of 0.1 ml of a 1:1 aqueous solution of Dy chloride to the eye did not result in any detectable damage to the cornea or iris. However, it did cause conjunctivitis (scoring 16-18 out of a maximum possible score of 20). For the topical skin irritation test 0.5 g of Dy chloride was applied to the skin. No irritant effect was observed on intact skin. However, severe irritation was produced on abraded skin (scoring 6-8 out of a maximum possible score of 8).

Durbin et al. (1956) found that Dy was preferentially deposited in the skeleton of the rat relative to other tissues, and was only slowly eliminated.

No data regarding the carcinogenicity of Dy were located in the available literature.

No information regarding Dy was available from the USEPA IRIS database or the Regional Screening Levels (USEPA, 2014a,b).

No OELs have been established for Dy by OSHA, NIOSH, or ACGIH (OSHA, 2014).

Ecological Effects

Tai et al. (2010) determined a 72 hour EC50 of 28.3 µmol/L for growth inhibition of the marine algae, Skeletonema costatum, by Dy nitrate.

The mean background concentration of Dy in fish collected from an unimpacted reservoir in Washington state was 0.004 mg/kg dry weight (whole body basis) (Mayfield and Fairbrother, 2015).

5. Erbium

Erbium (Er) (atomic number 68) is a lanthanide REE used as a glass and ceramic colorant, and in metal alloys (Harbison, 1998). Very limited information regarding the health effects and ecotoxicity of Er is available. Virtually all of the basic mammalian toxicology information available to date has been developed by Haley et al. (1966). This work is discussed in detail below.

Health Effects

Haley et al. (1966) determined the acute LD50 of Er chloride in mice to be 6200 mg/kg via the oral route and 535 mg/kg via the ip route. The symptoms of acute toxicity included writhing, ataxia (loss of muscular coordination), labored breathing, stretching of limbs while walking, and excessive tearing.

Rats fed up to 1.0% Er chloride in the diet for 12 weeks showed no adverse effects on growth or hematological parameters (total erythrocyte counts, differential cell count, thrombocyte count, hemoglobin or hematocrit). All organs appeared normal based on gross appearance and histopathological examination (Haley et al., 1966).

The Draize test was used to evaluate skin and eye irritation in rabbits (Haley et al., 1966). Administration of 0.1 ml of a 1:1 aqueous solution of Er chloride to the eye did not result in any detectable damage to the cornea or iris. However, it did cause conjunctivitis (scoring 16-18 out of a maximum possible score of 20). For the topical skin irritation test 0.5 g of Er chloride was applied to the skin. No irritant effect was observed on intact skin. However, severe irritation was produced on abraded skin (scoring 6-8 out of a maximum possible score of 8).

Durbin et al. (1956) found that Er was preferentially deposited in the skeleton of the rat relative to other tissues, and was only slowly eliminated.

No data regarding the carcinogenicity or mutagenicity of Er were located in the available literature.

No information regarding Er was available from the USEPA IRIS database or the Regional Screening Levels (USEPA, 2014a,b).

No OELs have been established for Er by OSHA, NIOSH, or ACGIH (OSHA, 2014).

Ecological Effects

Tai et al. (2010) determined a 72 hour EC50 of 28.7 µmol/L for growth inhibition of the marine algae, *Skeletonema costatum*, by Er nitrate.

The mean background concentration of Er in fish collected from an unimpacted reservoir in Washington state was 0.003 mg/kg dry weight (whole body basis) (Mayfield and Fairbrother, 2015).

6. Europium

Europium (Eu) (atomic number 63) is the most reactive REE (Ohnishi et al., 2011). Eu is a lanthanide REE used in lasers, for control rods in nuclear reactors, in compact fluorescent lamps, and as a phosphor in medical imaging and other visual displays (e.g. televisions and computer screens) (Harbison, 1998; Ohnishi, 2011; Rim et al., 2013).

Health Effects

Bruce et al. (1963) determined an oral LD50 in female rats of >5000 mg/kg for Eu nitrate. Oral doses of the corresponding oxide form of 1000 mg/kg were well tolerated. Haley et al. (1965) determined an oral LD50 for Eu chloride of 5000 mg/kg. Symptoms of acute toxicity included arched back, ataxia (lack of muscular coordination), writhing, lacrimation (excessive tearing), stretching of the hind limbs while walking, and labored breathing.

Rats fed Eu chloride at concentrations up to 1% in the diet for 12 weeks showed no adverse effects on growth or hematological parameters (Haley et al., 1965). All organs appeared normal based on gross appearance and histopathological examination. Hutcheson et al. (1975) fed mice a combination REE diet that contained up to 36 ppm Eu (as the oxide). Mice were fed for three generations. No adverse effects on mortality, morbidity, growth rate, hematology, morphological development, maturation, reproduction, litter size or lactational performance were observed.

Rabbits treated with 0.1 ml of a 1:1 aqueous solution of Eu chloride in the eye showed no damage to the cornea or iris. However, conjunctivitis was apparent within 1 hour of treatment and it persisted for 7 days. Irritation was scored at 20 out of a maximum score of 20. Healing was complete at 36 days (Haley et al., 1965).

To test the skin irritation potential of Eu, 0.5 g of Eu chloride was applied to the abraded and unabraded skin of the rabbit. Eu caused average irritation on the abraded skin (score of 7.5) and no effect on the unabraded skin (Haley et al., 1965). Eu has been found to induce inflammatory and fibrotic responses in the skin similar to those produced by Gd, the latter of which is more commonly associated with nephrogenic systemic fibrosis (NSF) (Pietsch et al., 2011).

Durbin et al. (1956) found that less than 0.1% of an orally administered (gavage) dose of Eu was absorbed from the gastrointestinal tract. Thirty percent of Eu was found in the liver and 40% in the skeleton.

Eu is poorly excreted in the urine. Rats were given single oral doses of Eu ranging from 100 to 40,000 µg/rat and urinary excretion was measured over 24 hours (Kitamura et al., 2012). Less than 2% of Eu was excreted in the urine at the lowest dose and less than 0.1% of Eu was excreted at all higher doses. The effect of Eu on renal function was evaluated in rats (Ohnishi, 2011). Rats were given single oral doses of Eu ranging from 100 to 40,000 µg/rat and renal function parameters were monitored. Creatinine excretion was decreased at higher dose groups, indicating an adverse effect on the glomerular basement membrane

and a decreased glomerular filtration rate. N-acetyl-β-D-glucosaminidase (NAG) was significantly increased in the three highest dose groups, indicating an adverse effect on the proximal convoluted tubule.

No data regarding the carcinogenicity or mutagenicity of Eu were located in the available literature.

No information regarding Eu was available from the USEPA IRIS database or the Regional Screening Levels (USEPA, 2014a,b).

No OELs have been established for Eu by OSHA, NIOSH, or ACGIH (OSHA, 2014).

Ecological Effects

Tai et al. (2010) determined a 72 hour EC50 of 29.2 µmol/L for growth inhibition of the marine algae, *Skeletonema costatum*, by Eu nitrate.

The mean background concentration of Eu in fish collected from an unimpacted reservoir in Washington state was 0.003 mg/kg dry weight (whole body basis) (Mayfield and Fairbrother, 2015). Concentrations in fillet (with skin) were non-detect. Geometric mean bioaccumulation factors were 301 and 230 for carcass and whole body, respectively.

7. Gadolinium

Gadolinium (Gd) (atomic number 64) is a lanthanide REE used in nuclear reactor control rods, metal alloys, and medical (X-ray and magnetic resonance) imaging (Harbison, 1998; Rim et al., 2013).

Health Effects

Bruce et al. (1963) determined an oral LD50 in female rats of >5000 mg/kg for Gd nitrate. Oral doses of the corresponding oxide form of 1000 mg/kg were well tolerated. Symptoms of acute toxicity in rats following ip injection of Gd chloride included labored breathing, lethargy, abdominal cramps and diarrhea (Haley et al., 1961). The LD50 via the ip route of exposure was 550 mg/kg. Oral administration of doses up to 2000 mg/kg did not produce any lethality.

Spencer et al. (1997) investigated the acute toxicity of Gd chloride in rats. Rats were given a single iv injection of Gd chloride at doses ranging from 0.07, 0.14 or 0.35 mmol/kg. Effects on hematologic parameters and organs were observed in rats dosed with 0.14 or 0.35 mmol/kg. These effects included increases in the white blood cell count, alanine aminotransferase, aspartate aminotransferase, lacatate dehydrogenase, prothrombin time, cholesterol and triglycerides, and decreases in platelet numbers, albumin and blood glucose. Tissue effects included mineral deposition in the capillary beds (especially the lung and kidney), phagocytosis of mineral by mononuclear phagocytes, necrosis of the spleen and liver, and increases in liver and spleen weight.

Rats fed up to 1.0% Gd chloride in the diet for 12 weeks showed no adverse effects on growth or hematological parameters (total erythrocyte counts, differential cell count, thrombocyte count, hemoglobin or hematocrit (Haley et al., 1961). In general, all organs appeared normal based on gross appearance and histopathological examination. However, perinuclear vacuolization of the parenchymal cells of the liver was observed in male rats and was most pronounced at the highest treatment level.

The inhalation toxicity of Gd oxide was investigated in mice (Ball and VanGelder, 1966). Mice were exposed to a nominal concentration of 30 mg/m^3 for 6 hours/day, 5 days/week for 20 to 120 days. Pneumonia was increased in most of the exposed groups but was not related to the duration of exposure. Calcification of the lung was also observed in 32-95% of the exposed mice but not in controls. This calcification was not related to the duration of exposure. The investigators concluded that 17.9 mg Gd/m^3 was a Frank Effect Level (FEL) (clear evidence of adverse effect).

The application of 1 mg of Gd chloride in the eyes of rabbits produced increased blinking and some redness but did not cause conjunctivitis, or any damage to the cornea or iris (Haley et al., 1961). The application of Gd chloride crystals to the intact skin of rabbits produced no irritation but produced severe irritation when applied to abraded skin (Haley et al., 1961).

Vassallo et al. (2011) noted that even at low doses Gd increases the production of free radicals and angiotensin II, leading to vasoconstriction of the vascular endothelium.

A rare but hallmark toxic effect of Gd is nephrogenic systemic fibrosis (NSF) (Broome, 2008; Perazella, 2009; Pietsch et al., 2011). NSF has been strongly associated with the use of Gd-based medical imaging contrast agents in patients with severe or end-stage kidney disease. This condition principally involves thickening and hyperpigmentation of the skin, although it can also affect other areas of the body. Initial symptoms include pain, pruritis (itching) swelling, erythema (redness) of the skin, transient hair loss, nausea, vomiting, diarrhea and abdominal pain. Subsequent symptoms include stiffness of the joints, deep bone pain, and muscle weakness. The condition may ultimately result in disability or death.

Gd is poorly absorbed from the gastrointestinal tract. Durbin (1956) determined that less than 0.1% of an orally administered dose of Gd-citrate complex was absorbed.

The mutagenicity and cytotoxicity of Gd was evaluated using human peripheral blood lymphocytes (Yongxing et al., 2000). To test cytotoxicity, cells were exposed for 24 hr to Gd concentrations ranging from 0.0015 to 0.5 mM. The LC50 for cytotoxicity was 0.063 mM. The mutagenicity of Gd was evaluated using a micronucleus assay, a single stranded DNA break assay, and an unscheduled DNA synthesis assay. Micronuclei were significantly increased at concentrations of 0.250 and 0.625 mM. Single stranded DNA breaks and unscheduled DNA synthesis were substantially increased at 0.025 mM. These results demonstrate chromosomal effects are more sensitive than micronuclei induction in detecting the mutagenicity of Gd.

The carcinogenicity of Gd implants was determined in mice following subcutaneous administration of a 200 mg pellet and lifetime exposure (Ball et al., 1970). There was no difference in the incidence of sarcomas between treatment and sham-implanted control groups. No other information regarding the potential carcinogenicity of Gd could be located in the literature.

No information regarding Gd was available from the USEPA IRIS database or the Regional Screening Levels (USEPA, 2014a, b). In 2007 USEPA concluded there was inadequate toxicity information to support the development of provisional risk assessment toxicity criteria for Gd (USEPA, 2007a).

No OELs have been established for Gd by OSHA, NIOSH, or ACGIH (OSHA, 2014).

Ecological Effects

Tai et al. (2010) determined a 72 hour EC50 of 29.8 µmol/L for growth inhibition of the marine algae, *Skeletonema costatum*, by Gd nitrate. This value was similar to the EC50 values determined for all other lanthanides.

Qiang et al. (1994) determined bioconcentration factors (BCFs) of Gd in carp (*Cyprinus carpio*) of 5.0, 3.5, 14 and 105 in skeleton, muscle, gills, and internal organs, respectively.

The mean background concentration of Gd in fish collected from an unimpacted reservoir in Washington state was 0.008 mg/kg dry weight (whole body basis) (Mayfield and Fairbrother, 2015).

8. Holmium

Holmium (Ho) (atomic number 67) is a lanthanide REE used primarily in magnets, lasers, and cancer radiotherapy (Harbison, 1998; Bayouth et al., 2014). It has the highest magnetic strength of any element (http://en.wikipedia.org/wiki/Holmium). Very limited information regarding the health effects and ecotoxicity of Ho is available. Virtually all of the basic mammalian toxicology information available to date has been developed by Haley et al. (1966). This work is discussed in detail below.

Health Effects

Haley et al. (1966) determined the acute LD50 of Ho chloride in mice to be 7200 mg/kg via the oral route and 560 mg/kg via the ip route. The symptoms of acute toxicity included writhing, arched back, ataxia (loss of muscular coordination), labored breathing, stretching of limbs while walking, and excessive tearing. Bruce et al. (1963) determined an oral LD50 in female rats of 3000 mg/kg for Ho nitrate. Oral doses of the corresponding oxide form of 1000 mg/kg were well tolerated.

Rats fed up to 1.0% Ho chloride in the diet for 12 weeks showed no adverse effects on growth or hematological parameters (total erythrocyte counts, differential cell count, thrombocyte count, hemoglobin or hematocrit). All organs appeared normal based on gross appearance and histopathological examination (Haley et al., 1966).

The Draize test was used to evaluate skin and eye irritation in rabbits (Haley et al., 1966). Administration of 0.1 ml of a 1:1 aqueous solution of Ho chloride to the eye did not result in any detectable damage to the cornea or iris. However, it did cause conjunctivitis (scoring 16-18 out of a maximum possible score of 20). For the topical skin irritation test 0.5 g of Ho chloride was applied. No irritant effect was observed on intact skin. However, severe irritation was produced on abraded skin (scoring 6-8 out of a maximum possible score of 8).

Ho has been found to induce inflammatory and fibrotic responses in the skin similar to those produced by Gd, the latter of which is most commonly associated with NSF in patients with end-stage kidney disease (Pietsch et al., 2011).

Durbin et al. (1956) found that Ho was preferentially deposited in the skeleton of the rat (60%) relative to other tissues, and was only slowly eliminated.

No data regarding the carcinogenicity of Ho were located in the available literature.

No information regarding Ho was available from the USEPA IRIS database or the Regional Screening Levels (USEPA, 2014a,b).

No OELs have been established for Ho by OSHA, NIOSH, or ACGIH (OSHA, 2014).

Ecological Effects

Tai et al. (2010) determined a 72 hour EC50 of 29.3 µmol/L for growth inhibition of the marine algae, Skeletonema costatum, by Ho nitrate. This value was similar to the EC50 values determined for all other lanthanides.

The growth of root tips of *Vicia faba* (fava bean) was accelerated at concentrations of Ho trioxide less than 4 mg/L (Qu et al., 2004). However at higher concentrations mutagenic and cytotoxic effects were indicated by an increase in chromosomal aberrations and micronuclei, and a decrease in the mitotic index.

The mean background concentration of Ho in fish collected from an unimpacted reservoir in Washington state was 0.001 mg/kg dry weight (whole body basis) (Mayfield and Fairbrother, 2015).

9. Lanthanum

Lanthanum (La) (atomic number 57) is a lanthanide REE used in carbon arc lamps for movie projection, as a phosphor in fluorescent lamps, in camera and telescope lenses, as a catalyst for cracking crude petroleum, and in glass coloring (Harbison, 1998; Rim et al., 2013).

Health Effects

He et al. (2003) fed rats diets containing either 75 or 150 mg/kg La (as $LaCl_3 \cdot 6H_20$) for 18 days. Growth was normal, no adverse effects were observed, and blood serum parameters were generally normal (serum concentrations of glucose were significantly lower than controls). However, the rats fed 150 mg/kg La showed a 20% increase in thymus weight.

Hutcheson et al. (1975) fed mice a combination REE diet that contained up to 400 ppm La (as the oxide). Mice were fed for three generations. No adverse effects on mortality, morbidity, growth rate, hematology, morphological development, maturation, reproduction, litter size or lactational performance were observed.

La chloride was highly toxic to pulmonary alveolar macrophages *in vitro* (LC50 of 52 µM), whereas La oxide was only minimally toxic (LC50 of 980 µM) (Palmer et al., 1987). The authors concluded that La is cytotoxic to lung tissue and potentially fibrogenic.

The mutagenicity of La was studied using a wide range of independent test systems for mutagenicity and clastogenicity, including the Ames test, *in vitro* cytogenetics assay, the hgprt gene mutation assay using Chinese hamster ovary cells, the *in vivo* rat bone marrow micronucleus test, the *in vivo* mouse bone marrow micronucleus test and the *in vitro/in vivo* rat liver unscheduled DNA synthesis (UDS) assay (Damment et al., 2005). No mutagenic activity was observed in the Ames test or the hgprt assay. However, chromosome aberrations were observed using the *in vitro* cytogenetics assay. These aberrations were attributed to overt cell toxicity. No mutagenic activity was observed using the two rodent micronucleus assays or the UDS assay. The investigators concluded that La is not genotoxic.

No data regarding the carcinogenicity of La were located in the available literature.

No information regarding La was available from the USEPA IRIS database or the Regional Screening Levels (USEPA, 2014a,b).

No OELs have been established for La by OSHA, NIOSH, or ACGIH (OSHA, 2014).

Ecological Effects

Acute ip administration of a single oral dose of 250 mg/kg La chloride to newborn checks resulted in the inhibition of calcium binding to brain synaptosomal membrane (Basu et al., 1982). The activities of the enzymes Ca^{2+}-ATPase, Mg^{2+}-ATPase, and cholinesterase were also significantly reduced. This reduction

is consistent with the general tendency of the lanthanides, particularly La, to inhibit Ca- and Mg-dependent enzymes (Pałasz and Czekaj, 2000).

Broiler chickens were fed a REE-chloride diet containing up to 11 mg/kg La and 15 mg/kg Ce for 35 days. No toxic effects were observed and hematological parameters were not significantly affected. Concentrations of La in the liver and muscles were less than 1 mg/kg (He et al., 2008).

La has been shown to cause embryotoxic and developmental effects in fish. Zebrafish embryos were exposed to La (as La^{3+}) or Yb^{3+} at concentrations ranging from 0.01 to 1.0 mmol/L (Cui et al., 2012). Exposure to La^{3+} resulted in delayed embryo and larval development, reduced survival and hatching rates, and induced tail malformations. These effects were concentration dependent, with adverse effects observed at concentrations as low as 0.1 mmol/L. The toxic effects of La^{3+} were considered to be due to possible interference with calcium homeostasis in the zebrafish embryo. The toxic effects of the light rare earth La^{3+} were less severe than the heavy rare earth Yb^{3+}. The authors suggested this was possibly due to the greater stability of Yb^{3+} complexes with biological molecules relative to La^{3+}.

Exposure of sea urchin embryos (*Paracentrotus lividus*) to 10^{-5} M La^{3+} resulted in 100 percent developmental effects with an EC50 of 6E-06 M (Oral et al., 2010). However, no mitotic aberrations or embryo mortality were observed. Exposure of sea urchin sperm to this same concentration resulted in a significant reduction of fertilization success but no increase in developmental effects.

Exposure of common duckweed (*Lemna minor* L.) to La nitrate (10 mM) for 5 days resulted in toxic effects, including enlargement of root tips and yellowing of leaves (Paola et al., 2007). Other effects included significant increases in antioxidant content (ascorbate and glutathione) and antioxidant enzyme activity, and decreases in protein content. Exposure of a variety of crop and Canadian native plants to La in soil (as $LaCl_3$, at concentrations up to 700 mg/kg dry soil) did not inhibit germination but did result in a reduction of biomass in two native species (Thomas et al., 2014). Exposure of Vicia faba seedlings to La resulted in increased concentrations of La in the seedling roots, and increases in the antioxidant enzymes superoxide dismutase, catalase, guaiacol peroxidase, and ascorbate peroxidase at the highest exposure concentrations (Wang et al., 2011).

Barry and Meehan (2000) investigated the acute and chronic toxicity of La to *Daphnia carinata*. The 24-hr EC50 was determined be 484 and 1232 µg/L in soft tap water and hard water, respectively. The 48-hr EC50 was determined to be 49, 43.2 and 1180 µg/L in dilute seawater, soft tap water, and hard water, respectively. In the chronic test La concentrations equal to or greater than 80 µg/L resulted in 100% mortality after 6 days of exposure in dilute seawater. La also caused a delay in maturation at concentrations equal to or greater than 39 µg/L. At concentrations greater than 10 µmol/L La3+ had significant adverse effects on the growth and reproduction of the roundworm, *Caenorhabditis elegans* (Zhang et al., 2010).

Tai et al. (2010) determined a 72 hour EC50 of 29.2 µmol/L for growth inhibition of the marine algae, *Skeletonema costatum*, by La nitrate. This value was similar to the EC50 values determined for all other lanthanides.

At low concentrations of La^{3+} (<100 ppm), membrane permeability increased and the absorbability of nutrient ions was increased in *E. coli* (Peng et al., 2006). However, at higher La^{3+} concentrations, starting

at 100 ppm, a dramatic increase in membrane permeability was observed which was associated with significant accumulation of La^{3+} in the cells. The authors concluded that the frequently observed growth stimulation effect of lanthanides on microbes may be the result of an increased permeability to key nutrients and limited permeability to the lanthanide at low exposure concentrations. However, at higher concentrations further increases in permeability lead to a significant influx of the lanthanide and associated toxic effects.

The mean background concentration of La in fish collected from an unimpacted reservoir in Washington state was 0.052 mg/kg dry weight (whole body basis) (Mayfield and Fairbrother, 2015). Geometric mean bioaccumulation factors were 56, 591, and 454 for fillet, carcass, and whole body, respectively.

Qiang et al. (1994) determined bioconcentration factors (BCFs) of La in carp (*Cyprinus carpio*) of 6.1, 3.2, 18 and 91 in skeleton, muscle, gills, and internal organs, respectively.

10. Lutetium

Lutetium (Lu) (atomic number 71) is the heaviest lanthanide. It is used in carbon arc lamps for movie projection, in lasers, in cancer radiotherapy, as a catalyst in petroleum cracking, and as a phosphor in LED light bulbs (Harbison, 1998; http://en.wikipedia.org/wiki/Lutetium). Very limited information regarding the health effects and ecotoxicity of Lu is available. Virtually all of the basic mammalian toxicology work for Lu has been developed by Haley et al. (1964a), and this work is discussed in detail below.

Health Effects

Haley et al. (1964a) determined the acute LD50 of Lu chloride in mice to be 7100 mg/kg via the oral route and 315 mg/kg via the ip route. The symptoms of acute toxicity included writhing, arched back, ataxia (loss of muscular coordination), labored breathing, stretching of limbs while walking, and excessive tearing. Bruce et al. (1963) determined an oral LD50 in female rats of 3000 mg/kg for Lu nitrate. Oral doses of the corresponding oxide form of 1000 mg/kg were well tolerated.

Rats fed up to 1.0% Lu chloride in the diet for 90 days showed no adverse effects on growth or hematological parameters (total erythrocyte counts, differential cell count, thrombocyte count, hemoglobin or hematocrit) (Haley et al., 1964a). All organs appeared normal based on gross appearance and histopathological examination.

The Draize test was used to evaluate skin and eye irritation from Lu chloride in rabbits (Haley et al., 1964a). Administration of 0.1 ml of a 1:1 aqueous solution of Lu chloride to the eye did not result in any detectable damage to the cornea. However, it did cause conjunctivitis which scored an irritation index of 20 at 24 hr (out of a maximum possible score of 20). Two weeks were required for complete healing. For the topical skin irritation test, 0.5 g of crystalline Lu chloride was applied to skin of the rabbit. No irritant effect was observed on intact skin. However, severe irritation was produced on abraded skin, scoring 8 out of a maximum possible irritation index score of 8 at 24 h.

Following intramuscular (im) injection of Lu in mice, approximately 20% of the absorbed dose of Lu was excreted, 65% was deposited in bone, and less than 5% was deposited in the liver (Durbin et al., 1956).

No data regarding the carcinogenicity or mutagenicity of Lu were located in the available literature.

No information regarding Lu was available from the USEPA IRIS database or the Regional Screening Levels (USEPA, 2014a,b). However, USEPA has developed a provisional subchronic oral RfD for Lu of 0.5 mg/kg/day (USEPA, 2007b). USEPA defines the subchronic RfD as follows (USEPA, 1989):

> An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a portion of a lifetime (as a Superfund program guideline, two weeks to seven years).

No OELs have been established for Lu by OSHA, NIOSH, or ACGIH (OSHA, 2014).

Ecological Effects

Tai et al. (2010) determined a 72 hour EC50 of 28.6 µmol/L for growth inhibition of the marine algae, *Skeletonema costatum*, by Lu chloride. This value was similar to the EC50 values determined for all other lanthanides.

Weltje et al. (2004) used a microbial bioassay based on the luminescent bacterium, *Vibrio fischeri*, to show that the toxic effect of Lu in aqueous solution was related to the hydrated free-ion concentration rather than the total dissolved Lu concentration. In this bioassay the degree of luminescence is inversely proportional to the toxic stress. Based on the EC50 of 1.5 µM, the toxicity of Lu^{3+} was greater than that for cadmium (2+) and zinc (2+), less than that for lead (2+) and similar to that for copper (2+). Lu was also 200 times more toxic than La.

The mean background concentration of Lu in fish collected from an unimpacted reservoir in Washington state was 0.001 mg/kg dry weight (whole body basis) (Mayfield and Fairbrother, 2015).

11. Neodymium

Neodymium (Nd) (atomic number 60) is a lanthanide REE used in carbon arc lamps for movie projection, metal alloys, high performance magnets, lasers, as a catalyst for cracking crude petroleum, and in glass coloring (Harbison, 1998; USEPA, 2009; Rim et al., 2013). Very limited information regarding the health effects and ecotoxicity of Nd is available. Virtually all of the basic mammalian toxicology information available for Nd has been developed by Haley et al. (1964b). This work is discussed in detail below.

Health Effects

Haley et al. (1964b) determined the acute LD50 of Nd chloride in mice to be 5250 mg/kg via the oral route and 600 mg/kg via the ip route. The symptoms of acute toxicity included writhing, ataxia (loss of muscular coordination), labored breathing, sedation, and stretching of limbs while walking. Bruce et al. (1963) determined an oral LD50 in female rats of 2750 mg/kg for Nd nitrate. Oral doses of the corresponding oxide form of 1000 mg/kg were well tolerated.

Rats fed up to 1.0% Nd chloride in the diet for 90 days showed no adverse effects on growth or hematological parameters (total erythrocyte counts, differential cell count, thrombocyte count, hemoglobin or hematocrit). All organs appeared normal based on gross appearance and histopathological examination (Haley et al., 1964b). Based on this study USEPA calculated No Observed Adverse Effect Levels (NOAELs) for Nd chloride of 840 mg/kg/day in male rats and 950 mg/kg/day in female rats (USEPA, 2009b)

The Draize test was used to evaluate skin and eye irritation from Nd chloride in rabbits (Haley et al., 1964b). Administration of 0.1 ml of a 1:1 aqueous solution of Nd chloride to the eye did not result in any detectable damage to the cornea. However, it did cause conjunctivitis which scored an irritation index of 20 at 24 hr (out of a maximum possible score of 20). One week was required for complete healing. For the topical skin irritation test, 0.5 g of crystalline Nd chloride was applied to skin of the rabbit. No irritant effect was observed on intact skin. However, severe irritation was produced on abraded skin, scoring 8 out of a maximum possible irritation index score of 8 at 24 h.

Like many of the REE, Nd salts have anticoagulative properties. Beaser et al. (1942) administered various Nd salts (Nd nitrate, Nd lactate, Nd acetate) intravenously (iv) to volunteers at doses ranging from 3-18 mg salt/kg body weight. All of the salts increased blood clotting time by 2-4 fold, with this effect peaking at approximately 1 hr post-dosing. Adverse effects noted included fever, chills, muscle aches, abdominal cramps, hemoglobinemia, and hemoglobinuria.

Nd oxide was toxic to pulmonary alveolar macrophages *in vitro* (LC50 of 101 μM), whereas Nd chloride was only minimally toxic (LC50 of 1495 μM) (Palmer et al., 1987). These findings were contrary to those for Ce and La in which the chloride forms were much more toxic than the oxide forms. The authors concluded that Nd is cytotoxic to lung tissue and potentially fibrogenic.

No data regarding the carcinogenicity or mutagenicity of Nd were located in the available literature.

No information regarding Nd was available from the USEPA IRIS database or the Regional Screening Levels (USEPA, 2014a,b). However, USEPA has developed a provisional subchronic RfD for Nd chloride of 8E-01 mg/kg/day (USEPA, 2009b).

No OELs have been established for Nd by OSHA, NIOSH, or ACGIH (OSHA, 2014).

Ecological Effects

Tai et al. (2010) determined a 72 hour EC50 of 30.3 µmol/L for growth inhibition of the marine algae, *Skeletonema costatum*, by Nd chloride. This value was similar to the EC50 values determined for all other lanthanides.

The mean background concentration of Nd in fish collected from an unimpacted reservoir in Washington state was 0.041 mg/kg dry weight (whole body basis) (Mayfield and Fairbrother, 2015).

12. Praseodymium

Praseodymium (Pr) (atomic number 59) is a lanthanide REE used in carbon arc lamps for movie projection, metal alloys for the aerospace industry, as a catalyst for cracking crude petroleum, and glass coloring (Harbison, 1998; USEPA, 2009a; Rim et al., 2013). Very limited information regarding the health effects and ecotoxicity of Pr is available. Virtually all of the basic mammalian toxicology information available to date has been developed by Haley et al. (1964b), and this work is discussed in detail below.

Health Effects

Haley et al. (1964b) determined the acute LD50 of Pr chloride in mice to be 4500 mg/kg via the oral route and 600 mg/kg via the ip route. The symptoms of acute toxicity included writhing, ataxia (loss of muscular coordination), labored breathing, sedation, and stretching of limbs while walking. Bruce et al. (1963) determined an oral LD50 in female rats of 3500 mg/kg for Pr nitrate. Oral doses of the corresponding oxide form of 1000 mg/kg were well tolerated.

Rats fed up to 1.0% Pr chloride in the diet for 12 weeks showed no adverse effects on growth or hematological parameters (total erythrocyte counts, differential cell count, thrombocyte count, hemoglobin or hematocrit). All organs appeared normal based on gross appearance and histopathological examination (Haley et al., 1964b).

The Draize test was used to evaluate skin and eye irritation in rabbits (Haley et al., 1964b). Administration of 0.1 ml of a 1:1 aqueous solution of Pr chloride to the eye did not result in any detectable damage to the cornea or iris. However, it did cause irritation of the conjunctiva (scoring 20 out of a maximum possible irritation index score of 20). For the topical skin irritation test 0.5 g of Pr chloride was applied to the skin. No irritant effect was observed on intact skin. However, severe irritation was produced on abraded skin (scoring 8 out of a maximum possible score of 8 at 24 hr).

No data regarding the carcinogenicity or mutagenicity of Pr were located in the available literature.

No information regarding Pr was available from the USEPA IRIS database or Regional Screening Levels (USEPA, 2014a,b). However, USEPA developed a provisional subchronic oral RfD for Pr chloride of 8E-01 mg/kg/day (USEPA, 2009c).

No OELs have been established for Pr by OSHA, NIOSH, or ACGIH (OSHA, 2014).

Ecological Effects

Information regarding the ecological effects of Pr is virtually nonexistent. The mean background concentration of Pr in fish collected from an unimpacted reservoir in Washington state was 0.011 mg/kg dry weight (whole body basis) (Mayfield and Fairbrother, 2015).

13. Samarium

Samarium (Sm) (atomic number 62) is a lanthanide REE used in lasers, magnets, as a catalyst for cracking crude petroleum (Harbison, 1998).

Health Effects

Bruce et al. (1963) determined an oral LD50 in female rats of 2900 mg/kg for Sm nitrate. Oral doses of the corresponding oxide form of 1000 mg/kg were well tolerated. Symptoms of acute toxicity in rats following ip injection of Sm chloride included labored breathing, lethargy, muscular spasms, abdominal cramps and diarrhea (Haley et al., 1961). The LD50 via the ip route of exposure was 585 mg/kg. Oral administration of doses up to 2000 mg/kg did not produce any lethality.

Rats fed up to 1.0% Sm chloride in the diet for 12 weeks showed no adverse effects on growth or hematological parameters (total erythrocyte counts, differential cell count, thrombocyte count, hemoglobin or hematocrit). All organs appeared normal based on gross appearance and histopathological examination (Haley et al., 1961).

Hutcheson et al. (1975) fed mice a combination REE diet that contained up to 800 ppm Sm (as the oxide). Mice were fed for three generations. No adverse effects on mortality, morbidity, growth rate, hematology, morphological development, maturation, reproduction, litter size or lactational performance were observed.

Rats administered 3, 4.5 or 6 mg/L Sm nitrate in the drinking water for five months showed a dose-dependent decrease in growth and adverse effects on the liver, including: higher liver weight/body weight ratio, a substantial reduction in the antioxidant enzyme superoxide dismutase, and an increase in the amount of malondialdehyde (Weilin et al., 2006a). Similar but less significant changes were observed in the kidney.

The effect of Sm on rat learning and memory was studied (Weilin et al., 2006b). Rats were treated with Sm in the drinking water for four months at 3, 4.5 and 6 mg/L. Brain weight decreased but the brain/body weight ratio increased at the highest concentration. Brain levels of the antioxidant enzyme superoxide dismutase were significantly reduced at the two highest concentrations. A time-to-learn measure increased slightly at the 3 and 4.5 mg/L exposures, while memory retention decreased slightly at these intermediate exposure levels. Learning and memory at the highest exposure level was not affected.

Application of 1 mg of Sm chloride in the eyes of rabbits produced increased blinking and some redness but did not cause conjunctivitis, or any damage to the cornea or iris (Haley et al., 1961).

Application of Sm chloride crystals to the intact skin of rabbits produced no irritation but produced severe irritation when applied to abraded skin (Haley et al., 1961).

Sm oxide showed no evidence of cytotoxicity after osteoblast-like cells were exposed on Sm oxide discs for 28 days (Herath et al., 2010). An absence of cytotoxicity was noted based on cell morphology, cell membrane effects, cell growth and proliferation, and cell phenotype and differentiation.

No data regarding the carcinogenicity or mutagenicity of Sm were located in the available literature.

No information regarding Sm was available from the USEPA IRIS database or the Regional Screening Levels (USEPA, 2014a,b). However, the USEPA has developed provisional toxicity values for Sm chloride and Sm nitrate (USEPA, 2009d). These include subchronic oral RfDs of 9E-01 mg/kg/day for Sm chloride ($Sm[Cl_3]_3$) and 4E-05 mg/kg/day for Sm nitrate ($Sm[NO_3]_3$).

No OELs have been established for Sm by OSHA, NIOSH, or ACGIH (OSHA, 2014).

Ecological Effects

Information regarding the ecological effects of Sm is very limited. Tai et al. (2010) determined a 72 hour EC50 of 28.7 µmol/L for growth inhibition of the marine algae, *Skeletonema costatum*, by Sm chloride. This value was similar to the EC50 values determined for all other lanthanides.

The mean background concentration of Sm in fish collected from an unimpacted reservoir in Washington state was 0.008 mg/kg dry weight (whole body basis) (Mayfield and Fairbrother, 2015).

14. Terbium

Terbium (Tb) (atomic number 65) is a lanthanide REE used primarily in fluorescent phosphors in visual displays (e.g. televisions and computer screens) (Harbison, 1998; Rim et al., 2013). Very limited health or ecotoxicity information is available for Tb.

Health Effects

Bruce et al. (1963) determined an oral LD50 in female rats of >5000 mg/kg for Tb nitrate. Oral doses of the corresponding oxide form of 1000 mg/kg were well tolerated. Haley et al. (1963) determined an oral LD50 of 5100 mg/kg for Tb chloride in mice.

Hutcheson et al. (1975) fed mice a combination REE diet that contained up to 1200 ppm Tb (as the oxide). Mice were fed for three generations. No adverse effects on mortality, morbidity, growth rate, hematology, morphological development, maturation, reproduction, litter size or lactational performance were observed.

Durbin et al. (1956) found that less than 0.1% of an orally administered (gavage) dose of Tb was absorbed from the gastrointestinal tract.

No data regarding the carcinogenicity or mutagenicity of Tb were located in the available literature.

No information regarding Tb was available from the USEPA IRIS database or the Regional Screening Levels (USEPA, 2014a,b).

No OELs have been established for Tb by OSHA, NIOSH, or ACGIH (OSHA, 2014).

Ecological Effects

Exposure of horseradish cells to Tb^{3+} at a concentration of 5 mg/L resulted in accumulation of Tb on the cell membrane but no entry into the cell (Wang et al., 2010). However, exposure to 60 mg/L resulted in peroxidative damage of the cell membrane and entry of Tb^{3+} into the cell, producing cell toxicity.

Tai et al. (2010) determined a 72 hour EC50 of 28.5 µmol/L for growth inhibition of the marine algae, *Skeletonema costatum*, by Tb chloride. This value was similar to the EC50 values determined for all other lanthanides.

The mean background concentration of Tb in fish collected from an unimpacted reservoir in Washington state was 0.001 mg/kg dry weight (whole body basis) (Mayfield and Fairbrother, 2015).

15. Thulium

Thulium (Tm) (atomic number 69) is a lanthanide REE used primarily as a radiation source (Harbison, 1998). Very limited health or ecotoxicity information is available for Tm.

Health Effects

Haley et al. (1963) determined an oral LD50 of 6250 mg/kg for Tm chloride in mice.

Hutcheson et al. (1975) fed mice a combination REE diet that contained up to 80 ppm Tm (as the oxide). Mice were fed for three generations. No adverse effects on mortality, morbidity, growth rate, hematology, morphological development, maturation, reproduction, litter size or lactational performance were observed.

Durbin et al. (1956) found that less than 0.1% of an orally administered (gavage) dose of Tm was absorbed from the gastrointestinal tract.

No data regarding the carcinogenicity or mutagenicity of Tm were located in the available literature.

No information regarding Tm was available from the USEPA IRIS database or the Regional Screening Levels (USEPA, 2014a,b).

No OELs have been established for Tm by OSHA, NIOSH, or ACGIH (OSHA, 2014).

Ecological Effects

Tai et al. (2010) determined a 72 hour EC50 of 28.8 µmol/L for growth inhibition of the marine algae, *Skeletonema costatum*, by Tm chloride. This value was similar to the EC50 values determined for all other lanthanides.

In a study of REE concentrations in fish collected from an unimpacted reservoir in Washington state, Tm was not detected (Mayfield and Fairbrother, 2015).

16. Ytterbium

Ytterbium (Yb) (atomic number 70) is a lanthanide REE used in lasers, and x-ray and other radiation devices (Harbison, 1998). Very limited health or ecotoxicity information is available for Yb.

Health Effects

Bruce et al. (1963) determined an oral LD50 in rats of 3100 mg/kg for Yb nitrate. Oral doses of the corresponding oxide form of 1000 mg/kg were well tolerated. Haley et al. (1963) determined an oral LD50 of 6700 mg/kg for Yb chloride in mice.

Hutcheson et al. (1975) fed mice a combination REE diet that contained up to 120 ppm Yb (as the oxide). Mice were fed for three generations. No adverse effects on mortality, morbidity, growth rate, hematology, morphological development, maturation, reproduction, litter size or lactational performance were observed.

Radiolabeled Yb oxide was administered to rats via intratracheal instillation and its distribution studied for 30 days (Rhoads and Sanders, 1985). Clearance of Yb oxide from the lung followed a single phase exponential. At 30 days approximately 40% of the administered dose was retained in the body and virtually all of this was in the lung. The investigators concluded that the limited translocation of Yb from the lungs was due to the low solubility of Yb oxide in the lungs. Excretion was primarily via the feces (55%), being 10 times greater than via urine.

No data regarding the carcinogenicity or mutagenicity of Yb were located in the available literature.

No information regarding Yb was available from the USEPA IRIS database or the Regional Screening Levels (USEPA, 2014a,b).

No OELs have been established for Yb by OSHA, NIOSH, or ACGIH (OSHA, 2014).

Ecological Effects

Yb has been shown to cause embryotoxic and developmental effects in fish. Zebrafish embryos were exposed to Yb (as Yb^{3+}) or La (as La^{3+}) at concentrations ranging from 0.01 to 1.0 mmol/L (Cui et al., 2012). Exposure to Yb^{3+} resulted in delayed embryo and larval development, reduced survival and hatching rates, and induced tail malformations. These effects were concentration dependent, with adverse effects observed at Yb^{3+} concentrations as low as 0.1 mmol/L. The toxic effects of Yb^{3+} were considered to be due to possible interference with calcium homeostasis in the zebrafish embryo. The toxic effects of the heavy rare earth Yb^{3+} were more severe than the light rare earth La^{3+}, possibly due to the greater stability of Yb^{3+} complexes with biological molecules relative to La^{3+}.

Tai et al. (2010) determined a 72 hour EC50 of 28.5 µmol/L for growth inhibition of the marine algae, *Skeletonema costatum*, by Yb chloride. This value was similar to the EC50 values determined for all other lanthanides.

Hongyan et al. (2002) investigated the effect of Yb^{3+} on liver and antioxidant enzymes in the goldfish (*Carassius auratus*). Goldfish were exposed to Yb^{3+} at concentrations ranging from 0.01 to 1 mg/L. Catalase activity was significantly decreased at all concentrations relative to controls, although not in a concentration dependent manner. Superoxide dismutase was elevated at Yb^{3+} concentrations of 0.05 or more. Changes in glutathione peroxidase and glutathione S-transferase were not concentration related. The authors suggested that liver catalase activity could be used to monitor exposure of fish to REE.

The mean background concentration of Yb in fish collected from an unimpacted reservoir in Washington state was 0.003 mg/kg dry weight (whole body basis) (Mayfield and Fairbrother, 2015).

17. Yttrium

Yttrium (Y) (atomic number 39) is one of the two REE that are not lanthanides. It is used in lasers, fiber optics, fluorescent lights, optical glass and metal alloys, and as a phosphor in visual displays (e.g. televisions and computer screens) (Harbison, 1998; Rim et al., 2013).

Health Effects

The effect of Y on renal function in the rat was studied (Hayashi et al., 2006). Rats received Y chloride doses of 14.6 to 116.7 mg per rat and several parameters of renal function were monitored, including: urine volume (UV), N-acetyl-β-D-glucosaminidase (NAG), and creatinine (CRT) excretion. Following treatment, UV decreased by greater than 30% and CRT decreased by at least 10%. NAG was unchanged. The authors concluded that Y has an adverse effect on glomerular function at doses of 58.3 to 116.7 mg/rat.

Inhalation exposure of workers to Y compounds may result in shortness of breath, coughing, chest pain, and cyanosis (Rim et al., 2013).

When rats were given single doses 0.2 to 2 mg Y chloride per rat iv, spleen and liver concentrations of calcium increased substantially at doses of 1 or 2 mg (Hirano et al., 1993). The liver function enzymes glutamic-oxaloacetic transaminase and glutamic-pyruvate transaminase were also increased. The authors concluded that the liver and spleen are the target organs of Y.

Y is poorly excreted in the urine. Rats were given single oral doses of Y ranging from 14.6 to 116.7 mg/rat and urinary excretion was measured over 24 hours (Kitamura et al., 2012). Less than 0.5% of Y was excreted in the urine.

No information regarding the mutagenicity of Y was located in the literature.

The effect of 5 ppm Y in the drinking water on growth, mortality and tumor induction was studied in rats (Schroeder and Mitchener, 1971). Rats were administered Y-treated drinking water from weaning until natural death. Growth was significantly reduced, however, survival was greater in Y-treated rats than in controls. The incidence of tumors was 33% in Y-treated rats and 14% in untreated controls. All of the tumors in the Y-treated rats were malignant and were mostly of the "lymphoma-leukemia" type, followed by adenocarcinoma or papillary adenocarcinoma of the lung.

The carcinogenicity of various implant materials containing Y oxide was evaluated by implantation in the thigh muscle of mice for 24 months (Takamura et al., 1994). Implants comprised of a combination of aluminum oxide and Y oxide, and implants comprised of a combination of zirconium oxide and Y oxide showed no evidence of carcinogenicity.

No information regarding Y was available from the USEPA IRIS database or the Regional Screening Levels (USEPA, 2014a,b).

Y is the only REE for which an OEL has been established. NIOSH, OSHA, and ACGIH have established an OEL for Y of 1 mg/m^3 (OSHA, 2014).

Ecological Effects

Qiang et al. (1994) determined bioconcentration factors (BCFs) of Y in carp (*Cyprinus carpio*) of 3.8, 1.3, 8.0 and 54 in skeleton, muscle, gills, and internal organs, respectively.

Exposure of a variety of crop and Canadian native plants to Y in soil resulted in reduced germination and a reduction of biomass. However, the reduction in biomass was not clearly concentration dependent (Thomas et al., 2014). Tai et al. (2010) determined a 72 hour EC50 of 43.2 µmol/L for growth inhibition of the marine algae, *Skeletonema costatum*, by Y nitrate. This value was significantly higher than the EC50 values determined for all other lanthanides.

The mean background concentration of Y in fish collected from an unimpacted reservoir in Washington state was 0.024 mg/kg dry weight (whole body basis) (Mayfield and Fairbrother, 2015). Concentrations in fillet (with skin) were much lower than in whole body or carcass. Geometric mean bioaccumulation factors were 80, 351, and 261 for fillet, carcass, and whole body, respectively.

18. Summary and Conclusions

A comprehensive review of the toxicity information regarding REE was conducted. This review included both health and ecological effects. A summary of conclusions from this review are provided in Table 4.

The REE share very similar chemical and physical properties and this similarity results in very similar toxicological properties across this chemical group. A common feature of REE that may underlie their toxicity is their ability to displace calcium from binding sites in key biomolecules (such as enzymes), leading to biochemical dysfunction. The REE have low acute and chronic toxicity via the ingestion route of exposure. The target organ following ingestion exposure is the liver, whereas the lung is the target organ for inhalation exposure. Liver effects include fatty degeneration of the liver and necrosis, while lung effects include pneumoconiosis and pulmonary fibrosis. The REE typically show an anticoagulative effect on the blood as well. The REE are irritants to both the eye and skin and are poorly absorbed via either the gastrointestinal tract or the skin. The light REE are excreted primarily in the feces while the heavy REE are excreted in the urine. There is very little data regarding the mutagenicity and carcinogenicity of the REE. The available data provides some evidence for a mutagenic effect of Ce and Ho and a carcinogenic effect of Y. However, the USEPA at this time has not classified any of the REE as carcinogens. Although the REE have consistent effects on the lung, an occupational exposure limit has only been established for Y. There is a paucity of data regarding the ecotoxicity of the REEs. However, adverse effects on the growth of algae have been observed at REE concentrations as low as 30 μmol/L.

19. References

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TABLES

Table 1

The Rare Earth Elements

Element	Symbol	Most Common Valence State[1]
Cerium	Ce	+3, +4
Dysprosium	Dy	+3
Erbium	Er	+3
Europium	Eu	+3
Gadolinium	Gd	+3
Holmium	Ho	+3
Lanthanum	La	+3
Lutetium	Lu	+3
Neodymium	Nd	+3
Praseodymium	Pr	+3
Promethium	Pm	+3
Samarium	Sm	+3
Scandium	Sc	+3
Terbium	Tb	+3
Thulium	Tm	+3
Ytterbium	Yb	+3
Yttrium	Y	+3

[1]Source: http://en.wikipedia.org/wiki/List_of_oxidation_states_of_the_elements

Table 2

Acute Oral Toxicity of the Rare Earth Elements

Element	LD50 (mg/kg)	Chemical Form	Species	Reference
Cerium	4200	Ce nitrate	rats	Bruce et al. (1963)
Dysprosium	7650	Dy chloride	mice	Haley et al. (1966)
	3100	Dy nitrate	rats	Bruce et al. (1963)
Erbium	6200	Er chloride	mice	Haley et al. (1966)
Europium	>5000	Eu nitrate	rats	Bruce et al. (1963)
	5000	Eu chloride	mice	Haley et al. (1965)
Gadolinium	>5000	Gd nitrate	rats	Bruce et al. (1963)
Holmium	7200	Ho chloride	mice	Haley et al. (1966)
	3000	Ho nitrate	rats	Bruce et al. (1963)
Lanthanum	NA			
Lutetium	7100	Lu chloride	mice	Haley et al. (1964a)
Neodymium	2750	Nd nitrate	rats	Bruce et al. (1963)
	5250	Nd chloride	mice	Haley et al. (1964b)
Praseodymium	3500	Pr nitrate	rats	Bruce et al. (1963)
	4500	Pr chloride	mice	Haley et al. (1964b)
Samarium	2900	Sm nitrate	rats	Bruce et al. (1963)
Terbium	>5000	Tb nitrate	rats	Bruce et al. (1963)
	5100	Tb chloride	mice	Haley et al. (1963)
Thulium	6250	Tm chloride	mice	Haley et al. (1963)
Ytterbium	3100	Yb nitrate	rats	Bruce et al. (1963)
	6700	Yb chloride	mice	Haley et al. (1963)
Yttrium	NA			

NA = Not available.

Table 3

Currently Available Toxicity Criteria for the Rare Earth Elements

Element	RfD (mg/kg/day)		Reference	RfC (mg/m^3)	Reference
	Oral Route	Inhalation Route			
Cerium					
Ceric oxide				3.E-04	TERA (1999)
Cerium oxide				9.E-04	USEPA (2011)
Dysprosium					
Erbium					
Europium					
Europium chloride	3.E-02		TERA (1999)		
Europium oxide	2.E-03		TERA (1999)		
Gadolinium					
Gadolinium oxide				2.E-03	TERA (1999)
Holmium					
Lanthanum					
Lanthanum carbonate	5.E-01		USEPA (2012)		
Lanthanum chloride	5.E-03		TERA (1999)		
Lanthanum oxide	2.E-02		TERA (1999)		
Lutetium					
Lutetium chloride[a]	5.E-01		USEPA (2007b)		
Neodymium					
Neodymium chloride[a]	8.E-01		USEPA (2009a)		
Praseodymium					
Praseodymium chloride[a]	8.E-01		USEPA (2009b)		
Samarium					
Samarium chloride[a]	9.E-01		USEPA (2009c)		
Samarium nitrate[a]	4.E-05		USEPA (2009c)		
Terbium					
Thulium					
Ytterbium					
Yttrium					
Yttrium chloride	4.E-03		TERA (1999)		

Notes:

RfD = Reference Dose

RfC = Reference Concentration

[a]Provisional subchronic RfD

Table 4

Summary of Available Toxicity Information for the Rare Earth Elements

Toxic Parameter	Element				
	Ce	**Dy**	**Er**	**Eu**	**Gd**
Acute toxicity	Low	Low	Low	Low	Low
Chronic effects - inhalation exposure route	pneumoconiosis pulmonary fibrosis	pneumoconiosis pulmonary fibrosis	pneumoconiosis pulmonary fibrosis	pneumoconiosis pulmonary fibrosis	pneumoconiosis pulmonary fibrosis
Chronic effects - ingestion exposure route	liver toxicity anticoagulation	liver toxicity anticoagulation	liver toxicity anticoagulation	liver toxicity anticoagulation	liver toxicity anticoagulation
Skin and eye irritation	Yes	Yes	Yes	Yes	Yes
Gastrointestinal absorption	Very low	Very low	Very low	Very low	Very low
Dermal absorption	Very low	Very low	Very low	Very low	Very low
Evidence of mutagenicity	Yes	No data	No data	No data	Yes
Evidence of carcinogenicity	None	None	None	None	None
USEPA PRGs available?	Yes	No	No	No	No
USEPA RfD available?	No	No	No	Yes	No
USEPA RfC available?	Yes	No	No	No	Yes
Occupational exposure limit available?	No	No	No	No	No
Aquatic ecotox threshold concentration	EC50 = 29.7 µmol/L	EC50 = 28.3 µmol/L	EC50 = 28.7 µmol/L	EC50 = 29.2 µmol/L	EC50 = 29.8 µmol/L

Table 4 (continued)

Summary of Available Toxicity Information for the Rare Earth Elements

Toxic Parameter	Element				
	Ho	**La**	**Lu**	**Nd**	**Pr**
Acute toxicity	Low	Low	Low	Low	Low
Chronic effects - inhalation exposure route	pneumoconiosis pulmonary fibrosis	pneumoconiosis pulmonary fibrosis	pneumoconiosis pulmonary fibrosis	pneumoconiosis pulmonary fibrosis	pneumoconiosis pulmonary fibrosis
Chronic effects - ingestion exposure route	liver toxicity anticoagulation	liver toxicity anticoagulation	liver toxicity anticoagulation	liver toxicity anticoagulation	liver toxicity anticoagulation
Skin and eye irritation	Yes	Yes	Yes	Yes	Yes
Gastrointestinal absorption	Very low	Very low	Very low	Very low	Very low
Dermal absorption	Very low	Very low	Very low	Very low	Very low
Evidence of mutagenicity	No data	Not mutagenic	No data	No data	No data
Evidence of carcinogenicity	None	None	None	None	None
USEPA PRGs available?	No	No	No	No	No
USEPA RfD available?	No	Yes	Yes	Yes	Yes
USEPA RfC available?	No	No	No	No	No
Occupational exposure limit available?	No	No	No	No	No
Aquatic ecotox threshold concentration	EC50 = 29.3 µmol/L	EC50 = 6 µmol/L	EC50 = 1.5 µmol/L	EC50 = 30.3 µmol/L	No data

Table 4 (continued)

Summary of Available Toxicity Information for the Rare Earth Elements

Toxic Parameter	Element				
	Sm	**Tb**	**Tm**	**Yb**	**Y**
Acute toxicity	Low	Low	Low	Low	Low
Chronic effects - inhalation exposure route	pneumoconiosis pulmonary fibrosis	pneumoconiosis pulmonary fibrosis	pneumoconiosis pulmonary fibrosis	pneumoconiosis pulmonary fibrosis	pneumoconiosis pulmonary fibrosis
Chronic effects - ingestion exposure route	liver toxicity anticoagulation	liver toxicity anticoagulation	liver toxicity anticoagulation	liver toxicity anticoagulation	liver toxicity anticoagulation
Skin and eye irritation	Yes	Yes	Yes	Yes	Yes
Gastrointestinal absorption	Very low	Very low	Very low	Very low	Very low
Dermal absorption	Very low	Very low	Very low	Very low	Very low
Evidence of mutagenicity	No data	No data	No data	No data	No data
Evidence of carcinogenicity	None	None	None	None	Yes
USEPA PRGs available?	No	No	No	No	No
USEPA RfD available?	No	No	No	No	Yes
USEPA RfC available?	No	No	No	No	No
Occupational exposure limit available?	No	No	No	No	Yes
Aquatic ecotox threshold concentration	EC50 = 28.7 µmol/L	EC50 = 28.5 µmol/L	EC50 = 28.8 µmol/L	EC50 = 28.5 µmol/L	EC50 = 43.2 µmol/L