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Human health risk associated with the management of phosphorus in freshwaters using lanthanum and aluminium

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Abstract

The use of geo-engineering materials to manage phosphorus in lakes has increased in recent years with aluminium and lanthanum based materials being most commonly applied. Hence the potential impact of the use of these compounds on human health is receiving growing interest. This review seeks to understand, evaluate and compare potential unintended consequences on human health and ecotoxicological risks associated with the use of lanthanum- and aluminium-based materials to modify chemical and ecological conditions in water bodies. In addition to their therapeutic use for the reduction of intestinal phosphate absorption in patients with impaired renal function, the phosphate binding capacity of aluminium and lanthanum also led to the development of materials used for water treatment. Although lanthanum and aluminium share physicochemical similarities and have many common applications, their uptake and kinetics within the human body and living organisms importantly differ from each other which is reflected in a different toxicity profile. Whilst a causal role in the development of neurological pathologies, skeletal lesions, hematopoietic disorders and respiratory effects has unequivocally been demonstrated with increased exposure to aluminium, studies until now have failed to find such a clear association after exposure to lanthanum although caution is warranted. Our review indicates that lanthanum and aluminium have a distinctly different profile with respect to their potential effects on human health. Regular monitoring of both aluminium and lanthanum concentrations in lanthanum-/aluminium-treated water by the responsible authorities is recommended to avoid acute accidental or chronic low level accumulation.

Highlights

- Geo-engineering materials containing La and Al used to manage P in lakes
- Potential impact of the use of these compounds on human health is of interest
- La and Al uptake, kinetics and toxicity profile differ within the humans and organisms
- Monitoring of La and Al is recommended to avoid acute and chronic exposure.

Keywords

Lanthanum, aluminium, geo-engineering, human health, ecotoxicity

Introduction

Aluminium is a ubiquitous substance encountered both naturally (as the third most abundant element) and intentionally (used in water treatment, foods, pharmaceuticals, and vaccines); it is also present in ambient and occupational airborne particulates. Existing data underscore the importance of the physicochemical characteristics of aluminium in relation to its uptake, accumulation, and systemic bioavailability (Van Landeghem et al. 1997; Willhite et al. 2014). Aluminium has been shown to have the potential to be a toxicant to the central nervous, skeletal and hematopoietic systems. This is most prevalent through exposure to aluminium-contaminated dialysis and intravenous fluids and oral consumption of large amounts of aluminium-containing antacids and phosphate binders, especially in patients with impaired renal function. Although caricatural aluminium overload, reflected by blood and tissue levels being up to 1000 times higher compared to those currently observed has now disappeared, data in the literature suggest that low level exposure to aluminium via drinking water in individuals with normal renal function may be a contributing factor in the development of Alzheimer's disease and related disorders (Yokel and McNamara 2000, Bondy 2016). With regard to drinking water exposure, an important question is whether the aluminium is derived from natural sources for instance from ingestion of clay minerals (geophagia) or as a consequence of water treatment methods. Water treatment using aluminium sulphate, i.e. alum, generally increases the percentage of dissolved, low molecular weight, (poly) aluminium species that are chemically reactive and possibly more readily absorbed, especially when used in lakes with low to moderate alkalinity (Cooke et al. 1993; Stevenson and Vance 1989; Yokel and McNamara, 2000).

In comparison to aluminium, the ubiquity of *lanthanum* in the environment as well as the element's industrial applications and use in daily life is significantly less. As compared to aluminium there is less evidence for lanthanum toxicity through environmental and medical exposure which is mainly due to differences in gastrointestinal absorption, uptake kinetics, tissue accumulation and routes of elimination. Importantly, however, that with exception of its therapeutic use of lanthanum in uremic patients, much less experimental and epidemiological studies have been performed so far that have evaluated the potential toxicity of long-term low level environmental exposure. With the relatively recent introduction of the lanthanum-modified bentonite (LMB), commercially known as Phoslock (Douglas 2002; Douglas et al. 2004, 2008; Robb et al. 2003) for use in phosphorus management in

polluted freshwaters, an assessment of the potential effects of lanthanum on human health deserves increasing attention.

The use of geo-engineering materials to control phosphorus in lakes has increased in recent years with aluminium and lanthanum based materials being most commonly applied (Copetti et al. 2016; Huser et al. 2016). Given that these materials are used to achieve improvements in chemical and ecological conditions in water bodies it is understandable that efforts to forecast potential unintended consequences have focused on *ecotoxicological* risks associated with aluminium (Reitzel et al. 2013) and lanthanum (Spears et al. 2013). However, as these materials are frequently used to control harmful algal blooms in recreational water bodies (Lürling and van Oosterhout 2013; Lurling and Tolman 2010; Meis et al. 2012), direct contact with treated waters by humans is unavoidable. For example, LMB was used as a preventative measure in both Strathclyde Loch and The Serpentine during the Commonwealth Games (Glasgow, 2014), and Olympic Games (London, 2012), respectively, to reduce the risk of human health effects associated with cyanobacteria during open water swimming events. In addition, the use of geo-engineering materials in drinking water reservoirs has received attention given the potential for mass human exposure through drinking water supplies (Perkins and Underwood 2001; Schintu et al. 2000). Assessments of the risk posed by human consumption of fish in treated waters have also been conducted (Landman and Ling 2006; Landman et al. 2007). In recognition of these concerns, the use of LMB has been assessed in the context of human and environmental health protection and associated legislative mechanisms (NICNAS, 2014).

To aid water managers in the selection and appropriate use of geo-engineering materials it is important to comprehensively assess the potential for heightened human health risks across a wide range of water body types. To address this, we review here the occurrence, metabolism, routes of exposure, and potential toxicity associated with water bodies treated with lanthanum and aluminium, two of the most commonly used materials for phosphorus control (Lürling et al. 2016). We draw on evidence of concentrations of chemical species reported for treated water bodies and provide recommendations for use of materials in the context of dose and effect scenarios. The assessment approach used here has relevance for the comparative assessment of other materials proposed for use in water bodies.

General aspects

Occurrence and exposure of lanthanum

Lanthanum, a member of the element group called rare earth elements (REE) or lanthanides, is relatively common in the earth's crust. Its abundance may be as high as 18 parts per million (Redling 2006), making it nearly as common as copper or zinc. Lanthanum is widely dispersed throughout the earth's crust, most commonly occurring in REE minerals such as monazite and bastnasite. These minerals generally contain all of the other REE, often in variable abundance. Reports on environmental pollution by lanthanum are scarce and mainly originate from particular regions in China (Zhao et al. 2013). The element, lanthanum, is increasingly used in industrial applications with some of its compounds being used in lamps, color televisions, cigarette lighters, optical fibers and hybrid engines (Behets 2005; Das et al. 1988). According to a recent survey, the annual production of lanthanum was 12,500 tonnes worldwide (Hague et al., 2014). Plants generally do not accumulate lanthanum, although in some instances, accumulation of REE has been described for tea, cucumber, maize and pine leaves (Xu et al. 2003). Mosses and lichen generally contain the highest lanthanum concentrations (up to 100 ppm) (Behets 2005, Das et al. 1988; Xu et al. 2012).

Occurrence and exposure of aluminium

Aluminium (Al) is the most abundant metallic element within the lithosphere, occurring at about 8% by weight (so over 4000 times more enriched relative to lanthanum) and the third most abundant element preceding iron (4.7%) but less abundant than oxygen and silicon. Aluminium exists primarily associated with silicates and oxides in minerals of low solubility, explaining the low (generally <1 mg/L) dissolved aluminium concentrations detected in rivers, lakes and sea water (Gensemer and Playle 1999). Nevertheless, reports in the early 1980s pointed towards acidification of lakes as a result of acid rain thereby enhancing aluminium solubility below pH 6 and hence toxicity for fish and other biota including birds living in the immediate surroundings (Van Landeghem 1997).

Today the daily ingested dose via drinking water is estimated to be around 160 µg aluminium/day (Willhite et al. 2014). Thanks to governmental efforts to reduce the release of sulphur dioxide (SO_2) into the atmosphere emissions in the US and Europe dropped 40% and 70% respectively since the 1990s whilst according to the Pacific Research Institute, acid rain levels have dropped 65% since 1976 (http://en.wikipedia.org/wiki/Acid_rain). Human activities have also changed exposure of living organisms to aluminium in other ways since it is widely used in transportation, packaging,

construction, water treatment, a wide range of household items (Frumkin et al. 2008). In 2014 the global annual aluminium production had reached 54 million tons. It has been reported that exposure to aluminium may also occur through aluminium leaching from ceramic products (Bolle et al. 2011), migration from glass bottles (Fekete et al. 2012), smoking (Exley and Begum 2006a), in some antacids, and prescription phosphate binders. Hence, it is not surprising that depending on location, weather conditions, and type and level of industrial activity in the area, daily exposures may range from 0.005-0.18 μg/m^3 in clean ambient air to 0.4-8.0 μg/m^3 in urban and industrial areas. Hence exposure rates may be as little as 0.03 μg/kg/day (assuming a 70 kg body weight) in clean air to 233 μg/kg/day in polluted air to as high as 3500-5200 mg aluminium/day (i.e. 50 mg/kg/day-75 mg/kg/day) as a result of aluminium-based antacid consumption (D'Haese 1988; Krewski et al. 2007; https://www.atsdr.cdc.gov/phs/phs.asp?id=1076&tid=34). To appreciate health consequences of aluminium exposure it is important to consider that the speciation is more influential to health outcomes than exposure *per se* (Willhite et al. 2014), which is also applicable to other elements, including lanthanum.

Aqueous chemistry of lanthanum

Lanthanum (La), electron configuration (Xe) 5d^1 6s^2, atomic mass 138.91, is the most electropositive (cationic) element of the REE, is uniformly trivalent and its binding is generally ionic. It is a so-called hard electron acceptor with a strong preference for oxygen-containing anions. Therefore, the most common biological ligands with which it can form strong complexes are carboxyl and phosphate groups. Carbonates, phosphates and oxalates formed with lanthanum are essentially insoluble, while the chloride and sulphate complexes are soluble (Cetiner et al. 2005; Cetiner and Xiong 2008). In aqueous solutions without any other oxyanions present, chemical modelling indicates that the majority of lanthanum occurs as a free La^{3+} cation until pH8 (Figure 1). Above this pH a series of La-OH complexes coexist with the insoluble $La(OH)_3$ complex predominating between approximately pH9 and pH12. In lake restoration, lanthanum is used to intercept phosphate released from sediments and to reduce water column phosphate. Lanthanum and phosphate bind to rhabdophane ($LaPO_4$), a mineral with an extreme low solubility (Ksp $10^{-24.7}$ to $10^{-25.7}$ mol^2 l^{-2}) (Johannesson and Lyons 1994, Liu and Byrne 1997). The lanthanum-phosphate bond is only affected by conditions where pH is <4 or >12. The phosphate binding capacity of lanthanum is not affected by altered redox conditions such as those in anoxic waters (Ross et al. 2008). The formation of rhabdophane is not only predicted by

chemical equilibrium modelling, but also has been found in sediments of 10 treated lakes across Europe (Dithmer et al. 2016). Given that rhabdophane is extremely stable and will not "separate", the equilibrium is de facto a precipitation reaction. Consequently, any phosphate bound to lanthanum can be viewed as permanently removed from the biogeochemical cycling. An example of this is the persistence of $LaPO_4$ minerals in the weathering cycle that may span millions of years.

Aqueous chemistry of aluminium

Aluminium (Al), electron configuration (Ne) $3s^2\ 3p^1$, molecular mass 26.98, exists exclusively in the trivalent oxidation state. It is amphoteric, combining with both acids and bases to form, respectively, aluminium salts and aluminates. As it combines a relatively small ionic radius (0.54 Å) with a high charge the free Al^{3+} concentration in aqueous solutions is very low due to the formation of aluminium hydroxide complexes. The chemical nature of aluminium in water is essentially the chemistry of $Al(OH)_3$ which has an amphoteric character and a tendency to form complex ions and to polymerize. Evidence has been provided by chemical modelling that in solutions with a pH below 5, aluminium exists predominantly as $Al(H_2O)_6^{3+}$, with rising pH an insoluble $Al(OH)_3$ complex forms at circumneutral pH, which re-dissolves at higher pH as the $Al(OH)_4^-$ (aluminate) complex (Figure 1) (Anderson and Berkowitz 2010; Gensemer and Playle 1999; Reitzel et al. 2013). Importantly, the speciation of aluminium is remarkably similar to that of lanthanum, albeit with the majority of similar Al-OH species offset by 4-5 pH units lower (Figure 1). In lake restoration, aluminium is used as a coagulant to settle particulate matter, to complex with water column and sediment released phosphate (Cooke et al. 1993). The chemistry of aluminium is complex, as hydrolysis of aluminum is pH and temperature dependent, and amorphous aluminium hydroxide, bayerite, gibbsite with attached phosphates may form. These forms may either loose some of the attached phosphates or loose binding capacity because (i) $Al(OH)_3$ begins to crystallize after forming (Berkowitz et al. 2006; de Vincente et al. 2008), (ii) are stable over a smaller pH range compared to $LaPO_4$, but are just like lanthanum in that they are redox insensitive. Under high phosphate conditions minerals such as variscite ($AlPO_4 \cdot 2H_2O$) and kingite ($Al_3(PO_4)_2(OH)_3 \cdot 9H_2O$) may be formed.

Metabolism

Inhalation of lanthanum.

Lanthanum in combination with other REE may accumulate in the lungs after inhalation, mainly in occupational settings. Taking into account the limited pathological potential of REE for pulmonary lesions in combination with modern occupational exposure practices which efficiently restrict the respiratory intake of particles at work sites, health impairment is not readily expected (Redling 2006; Richter 2003). Electron microscopic evidence for cerium and lanthanum particles in the lung was provided in a single patient with an occupational history of REE exposure and affected by dendriform pulmonary ossification and pneumoconiosis (Yoon et al. 2005).

Inhalation of aluminium

Aluminium workers can encounter a mixture of aluminium fumes and inhalable (aerodynamic diameter <100μm), thoracic (<28μm), and respirable (<10μm) aluminium particles in the occupational environment (Willhite et al. 2014). A fraction of the aluminium present in dust remains indefinitely in the lungs after inhalation, thus without entering systemic blood circulation. Hence, unlike other tissue stores of aluminium, concentrations in the lung increase with age (Han et al. 2004).

Ingestion and gastrointestinal absorption of lanthanum

Lanthanum, as all lanthanide elements, forms soluble chlorides and nitrates, but their phosphates and carbonates are generally insoluble and therefore have a low potential for systemic absorption. Studies have shown that oral doses of lanthanum are only minimally absorbed from the gut. When given as lanthanum carbonate to rats, the oral bioavailability was 0.0007% (Damment and Pennick 2007) whilst in humans the average systemic bioavailability across different studies was 0.00089 ± 0.00084% (n=25) with the highest bioavailability in any subject being 0.00294%. No clear differences in bioavailability were seen between healthy volunteers and dialysis patients, i.e. the target population for phosphate binding treatment with lanthanum carbonate (Damment and Pennick 2008; Pennick et al. 2006;).

Ingestion and gastrointestinal absorption of aluminium

Daily intake of aluminium from food is considered small. Recent studies suggest that it is in the range of 2-5mg/day (Crisponi et al. 2013). The gastrointestinal absorption of aluminium is profoundly affected by speciation (e.g. aluminium citrate versus aluminium hydroxide) and reported fractional gastrointestinal absorption varies between 0.001% and 27% (Drüeke 2002). The main reasons for this lack of agreement are related to analytical detection, contamination and differences in experimental

protocols. With the introduction of accelerator mass spectrometry (AMS) and the possibility of using the ^{26}Al radioisotope more reliable data were generated, which however, still varied between 0.04% and 1.0% (Jouhanneau et al. 1993). A fractional gastrointestinal absorption of ± 0.2% is now generally accepted (Shirley and Lote 2005). It is believed that intestinal absorption of aluminium includes both (i) paracellular pathways along enterocytes and through tight junctions by passive processes and, (ii) transcellular pathways through enterocytes involving both active and passive processes. Other factors that have been reported to alter intestinal aluminium absorption include calcium, iron status, parathyroid hormone, vitamin D, and the uremic state (Van Landeghem et al. 1997).

Lanthanum in blood/plasma

Background concentrations in chronic renal failure patients not treated with lanthanum carbonate revealed concentrations of <0.05 to 0.90 µg/L in plasma whilst in subjects with normal renal function values consistently are below 0.05 µg/L (Pennick et al. 2006). *In vitro* binding studies demonstrated that lanthanum is extensively bound (>99.7%) to plasma proteins (Damment and Pennick 2007). In dialysis patients (N=93) treated with lanthanum carbonate on a daily basis over six years, plasma lanthanum concentrations > 2.0 µg/L were recorded in only 15 out of a total of 574 analyses with no evidence of safety concerns or increased frequency of adverse events (Hutchison et al. 2008).

Aluminium in serum/plasma

Serum aluminium concentrations in healthy non-exposed subjects as measured using appropriate contamination free techniques are below 2.0 µg/L and should not exceed 10 µg/L. (Guidelines for aluminum toxicity are mainly based on the toxic effects seen in patients with impaired renal function. In these patients a serum aluminum level (D'Haese and De Broe, 2007):

< 30 µg/L: aluminum-related bone disease is unlikely but possible particularly when patients are iron-overloaded

30-60 µg/L: aluminum-related bone disease is quite possible, especially if serum parathyroid hormone (PTH) levels are low or low-normal

> 60 µg/L: aluminum-related bone disease is probable, but not invariably present, especially if serum PTH levels are high, iron-transferrin saturation is low.

> 100 µg/L: aluminum-related bone disease is most probable unless patients are iron deficient. Neurologic disorders should be checked for by taking the patients' electroencephalogram.

Whilst in the past values up to >500 µg/L were seen in uremic patients treated with aluminium-containing phosphate binders either in combination with aluminium-contaminated dialysis fluids or not, nowadays with the introduction of aluminium-free medication and high performance water treatment systems concentrations above 10 µg/L are rarely seen. The majority (80-90%) of aluminium in serum is bound to transferrin which can accommodate two aluminium ions, the first at the C-lobe and the second at the N-lobe (Mujika et al. 2012), and is considered the most important, if not the sole, carrier protein of the element in plasma (Van Landeghem et al. 1994, 1998) with the remainder fraction bound to low molecular mass compounds. Hence, it is not surprising that the protein bound fraction is influenced by the iron status; i.e. iron-transferrin saturation, as both elements compete for binding to transferrin (Van Landeghem et al. 1997). This implies that when iron-transferrin saturation is high there is less binding of aluminium to transferrin, hence, more non-protein bound aluminium, i.e. free aluminium in circulation which thus becomes available (i) for being deposited in the calcified bone compartment thereby impairing bone mineralisation, (ii) to pass the blood brain barrier by which it may induce deleterious neurological effects. On the other hand when iron transferring saturation is low, more aluminium will bind to transferrin which however may be taken up by the parathyroid gland through transferrin-mediated endocytosis which in turn may lead to a decreased PTH secretion/synthesis, hence hypoparathyroidism ensuing in the so-called adymamic or low turn-over bone disease (D'Haese1988; Smans et al., 2000; Van Landeghem et al., 1997 & 1998a).

Once bound to transferrin, studies from Mujika et al. (2012) revealed that conformational changes under conditions where Tyr188 is protonated permit aluminium release from the protein.

Tissue distribution of lanthanum

Data on the tissue distribution in humans, with the exception of lanthanum concentrations measured in the framework of clinical studies evaluating the therapeutic use of lanthanum carbonate, are scarce. Studies in animals with normal renal function and chronic renal failure that were environmentally exposed revealed that lanthanum concentrations in various tissues did not exceed 0.08 µg/g wet weight and this was not dependent on renal function. In rats treated with lanthanum carbonate at an oral dose of 2000 mg/kg/day over a 12 week exposure, a substantial increase was seen, particularly in bone, liver and kidney with liver lanthanum concentrations in uremic rats being 2- to 3-fold higher than those seen in non-uremic rats (Slatopolsky et al. 2005). This may be ascribed to a disruption of the intercellular junctions in the intestinal epithelium inherent to chronic renal failure. A carefully controlled

time-course rat study, however, showed that steady-state concentrations of about 3 µg/g wet weight were achieved within 6-12 weeks of treatment, indicating hepatic lanthanum uptake and elimination to be in equilibrium (Bervoets et al. 2009). Lanthanum concentrations in bone biopsy samples of patients being treated with pharmacological doses of lanthanum carbonate during 12 months revealed concentrations of 1.8 µg/g wet weight (D'Haese et al. 2003) whilst in patients treated for 4-5 years the average measured bone lanthanum concentration was 5 µg/g wet weight (unpublished data).

Tissue distribution of aluminium

In adults with normal renal function the total aluminium burden is estimated to be 30 mg with the highest concentrations found in the lungs, skeleton and skeletal muscles. Chronic accumulation occurs in patients with end-stage renal disease because the major elimination route; i.e. the kidney, does not function. In these patients a somewhat different distribution pattern is seen particularly in those taking aluminium-containing medication or being treated with aluminium-contaminated dialysis fluids. In these patients highest concentrations were observed in the liver, bone (up to 200 µg/g wet weight), spleen and parathyroid glands (D'Haese 1988; D'Haese et al. 1999, 1999a). Tissue distribution/elimination further depends on the element's concentration and speciation (van Ginkel et al. 1993). Data from various studies indeed point toward a preferential transport of the circulating aluminium-transferrin complex to tissues expressing transferrin receptors such as the liver and the spleen. However, aluminium bound to citrate (or low molecular mass components in general) will in the presence of an intact renal function rapidly be excreted whereas in the absence of a renal function low molecular mass Al compounds will by preference be deposited at the bone mineralization surface, an area with no transferrin receptors (Van Landeghem et al. 1998).

Elimination of lanthanum

The kidneys are responsible for eliminating only a very small fraction of systemic lanthanum which also explains the lack of appreciable plasma lanthanum concentrations over time in uremic patients. Following intravenous administration of lanthanum chloride to rats, biliary excretion was the predominant route of elimination, with 85.6% of recovered lanthanum collected from bile over a period of 5 days. Experimental studies presented evidence for lanthanum to be transported and eliminated by the liver via a transcellular, endosomal-lysosomal-biliary canicular transport route (Bervoets et al. 2009).

316 ***Elimination of aluminium***

317 Although only a small fraction of ingested aluminium is absorbed, and thus enters the blood
318 compartment, it is vital that absorbed aluminium is quickly removed from the body because aluminium
319 accumulation is a risk factor in a number of disorders (see below). A small amount of aluminium is
320 excreted in the bile, but the major route of aluminium elimination is via the kidney. Hence it is not
321 surprising that most healthy adults can tolerate large repeated daily oral aluminium exposure (up to
322 3500 to 7200 mg/day from e.g. antacids or buffered aspirin) without any adverse effect but that other
323 people; i.e. preterm infants, young children and in particular patients with impaired renal function are at
324 serious risk of aluminium accumulation/toxicity at even much lower daily doses (Willhite et al. 2014). *In*
325 *vitro* determinations using artificial membranes indicated that ±10% of the total amount of circulating
326 aluminium is filtered at normal plasma concentrations which is similar to the unbound aluminium
327 fraction. However, when plasma aluminium is raised experimentally, its filterability falls, unless the
328 excess aluminium is complexed with citrate whereby the aluminium citrate complex appears to be
329 freely filtered. Information on tubular reabsorption of aluminium at normal plasma concentrations is
330 inconsistent. Filtered aluminium appears to be at least partially reabsorbed, although the reabsorptive
331 mechanisms remain speculative. A consensus is emerging that elevated plasma aluminium
332 concentrations result in a fall in fractional aluminium reabsorption, and a recent micropuncture study
333 indicates that under these circumstances the only significant site of aluminium reabsorption is the loop
334 of Henle (Shirley and Lote, 2005).

335 **General toxicity**

336 ***Lanthanum***

337 Although lanthanum has no known biological role, with the REE including lanthanum generally
338 considered to be of low toxicity, and depending on its chemical form, the acute oral dose of lanthanum
339 as assessed in rats varies from 3400 mg/kg body weight (lanthanum-ammonium nitrate) to > 10000
340 mg/kg body weight (as lanthanum oxide) (Redling, 2006). Evaluation of potential genotoxicity using a
341 range of *in vitro* assays in the presence and absence of post-mitochondrial fraction (S9) and *in vivo* in
342 three independent tests for mutagenicity and clastogenicity indicated that lanthanum is not genotoxic
343 and that lanthanum carbonate is unlikely to present a latent hazard in therapeutic use (Damment et al.,
344 2005). A single experimental study in mice reported nephrotoxic effects associated with oxidative

stress through exposure to lanthanides. The most severe damage was induced by epigastric exposure to cerium chloride followed by neodymium chloride whilst only minor damage was seen with lanthanum chloride (Zhao et al. 2013). Results from another experimental study in mice suggested that these lanthanides enter hepatocytes and mainly accumulate in the nuclei and induce oxidative damage in hepatic nuclei and mitochondria (Huang et al. 2011). To what extent these observations are clinically relevant needs to be determined. Hormetic concentration-related trends, implying stimulatory or protective effects at low levels, then adverse effects at higher concentrations have been reported for lanthanum in various models including seedings, bovine vascular smooth muscle cells and murine preosteoblast cells (Pagano et al. 2015).

Aluminium

Despite the ubiquity of aluminium in the environment and its presence in living organisms, albeit in small concentrations (ppb-ppm range), no biological function has so far been attributed. For this reason aluminium is considered to be a nonessential metal. Aluminium has long been considered inert for living organisms and as such was not regarded as a toxic element until the 1960s. At that time only a few reports dealt with the toxic effects of aluminium in humans and animals, which, however, did not receive much attention (Van Landeghem et al. 1998). In the 1970s, the element was linked to particular disease states noticed in patients with end-stage renal failure particularly those treated by dialysis (Alfrey et al. 1972, 1976; Berlyne et al. 1970). Although aluminium toxicity is mainly a matter of concern in dialysis patients and the element is adequately removed by the kidneys, occupationally exposed workers (e.g., welders) are also at risk for the deleterious effects of aluminium. In the latter population growing evidence is being provided for the element to cause pulmonary lesions (Kongerud et al. 2014; Raghu et al. 2014) as well as neurological disorders (Sińczuk-Walczak et al. 2003). Because of its persistence in the environment and the frequency of exposure of the general population, intensive research was been conducted during the last decades to unravel the mechanism(s) underlying the element's potential health effects. Owing to its physicochemical characteristics aluminium has been reported to perturb iron homeostasis, disrupt biological membranes, enhance reactive oxygen species, and damage DNA (Exley, 2004; Exley, 2006b; Kumar et al. 2009; Mailloux et al. 2011; Zatta et al. 2002). Exposure of neurons and astrocytes to aluminium is known to activate apoptotic cascades, provoke cell cycle arrest, and interfere with cell signaling pathways (Drago et al. 2008; Lemire et al. 2009). Hence it is not surprising that during the last decade

much attention has been paid to the potential neurotoxic effects of aluminium in humans and numerous groups assessed the aluminium content in the brain of subjects with various neurological disorders, in particular those with Alzheimer disease as well as non-affected individuals. Most of these data have been summarized by Exley and House (2011) reporting a normal range between 0.1 and 4.5 µg/g dry weight with the higher values (>2 µg/g dry weight) in brains of non-demented elderly, Alzheimer patients (up to 11.5 µg/g dry weight), dialysis encephalopathy (up to 14.1 µg/g dry weight – see below also), congophilic amyloid angiopathy (up to 23.0 µg/g dry weight) and other encephalopathies (up to 47.4 µg/g dry weight). Despite these numerous data the question as to whether in the general population, aluminium exposure is either the cause, a potential contributor to the onset, progression and aggressiveness, or increased concentrations in the brain are the consequence of the neurological condition itself, with exception to dialysis encephalopathy, has been a matter of debate for many years (Kawahara et al. 2011; Martyn et al. 1989; Willhite et al. 2014).

Therapeutic use

Lanthanum

Because of its low solubility, lanthanum carbonate was preferred to lanthanum chloride for further investigation on its therapeutic use as an intestinal phosphate binder. In the acidic environment of the stomach and upper small intestine, lanthanum dissociates sufficiently to become available for phosphate binding. *In vitro* more than 97% of phosphate was removed by a two-fold molar excess of lanthanum carbonate (Autissier et al. 2007). *In vivo* in a rat model with chronic renal failure, lanthanum carbonate was as effective as aluminium hydroxide and more effective than calcium carbonate or sevelamer (a polymeric amine that binds phosphate) at binding dietary phosphate at equivalent doses (Damment 2011). In contrast to concurrent phosphate binding agents intestinal phosphate binding of lanthanum carbonate does not depend on variations in intestinal pH (Autissier et al. 2007). As biliary excretion is the major route of elimination of lanthanum and gastrointestinal absorption of the element is minimal, its therapeutic use in individuals with a compromised renal function does not expose them to an increased risk of systemic accumulation as compared to subjects with normal renal function. Long-term experimental studies in which rats with either chronic renal failure or normal renal function were administered lanthanum carbonate by oral gavage on a daily base at doses up to 2000 mg/kg (corresponding to a daily dose of 150g/day in humans) did not show significant direct adverse effects on bone (Behets et al. 2005a, 2005b; Bervoets et al. 2006). In contrast to aluminium (see below), in

bone, lanthanum could be localized at sites of active as well as non-active bone remodeling/mineralization with no association between histological deposition sites and the typical bone pathologies observed in renal failure (Behets et al. 2005c). As mentioned above, in the liver the localization of the element is lysosomal whilst lanthanum treatment during 20 weeks at a daily 1000 mg/kg/day dose was not accompanied by an increased concentration of liver enzymes (Yang et al. 2006; Bervoets et al. 2009). Following gavage (863 mg/kg/day during several weeks) or intravenous (a route enabling >300-fold higher plasma lanthanum concentrations) administration (0.03 mg/kg/day) of lanthanum, median brain concentrations remained near the lower limit of quantification (2.4 ng/g). This together with data from ultrastructural studies thus provide strong evidence that lanthanum does not cross the blood-brain barrier (Damment et al. 2009). In patients, lanthanum carbonate monotherapy was effective and well tolerated for up to 6 years with no evidence of safety concerns or increased frequency of adverse events (Hutchison et al. 2008). A 2-year follow up study in hemodialysis patients indicated that lanthanum carbonate as a phosphate binder did not adversely affect cognitive function compared with standard therapy (Altmann et al. 2007) whilst a bone-biopsy based study in dialysis patients receiving a median daily dose of 1250 mg elemental lanthanum/day showed an evolution towards normal bone histology and absence of aluminium-like effects (see below) on bone after 1-year treatment (D'Haese et al., 2003).

Aluminium

Being widely used in the past, aluminium hydroxide has proven to be a highly effective phosphate binder. Its substantial gastrointestinal absorption and renal route of elimination however posed its target population for therapeutic use to an increased risk of accumulation. In the past aluminium-phosphate binder treatment, in particular when used in combination with aluminium-contaminated dialysis fluids (see below) led to the development of severe side-effects, mainly in the bone and brain. In bone, aluminium accumulates at the osteoid calcification front, a critical site of bone mineralization which at high exposure leads to the so-called aluminium-induced osteomalacia, a disease manifested by recurrent fractures and resistance to vitamin D therapy (Goodman 1985; Verbueken et al. 1984). This type of bone disease is characterized by an increased amount of osteoid due to a defective mineralization. Another type of aluminium-related bone disease is adynamic bone characterized by a dramatically reduced bone turn-over, and absence of osteoblasts, osteoclasts and osteoid (Goodman 1985). Aluminium is unquestionably neurotoxic in patients treated by dialysis. The so-called dialysis

encephalopathy syndrome, the result of acute intoxication of aluminium caused by the use of an aluminium-containing dialysate, was a common occurrence prior to 1980 (Rob et al. 2001; Ward et al. 1978). Although with the introduction of modern techniques of water purification, acute intoxication can now be avoided, occurrences of aluminium intoxication may still occur (D'Haese and De Broe, 1996; Simoes et al., 1994;), and chronic moderately elevated concentrations may still be seen in dialysis centres in particular regions (Hou et al. 2010). The neurologic symptoms may be precipitated by concomitant ingestion of aluminium-containing phosphorus binders and citrate (D'Haese and De Broe, 2007). Onset or exacerbation of neurological disorders has been observed during deferoxamine therapy, presumably because of redistribution of mobilized deferoxamine-bound aluminium into the brain (Barata et al. 1996). Main symptoms are speech disturbances, tremor, epilepsy and an altered electroencephalopathic pattern while the serum aluminium concentrations usually exceed 100 µg/L (Van Ginkel 1991). The disease progresses and ends mostly with the death of the patient within one year of initial symptoms. Although with the replacement of aluminium-based phosphate binders and adequate monitoring of dialysis fluids the major clinical manifestations have now disappeared, aluminium has also been implicated in more subtle diseases, such as microcytic hypochromic anemia, resistance to erythropoietin treatment and suppression of parathyroid hormone secretion. With regard to the latter, an increased effect of aluminium has been reported in the presence of a relative iron deficiency (Smans et al. 2000; Van Landeghem et al. 1997). Comparing different tissues of aluminium-intoxicated uremic patients, however, the relation between aluminium overload and toxicity is not straightforward. Whilst bone aluminium concentrations in aluminium-related bone disease, are distinctly elevated, comparable or even higher liver aluminium concentrations are seen without any apparent toxicity in humans. On the contrary, aluminium toxicity has been demonstrated in the brain at concentrations below 3 µg/g wet weight. This discrepancy points to the importance of the ultrastructural/subcellular localization of the element which determines its potential interference with physiological processes (Verbueken et al. 1984).

Potential exposure routes in water treatment

Lanthanum exposure and toxicity

Lanthanum is used as the active component of LMB, consisting of a bentonite carrier which holds the lanthanum cations within the clay interlayer where they retain their ability to bind with other ions such as phosphate and thus can be used to remove phosphorus from water bodies and reduce the

incidence of algal blooms (Robb et al. 2003). Some evidence indicates that 'free' (uncomplexed) lanthanum is toxic to some aquatic organisms (Reitzel et al. 2013a; Herrmann et al. 2016). Free metal ions are assumed to be responsible for detrimental effects, as in the widely used free ion activity model (FIAM) (Brown and Markich 2000). Speciation modelling is needed for getting such insight in complexation and in which species are present, but it might not just be the aqua ion that is mobile or bioavailable. FIAM predictions are not always confirmed for aluminum (Gensemer and Playle 1999). Lanthanum is highly reactive, easily giving up the $5d^1$ and $6s^2$ electrons and the free ion activity commonly will be very low in waters suffering from eutrophication, but not in low alkalinity water (see figure 4 in Spears et al. 2013). The biotic-ligand model assumes complexation of metals with reactive ligands on/in organisms, for instance by forming surface complexes at a metal transport sites on membranes (Niogi and Wood 2004). Lanthanum, however, will not easily persist as free La^{3+} in serum, in cytoplasm or in natural surface water, which makes us a bit reluctant in referring to FIAM/BLM. We fully agree that speciation modelling is essential and this is also commonly applied in LMB research (e.g. Lürling et al. 2017; Lürling et al. 2014; Spears et al., 2013,) and when aluminum is used (Magelhães et al., 2017).

Data from experimental studies where lanthanum was given as lanthanum chloride in drinking water to rats and mice suggested neurobehavioral impairment, although a clear dose-response relationship is often lacking (Briner et al. 2000; Damment 2007a; Feng et al. 2006, 2006a; He et al. 2008; Yang et al. 2013; Zarros et al. 2013). Given (i) the maximal amounts at which lanthanum is leached into the water following application of LMB to surface waters either as filterable lanthanum (nominally <0.2 or 0.45 µm), or total lanthanum or predicted 'free' (uncomplexed) ionic lanthanum (0.026 mg/L to 2.30 mg/L; 0.002 mg/L to 0.14 mg/L and <0.0004 mg/L to 0.12 mg/L respectively) (Spears et al. 2013), (ii) the duration and magnitude of exposure to lanthanum-treated water, (iii) the ability of 'free' lanthanum to directly bind phosphate and other oxyanions in the intestine resulting in a low bioavailability and, (iv) the absence of significant toxic effects when used therapeutically during years at doses up to 3000 to 5000 times higher than those seen in lanthanum-treated water, one may reasonably accept that exposure to lanthanum via the drinking water or leisure activities will pose no increased risk for toxicity in humans even in patients with impaired renal function as biliary excretion is the major route of elimination of lanthanum. Nevertheless, when using lanthanum treated water to prepare dialysis fluids, even in dialysis centers equipped with the highest standards of water purification (carbon filtration,

reverse osmosis, ultrafiltration, deionized water systems, ultraviolet TOC reduction/disinfection), co-measurement of lanthanum during regular monitoring of the in-house treated water and the dialysis fluid may be indicated as with dialysis treatment the gastrointestinal barrier is circumvented and a direct transfer of the element towards the blood compartment may occur, in particular for highly protein bound elements such as lanthanum.

It should be noted that lanthanum-modified bentonite is mostly used to counteract toxic cyanobacterial blooms, and that such blooms may pose potentially even more severe risks to bathers and definitely to patients receiving renal dialysis treatment as the 'Caruaru Syndrome' unambiguously elucidated with dozens of casualties (Azevedo et al. 2002; Jochimsen et al. 1998).

Aluminium exposure and toxicity

Varying concentrations of aluminium are present naturally in groundwater and surface water, including those used as sources of drinking water. The concentration of aluminium in surface water varies, ranging from 0.012 to 2.25 mg/L in North American rivers (Jones and Bennett, 1984). Furthermore, aluminium (aluminium sulphate and polyaluminium chloride) has been used for more than three decades to inactivate phosphate from migrating from lake bed sediments to the overlying waters (Berkowitz et al. 2006; Cooke et al. 1993a; Lewandowski et al. 2003; Reitzel et al. 2005, 2013; Rydin and Welch 1998; Rydin et al. 2000; Welch and Cooke 1999; Welch et al., 1988).

Aluminium can liberate from alum due to changes of pH and the presence of low alkalinity water (Aziz et al. 2007; Paul et al. 2008). Water treatment has been reported to increase the percentage of dissolved, low molecular weight, chemically reactive and possibly more readily absorbed aluminium species (La Zerte et al. 1997). The toxicity of aluminium to fish has been well documented, in particular when the pH decreases to below 6 (Gensemer and Playle 1999).

The hypothesis that aluminium exposure via drinking water is etiologically related to Alzheimer's disease has led to much debate. The possibility of such a relation was suggested by the presence of aluminium in senile plaques and neurofibrillary degeneration, two histologic lesions that are characteristic of the disease (Edwardson et al. 1992). Several studies have found that intake of aluminium (Praticò et al. 2002; El-Rahman 2003) increases expression of amyloid protein in rodent tissues, a step that may be critical to the development of Alzheimer's disease. Ecotoxicological studies have suggested that concentrations of aluminium in drinking water of 0.1 to 0.2 mg/L may increase the

risk of Alzheimer's disease, with relative risks or odds ratios ranging from 1.35 to 2.67 (Gauthier et al. 1999; Martyn et al. 1989; Rondeau et al. 2000).

With regard to the individual exposure via drinking water, reports have shown a high daily intake of aluminium (>0.1 mg/day) to be significantly associated with an increased risk of dementia. Conversely, a concomitant intake of aluminium with an increase of 10 mg/day in silica intake via drinking water was associated with a reduced risk of dementia (Rondeau et al. 2009).

Until the early 1980s aluminium in the dialysate appeared to be the major source of the metal in chronic renal failure patients who developed aluminium toxicity (Wills and Savory, 1985). As at that time adequate water purification systems were not available in all dialysis units, the aluminium concentration of the dialysate depended primarily on the aluminium concentration of the water with which it was prepared; whether further enriched with aluminium-contaminated chemicals or not in the concentrates which are added to the water to prepare the final dialysis fluids (D'Haese et al. 1990). With the introduction of modern water purification systems in the dialysis centers the incidence of caricatural aluminium intoxication has now disappeared. Nevertheless, as the concentration gradient between the dialysate aluminium and the non-protein bound aluminium fraction (<20%) in the serum compartment is the driving force for aluminium transfer during hemodialysis, chronic accumulation in a patient with a serum aluminium concentration of e.g. 10 µg/L theoretically may still occur in the presence of a dialysate aluminium accumulation as low as 3 µg/L. Moreover, accidental intoxications cannot be excluded (Berend et al. 2004; D'Haese and De Broe 1999a).

In Curaçao, in order to protect a water distribution pipe supplying water to a dialysis center from corrosion, the pipe was internally lined with a cement mortar. Because of the aggressiveness of the distilled water, calcium and aluminium leached from the cement mortar into the water used to prepare dialysate causing a possible hard water syndrome and definite acute aluminium encephalopathy resulting in the death of 10 patients (Berend et al. 2001). In the South of Portugal, the low rainfall in the early 1990s resulted in a subsequent decrease in the available water sources resulting in high concentrations of suspended particles which in turn necessitated the addition of alum as a flocculating/coagulating agent. The passage of this contaminated water through the water purification installation of a hemodialysis center resulted in the obstruction of the cartridge filters and malfunction of the reverse osmosis membranes. Finally insufficiently treated water was sent via dialysis to the

patients. This led to acute aluminium intoxication, manifested by the epidemic appearance of encephalopathy, microcytic anemia and death of 18 patients (Barata et al. 1996; Simoes et al. 1994)

Importance of chemical speciation and effects on toxicity

Lanthanum

Substantial information exists on the aqueous chemistry and speciation of the REE/lanthanides. Geochemical modelling with the chemical equilibrium model MINEQL+ indicated that dissolved lanthanides (Ln) are complexed mainly to carbonates and dissolved organic matter. In the aqueous phase, the relative abundance of the free ion, $LnCO_3^{2+}$, and humic complexes decreases from lanthanum to lutetium, whereas the relative abundance of $Ln(CO_3)_2^+$ increases (Moermond et al. 2001). As is the case for any element, the toxicity of lanthanum primarily depends on the inorganic salt (anion) with which it occurs, with LD_{50} values for oral doses in rats and mice varying between 2354 and > 10.000 mg/kg body weight for lanthanum chloride ($LaCl_3$) and lanthanum oxide (La_2O_3) respectively (Shimomura et al. 1980; Cochran et al. 1980). With regard to the use of LMB, concern has been raised regarding the potential for release of filterable lanthanum in lakes and surface waters and the potential unintended ecological implications of this release (Lürling and Tolman 2010; Spears et al. 2013). The speciation of filterable lanthanum ions is also important when considering the ecotoxicological impact and of all filterable lanthanum species (i.e. La^{3+}, $La(OH)^{2+}$, and $La(OH)_2^+$). The La^{3+} cation carries the greatest risk of biological effects (Das et al. 1988). In humans, once absorbed, lanthanum circulates >99.7% protein bound in plasma (Damment and Pennick 2007, 2008). High protein binding, to a certain extent, may explain (i) the low toxicity profile of lanthanum, as it is unlikely for the lanthanum-protein complex to cross the blood-brain barrier, incorporate in the calcified bone matrix or interfere with the various ionized calcium-regulated cell biological functions, and (ii) the almost unique biliary elimination of the element after transferrin-mediated endocytosis by the hepatocyte (Bervoets et al. 2009).

Aluminium

In the environment as well as in the human body aluminium occurs in various chemical species which have different physical, chemical and biological properties (Harris et al. 1996; Van Landeghem et al. 1998; Yokel and McNamara 2001). The chemical speciation of aluminium in drinking water is of particular interest, as the form of aluminium regulates its solubility, bioavailability and toxicity.

582 Absorption from the gut depends largely on the presence of complexing ligands, particularly carboxylic
583 acids, with which the metal can form absorbable neutral aluminium species.

584 One factor determining the form of aluminium in water is pH. In raw water with low concentrations of
585 dissolved organic compounds such as humic and fulvic acids, the dependence of dissolved aluminium
586 concentration on pH resembles a parabola with a sharp solubility minimum at around pH 6.5 (Driscoll
587 and Letterman 1995; Figure 1). The solubility of aluminium increases at lower pH owing to the
588 formation of $Al(OH)_2^+$, $Al(OH)^{2+}$ and $Al(H_2O)_6^{3+}$ - often abbreviated as Al^{3+} and sometimes referred to in
589 the literature as 'free' aluminium. The solid $Al(OH)_3$ is the predominant species between pH 5.2 and
590 8.8, whereas the soluble $Al(OH)_4^-$ predominates above pH 9 (Martell and Motekaitis 1989; Figure 1).

591 The form in which aluminium is present in drinking water is also dependent on whether the water is
592 fluoridated, as fluoride has a strong affinity for aluminium, particularly under acidic conditions (Nieboer
593 et al. 1995). When alum is added to raw water for treatment, the form of aluminium changes along a
594 number of pathways, depending on the quantity of alum added, the temperature, the pH, the types
595 and concentrations of dissolved materials as well as the types and surface area of particulate matter
596 present (Driscoll and Letterman 1988).

597 Concomitant intake of aluminium hydroxide with citrate has been demonstrated to increase
598 gastrointestinal absorption of the element which was reported to occur in the proximal bowel via the
599 paracellular pathway due to the ability of citrate to open the epithelial tight junctions (Froment et al.
600 1989). On the other hand, dissolved silicon has been regarded as an important factor in limiting the
601 absorption of dietary aluminium (Edwardson et al. 1993; Parry et al. 1998). Once absorbed in the
602 serum compartment, aluminium strongly binds to proteins mainly transferrin, the remaining
603 ultrafiltrable fraction to circulate as either bound to phosphate or citrate. Within the serum
604 compartment it has been demonstrated that aluminium may compete with iron for transferrin binding,
605 which to a certain extent also determines the tissue deposition and toxicity of aluminium (Van
606 Landeghem et al. 1997, 1998a; Smans et al. 2000). In contrast to the serum compartment in the brain
607 aluminium occurs as a non-protein bound, low molecular mass, probably silicate compound. This latter
608 finding is supported by the high molar ratio of both citrate/transferrin and silica/transferrin in
609 cerebrospinal fluid. The occurrence of 'free' aluminium might also explain the element's high toxicity at
610 very low concentrations and gives rise to a hypothesis to explain discrepancies in the neurotoxic
611 effects of aluminium in dialysis dementia and Alzheimer's disease (Van Landeghem et al. 1997a).

612 **Exposure pathways – practical considerations**

613 Application of either lanthanum- or aluminium-containing compounds to natural waters to reduce the
614 concentration of dissolved phosphorus will result in a range of potential exposure pathways to in-situ
615 and transient biota and humans over a range of temporal (including acute and chronic exposure) and
616 spatial scales. We consider the main exposure routes for humans to lanthanum or aluminium in
617 treated waterbodies to be through drinking treated water, consuming biota (e.g. crustaceans, fish and
618 plants), dermal exposure via water or sediment and through the inadvertent consumption of sediments
619 particularly in young children. We describe the likelihood of human health effects associated with
620 realistic exposure rates below for lanthanum and aluminium.

621 **Water**

622 During application of LMB the maximum reported total and filterable lanthanum concentrations in the
623 surface water of 16 treated lakes were up to 2.3 mg/L and 0.4 mg/L, respectively (Spears et al. 2013).
624 Smeltzer et al. (1999) reported dissolved aluminium concentrations in Lake Morey (USA) of up to 0.2
625 mg/L. Reitzel et al. (2013) determined experimentally that dissolved aluminium concentrations may
626 reach 0.85 mg/L following an application, as a result of diffusion from bed sediments back to the water
627 column following settlement. Wauer and Teien (2010) reported maximum concentrations of reactive
628 aluminium of 2.0 mg/L in field observations. Given that lanthanum as lanthanum carbonate when used
629 therapeutically (Fosrenol®, Shire Pharmaceuticals) is administered at doses up to 1500 mg per day
630 (~900 mg lanthanum/day) without toxicity to the patients after up to 10 years of treatment (Hutchison
631 et al. 2016), consumers would have to consume at least 390 L of the surface water per day to attain a
632 similar, nominally safe dose. Using the highest application dose of 333 mg/L LMB (Spears et al. 2013)
633 a consumption of 54 L is needed to attain a dose of 900 mg lanthanum. It is likely that in the absence
634 of episodic resuspension, the highest risk of exposure will occur within the following few days to
635 weeks.

636 **Sediment**

637 Following settling of the applied phosphorus removal agent, the bed sediments are the location of
638 treated waterbodies where lanthanum concentrations are highest following an application.
639 Consumption of these sediments, although unlikely, may be considered, for example, playing children
640 may express some geophagia, whereas pica disorder may result in considerable consumption of soil

641 material (Rose et al., 2000). Soil pica is referred to as eating 500 mg to more than 50 g of soil per day
642 (Callahan, 2003). Using the data presented in Table 2 in Spears et al. (2013) an average dose of 348
643 g LMB/m^2 (range 6-667) is derived. With an assumed maximum 5% weight of lanthanum in LMB this
644 makes an average of 17.4 g lanthanum/m^2 (range 0.3-33.3) or 1.74 mg lanthanum/cm^2. Using the data
645 presented by Reitzel et al. (2013) applied aluminium concentrations in bed sediments may reach 54 g
646 aluminium/m^2, although Wauer and Teien (2010) report sediment aluminium concentrations of up to
647 200 g aluminium/m^2. Assuming a specific density of 1 g/cm^3 and a thickness of 1 cm, a person would
648 need to consume 860 g of sediment to reach a nominally safe dose of 1500 mg lanthanum, or 450 g
649 using the highest lanthanum application dosing (3.33 mg lanthanum/cm^2).

650 Based on the Tolerable Weekly Intake (TWI) of 1 mg aluminium per kg body-weight as proposed by
651 the European Food and Safety Authority (2008), a 60 kg person would need to eat 3 to 11 g of
652 sediment following sediment aluminium content of Reitzel et al (2013a) and Wauer and Teien (2010),
653 respectively, to reach this TWI.

654 **Crustaceans**

655 Accumulation of lanthanum in the crustacean zooplankton *Daphnia magna* has been observed (Yang
656 et al., 1999), yet these small animals are not directly consumed by humans. Nonetheless, they may
657 provide a food chain vector of transmission via fish that may predate heavily on zooplankton. The most
658 obvious human exposure route is via bottom dwelling crustaceans, such as crayfish that may be
659 exposed for prolonged periods to relatively high concentrations of LMB. In Lake Rauwbraken (The
660 Netherlands) the lanthanum concentration in the flesh of crayfish (*Orconectes limosus*) increased from
661 0.12 ± 0.05 μg lanthanum/g dry-weight before application to 89 ± 42 μg lanthanum/g dry weight in
662 animals caught 4months after application and 37 ± 13 μg lanthanum/g dry weight in animals collected
663 14 months after treatment. In practical terms, this means that a person would have to consume daily
664 10 kg of crayfish with 89 μg lanthanum/g and 24 kg of crayfish with 37 μg lanthanum/g to reach the
665 recommended therapeutic prescription dose of lanthanum carbonate. In a controlled laboratory
666 experiment, exposure of marbled crayfish (*Procambarus fallax* f. *virginalis*) to 67 g LMB/m^2 led to a
667 maximum lanthanum concentration in the flesh of 13.6 μg lanthanum/g dry weight (Van Oosterhout et
668 al. 2014). Consequently, a daily consumption of 66 kg crayfish would equal the safe recommend
669 therapeutic dose of Fosrenol®. It should be noted that the lanthanum concentration is expressed per

unit dry-weight that only constitutes approximately 17% of the live-weight and thus daily crayfish consumption would need to be almost 390 kg to attain the nominally safe adult medication dose.

Data on aluminium concentrations in crustacea are sparse in relation to whole lake applications. However, Elangovan et al. (1999) reported uptake of aluminium into in the aquatic isopod *Asellus aquaticus* to reach about 2.4 mg aluminium/g dry weight and that aluminium uptake into tissue of the animal can be explained through a significant linear regression relationship with the aluminium concentration in the water column.

Fish

Data on La concentrations in edible fish parts after LMB applications are rare. Some lanthanum accumulation in the liver and hepatopancreas of fish collected from Lake Okareka (New Zealand) has been reported, while lanthanum in the flesh of trout and koura remained below the level of detection (Landman et al., 2007). Lanthanum concentrations in the livers of eel caught two years after a whole lake treatment showed a 94 fold increase compared to pre-intervention liver concentrations and a 133 fold increase in eels caught five years later (Waajen et al., 2017). Elevated lanthanum concentrations were also found in the flesh of fish collected before and after a whole lake application in Lake De Kuil, The Netherlands (Waajen et al., 2016), and from LMB treated and control compartments constructed in urban ponds (Waajen et al., 2016a; Waajen et al., 2017).. In Lake De Kuil, prior to application, the mean lanthanum concentration in the flesh of the five most abundant fish species (bream, eel, perch, pike, tench) was 0.03 ± 0.02 μg lanthanum/g dry weight (Waajen et al., 2017). Two years after the LMB application at a dose of 593 g LMB/m^2 Waajen et al., 2016), the lanthanum concentration in the muscle tissue of these five species had increased to an average of 0.10 ± 0.05 μg lanthanum/g dry weight and after 5 years the lanthanum had returned to pre-application concentrations (0.03 ± 0.01 μg lanthanum/g dry weight) in specimens of these five fish species. In two urban ponds in The Netherlands 300 m^2 (pond Dongen) and 400 m^2 sized compartments (pond Eindhoven) were constructed of which some were treated with 750 g LMB/m^2 and 1130 g LMB/m^2, respectively (Waajen et al., 2016a). The muscle tissue of fish collected after two years in the LMB treated compartments in pond Dongen contained on average 0.22 ± 0.34 μg lanthanum/g dry weight, while that of non-LMB exposed fish was on average 0.06 ± 0.09 μg lanthanum/g dry weight. In pond Eindhoven, muscle tissue in LMB exposed fish was 0.07 ± 0.06 μg lanthanum/g dry weight, while that of non-LMB

699 exposed fish was 0.03 ± 0.02 μg lanthanum/g dry weight. Although lanthanum from LMB thus may
700 accumulate in fish and raised lanthanum concentrations have been reported up to five years following
701 treatment with the highest lanthanum concentration found in liver, no toxic effects were observed
702 following LMB bentonite treatments (Waajen et al., 2017).

703 Taking the highest flesh lanthanum concentrations measured of all examined fish (0.81 μg
704 lanthanum/g dry weight) a person would have to consume more than 1000 kg of fish per day to reach
705 the nominally safe recommended therapeutic dose of lanthanum in adults.

706 Wauer and Teien (2010) reported concentrations of aluminium in the gills of perch (*Perca fluviatilis*)
707 and ruffe (*Gymnocephalus cemuus*) up to about 100 μg aluminium/g dry weight and 401 μg
708 aluminium/g dry weight respectively, although no similar observations were reported for roach (*Rutilus*
709 *rutilus*), bream (*Abramis brama*), or silver carp (*Hypophthalmichthys molitrix*). Given the >100-fold
710 higher aluminium concentrations in combination with a 10-100 higher gastrointestinal absorption as
711 compared to lanthanum (see above) potential aluminium toxicity should be considered. In this context
712 it is worth to be mentioned that given the fact that aluminium is eliminated via the kidney, the risk for
713 toxic effects, even with this degree of exposure is rather limited in subjects with normal renal function.
714 Nevertheless regular monitoring of aluminium in the drinking water and consumable fish by water and
715 health authorities should be performed. In individuals with impaired renal function regularly consuming
716 local fish or water, serum aluminium measurement is recommended, particularly in patients presenting
717 with undefined bone and/or neurologic complaints or signs of anemia. Here the first line of therapy
718 should consist in the withdrawal of these sources of aluminium exposure.

719

720 **Plants**

721 Aquatic plants may take up lanthanum and a lanthanum bioaccumulation factor of 138 for duckweed
722 has been reported (Yang et al., 1999). The aquatic macrophyte *Elodea nuttallii* was harvested on
723 three occasions from the different compartments in the above-mentioned urban waters (Waajen et al.,
724 2016a). Samples consisting of the complete plants including the roots and shoots were analysed for
725 lanthanum (Waajen et al., 2017). The mean La concentration of *E. nuttallii* from control compartments
726 varied between 0.35 and 7.03 μg lanthanum/g dry weight at pond Dongen and between 0.14 and
727 13.53 μg lanthanum/g dry weight at pond Eindhoven, the stocking plant material at the start of the

728 experiment contained on average 7.50 µg lanthanum/g dry weight. The mean lanthanum
729 concentration of *E. nuttallii* from the LMB treated compartments reached up to 380 µg lanthanum/g at
730 pond Dongen and 871 µg lanthanum/g at pond Eindhoven. Although consumption of macrophytes by
731 humans is restricted to a few species (e.g., lotus, water chestnut, water caltrop, water spinach,
732 watercress) and *E. nuttallii* is normally not one of the consumed aquatic plants, a person still would
733 need to ingest 2.4 kg per day of dry plant equivalent from Dongen and 1 kg of dried plant equivalent
734 per day from pond Eindhoven to attain the nominally safe lanthanum dose recommended for
735 therapeutic purposes. Use of harvested LMB exposed plant material in fish feed (Hasan and
736 Chakrabarti, 2009) or cattle fodder (Banerjee and Matai, 1990; Goopy and Murray, 2003), however,
737 warrants caution as no information on the magnitude of possible La transfer and bioaccumulation
738 exists.

739 Data on macrophyte uptake of aluminium following a whole lake treatment do not appear to be
740 available in the peer reviewed literature. However, we draw here on data published by Goulet et al
741 (2005) on a series of phytoremediation mesocosm experiments (at water concentrations of up to 1 mg
742 total dissolved aluminium/L) in which aluminium uptake across 4 different macrophyte species (i.e.
743 *Potamogeton epihydrus, Nuphar variegatum, Lemna minor and Typha latifolia*) ranged between < 0.01
744 and 17.2 mg aluminium/g dry weight for root tissues; 0.34 and 1.44 mg aluminium/g dry weight for
745 stem tissues and 0.18 and 6.25 mg aluminium/g dry weight for leaf tissues.

746 **General conclusions**

747 • Because of their inherently strong phosphate binding capacity over a wide range, and mostly
748 overlapping set of physico-chemical conditions, application of aluminium- and lanthanum-
749 based compounds has proven to be efficacious for water treatment and therapeutic phosphate
750 control in uremic patients.
751 • Kinetics as well as mechanisms underlying the possible toxic effects of aluminium and
752 lanthanum substantially differ from each other
753 • Although aluminium and lanthanum have physicochemical similarities their aqueous chemistry
754 differs with hydrolysis of lanthanum occurring at substantially higher pH than that of aluminium
755 • The speciation, concentration and exposure pathways to living organisms of lanthanum and
756 aluminium is strongly dependent on pH and salinity

- The extent of lanthanum leached into LMB-treated water reported so far, do not exceed concentrations that might be considered harmful, however, considerable care in manufacture and quality control needs to be exercised to minimize risk to receiving aquatic environments.
- Regular monitoring of both aluminium and lanthanum concentrations in lanthanum-/aluminium-treated water by the responsible authorities is recommended to avoid accidental acute or chronic lower level exposure

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Exposure route	Upper concentrations reported	Period of effect	Reference	Likelihood of exceeding exposure limits	Severity of impact	Risk rating
Water column						
	0.4 mg FLa/L	< 12 months	Spears et al., 2013	Low	Mod-High	Low
	0.2 mg FAl/L	>30 days	Scmeltzer et al., 1999	Low	Mod-High	Low
Bed sediments						
	33.3 g La/m^2	Unknown	Spears et al., 2013	Low	Mod-High	Low
	200 g Al/m^2	Unknown	Wauer and Teien, 2010	Low	Mod-High	Low
Crustacea						
Orconectes limosus	131 µg La/g DW	>14 months		Low	Mod-High	Low
Asellus aquaticus	2400 µg Al/g DW	< 1 month	Elangovan et al., 1999	Low	Mod-High	Low
Fish						
Perca fluviatilis	0.56 µg La/g DW	5 years	Waajen et al., 2017	Low	Mod-High	Low
Gymnocephalus cemuus	401 µg Al/g DW	Unknown	Wauer and Teien, 2010	Low	Mod-High	Low
Plants						
Elodea nuttallii	871 µg La/g DW	Unknown	Waajen et al., 2017	Low	Mod-High	Low
Lemna minor	17 mg Al/g DW	Unknown	Goulet et al., 2005	Low	Mod-High	Low

Table 1. Maximum reported concentrations for lanthanum (La) and aluminium (Al) in various abiotic and biotic components of lakes following additions of LMB or aluminium containing salts or waste waters, where data from eutrophication control studies were not available in the peer reviewed literature.

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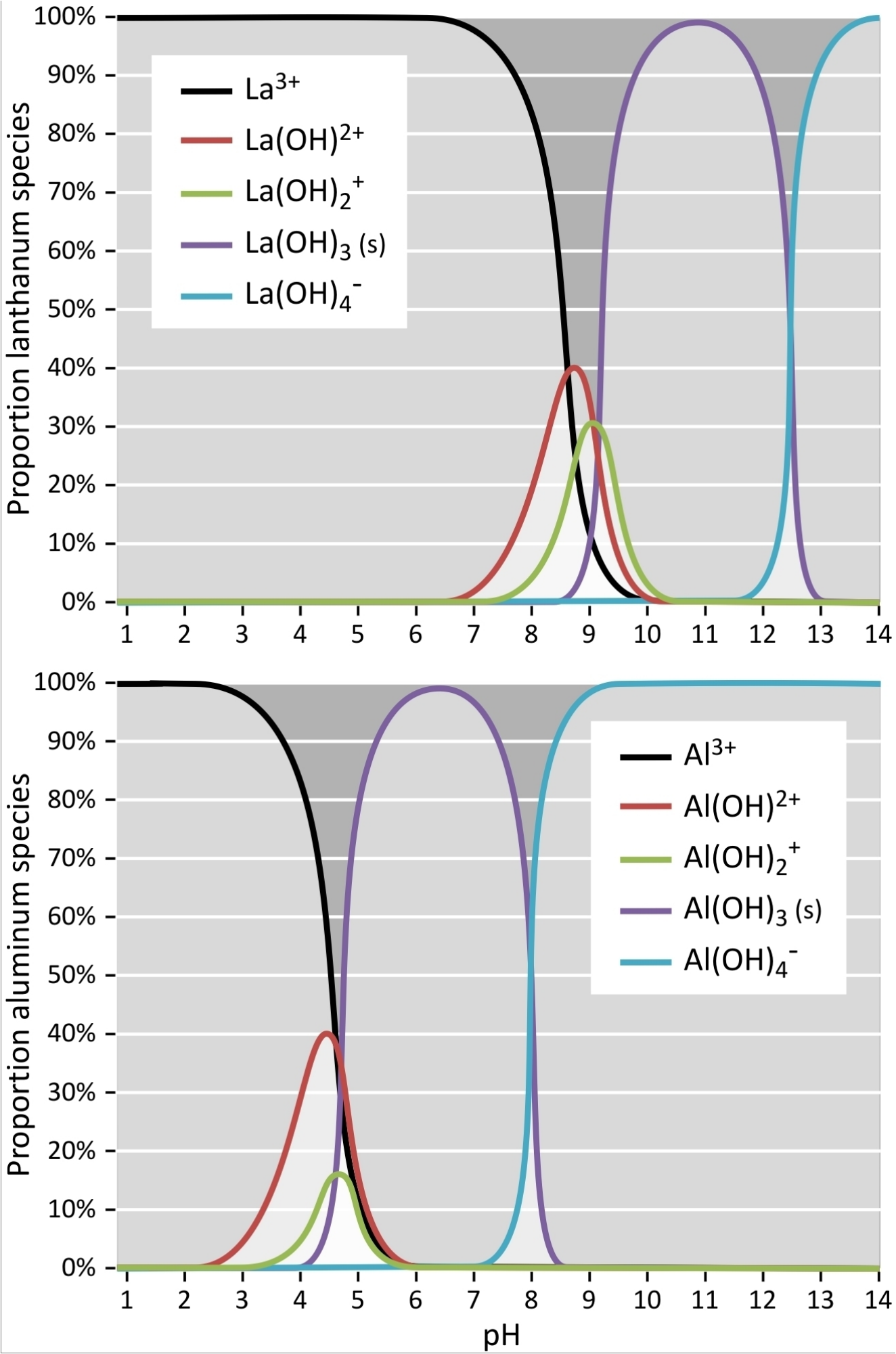
Legend to Figure

Effect of pH on the aqueous chemistry of lanthanum and aluminium. The speciation of lanthanum and aluminium was evaluated by chemical equilibrium modelling using the program CHEAQS Pro (release P2013.1; Verweij, 2013) in the pH range 1 – 14 with 1 µM La or Al and 1 mM NaCl. The five most prominent species are presented.

Figure 1. Lanthanum and aluminium speciation as a function of pH in the systems La-H_2O and Al-H_2O.

Highlights

- Geo-engineering materials containing La and Al used to manage P in lakes
- Potential impact of the use of these compounds on human health is of interest
- La and Al uptake, kinetics and toxicity profile differ within the humans and organisms
- Monitoring of La and Al is recommended to avoid acute and chronic exposure.


Proportion lanthanum species
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1
2
3
4
5
6
7
8
9
10
11
12
13
14
La3+
La(OH)2+
La(OH)2+
La(OH)3 (s)
La(OH)4-
Proportion aluminum species
Al3+
Al(OH)2+
Al(OH)2+
Al(OH)3 (s)
Al(OH)4-
pH