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

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

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24

**25 Abstract**

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

44

**45 Highlights**

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

50

**51 Keywords**

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

53

54 **Introduction**

55 *Aluminium* is a ubiquitous substance encountered both naturally (as the third most abundant element)  
56 and intentionally (used in water treatment, foods, pharmaceuticals, and vaccines); it is also present in  
57 ambient and occupational airborne particulates. Existing data underscore the importance of the  
58 physicochemical characteristics of aluminium in relation to its uptake, accumulation, and systemic  
59 bioavailability (Van Landeghem et al. 1997; Willhite et al. 2014). Aluminium has been shown to have  
60 the potential to be a toxicant to the central nervous, skeletal and hematopoietic systems. This is most  
61 prevalent through exposure to aluminium-contaminated dialysis and intravenous fluids and oral  
62 consumption of large amounts of aluminium-containing antacids and phosphate binders, especially in  
63 patients with impaired renal function. Although caricatural aluminium overload, reflected by blood and  
64 tissue levels being up to 1000 times higher compared to those currently observed has now  
65 disappeared, data in the literature suggest that low level exposure to aluminium via drinking water in  
66 individuals with normal renal function may be a contributing factor in the development of Alzheimer's  
67 disease and related disorders (Yokel and McNamara 2000, Bondy 2016). With regard to drinking  
68 water exposure, an important question is whether the aluminium is derived from natural sources for  
69 instance from ingestion of clay minerals (geophagia) or as a consequence of water treatment  
70 methods. Water treatment using aluminium sulphate, i.e. alum, generally increases the percentage of  
71 dissolved, low molecular weight, (poly) aluminium species that are chemically reactive and possibly  
72 more readily absorbed, especially when used in lakes with low to moderate alkalinity (Cooke et al.  
73 1993; Stevenson and Vance 1989; Yokel and McNamara, 2000).

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

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

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

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

111 **General aspects**

**112 Occurrence and exposure of lanthanum**

113 Lanthanum, a member of the element group called rare earth elements (REE) or lanthanides, is  
114 relatively common in the earth's crust. Its abundance may be as high as 18 parts per million (Redling  
115 2006), making it nearly as common as copper or zinc. Lanthanum is widely dispersed throughout the  
116 earth's crust, most commonly occurring in REE minerals such as monazite and bastnasite. These  
117 minerals generally contain all of the other REE, often in variable abundance. Reports on  
118 environmental pollution by lanthanum are scarce and mainly originate from particular regions in China  
119 (Zhao et al. 2013). The element, lanthanum, is increasingly used in industrial applications with some  
120 of its compounds being used in lamps, color televisions, cigarette lighters, optical fibers and hybrid  
121 engines (Behets 2005; Das et al. 1988). According to a recent survey, the annual production of  
122 lanthanum was 12,500 tonnes worldwide (Hague et al., 2014). Plants generally do not accumulate  
123 lanthanum, although in some instances, accumulation of REE has been described for tea, cucumber,  
124 maize and pine leaves (Xu et al. 2003). Mosses and lichen generally contain the highest lanthanum  
125 concentrations (up to 100 ppm) (Behets 2005, Das et al. 1988; Xu et al. 2012).

**126 Occurrence and exposure of aluminium**

127 Aluminium (Al) is the most abundant metallic element within the lithosphere, occurring at about 8% by  
128 weight (so over 4000 times more enriched relative to lanthanum) and the third most abundant element  
129 preceding iron (4.7%) but less abundant than oxygen and silicon. Aluminium exists primarily  
130 associated with silicates and oxides in minerals of low solubility, explaining the low (generally <1 mg/L)  
131 dissolved aluminium concentrations detected in rivers, lakes and sea water (Gensemer and Playle  
132 1999). Nevertheless, reports in the early 1980s pointed towards acidification of lakes as a result of  
133 acid rain thereby enhancing aluminium solubility below pH 6 and hence toxicity for fish and other biota  
134 including birds living in the immediate surroundings (Van Landeghem 1997).

135 Today the daily ingested dose via drinking water is estimated to be around 160 µg aluminium/day  
136 (Willhite et al. 2014). Thanks to governmental efforts to reduce the release of sulphur dioxide (SO<sub>2</sub>)  
137 into the atmosphere emissions in the US and Europe dropped 40% and 70% respectively since the  
138 1990s whilst according to the Pacific Research Institute, acid rain levels have dropped 65% since  
139 1976 ([http://en.wikipedia.org/wiki/Acid\\_rain](http://en.wikipedia.org/wiki/Acid_rain)). Human activities have also changed exposure of living  
140 organisms to aluminium in other ways since it is widely used in transportation, packaging,

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

#### 155 ***Aqueous chemistry of lanthanum***

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

171 chemical equilibrium modelling, but also has been found in sediments of 10 treated lakes across  
172 Europe (Dithmer et al. 2016). Given that rhabdophane is extremely stable and will not “separate”, the  
173 equilibrium is de facto a precipitation reaction. Consequently, any phosphate bound to lanthanum can  
174 be viewed as permanently removed from the biogeochemical cycling. An example of this is the  
175 persistence of  $\text{LaPO}_4$  minerals in the weathering cycle that may span millions of years.

### 176 ***Aqueous chemistry of aluminium***

177 Aluminium (Al), electron configuration (Ne)  $3s^2 3p^1$ , molecular mass 26.98, exists exclusively in the  
178 trivalent oxidation state. It is amphoteric, combining with both acids and bases to form, respectively,  
179 aluminium salts and aluminates. As it combines a relatively small ionic radius (0.54 Å) with a high  
180 charge the free  $\text{Al}^{3+}$  concentration in aqueous solutions is very low due to the formation of aluminium  
181 hydroxide complexes. The chemical nature of aluminium in water is essentially the chemistry of  
182  $\text{Al}(\text{OH})_3$  which has an amphoteric character and a tendency to form complex ions and to polymerize.  
183 Evidence has been provided by chemical modelling that in solutions with a pH below 5, aluminium  
184 exists predominantly as  $\text{Al}(\text{H}_2\text{O})_6^{3+}$ , with rising pH an insoluble  $\text{Al}(\text{OH})_3$  complex forms at circumneutral  
185 pH, which re-dissolves at higher pH as the  $\text{Al}(\text{OH})_4^-$  (aluminate) complex (Figure 1) (Anderson and  
186 Berkowitz 2010; Gensemer and Playle 1999; Reitzel et al. 2013). Importantly, the speciation of  
187 aluminium is remarkably similar to that of lanthanum, albeit with the majority of similar Al-OH species  
188 offset by 4-5 pH units lower (Figure 1). In lake restoration, aluminium is used as a coagulant to settle  
189 particulate matter, to complex with water column and sediment released phosphate (Cooke et al.  
190 1993). The chemistry of aluminium is complex, as hydrolysis of aluminum is pH and temperature  
191 dependent, and amorphous aluminium hydroxide, bayerite, gibbsite with attached phosphates may  
192 form. These forms may either lose some of the attached phosphates or lose binding capacity  
193 because (i)  $\text{Al}(\text{OH})_3$  begins to crystallize after forming (Berkowitz et al. 2006; de Vincente et al. 2008),  
194 (ii) are stable over a smaller pH range compared to  $\text{LaPO}_4$ , but are just like lanthanum in that they are  
195 redox insensitive. Under high phosphate conditions minerals such as variscite ( $\text{AlPO}_4 \cdot 2\text{H}_2\text{O}$ ) and  
196 kingite ( $\text{Al}_3(\text{PO}_4)_2(\text{OH})_3 \cdot 9\text{H}_2\text{O}$ ) may be formed.

### 197 **Metabolism**

#### 198 ***Inhalation of lanthanum.***



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

#### 206 ***Inhalation of aluminium***

207 Aluminium workers can encounter a mixture of aluminium fumes and inhalable (aerodynamic diameter  
208  $<100\mu\text{m}$ ), thoracic ( $<28\mu\text{m}$ ), and respirable ( $<10\mu\text{m}$ ) aluminium particles in the occupational  
209 environment (Willhite et al. 2014). A fraction of the aluminium present in dust remains indefinitely in  
210 the lungs after inhalation, thus without entering systemic blood circulation. Hence, unlike other tissue  
211 stores of aluminium, concentrations in the lung increase with age (Han et al. 2004).

#### 212 ***Ingestion and gastrointestinal absorption of lanthanum***

213 Lanthanum, as all lanthanide elements, forms soluble chlorides and nitrates, but their phosphates and  
214 carbonates are generally insoluble and therefore have a low potential for systemic absorption. Studies  
215 have shown that oral doses of lanthanum are only minimally absorbed from the gut. When given as  
216 lanthanum carbonate to rats, the oral bioavailability was 0.0007% (Damment and Pennick 2007) whilst  
217 in humans the average systemic bioavailability across different studies was  $0.00089 \pm 0.00084\%$   
218 ( $n=25$ ) with the highest bioavailability in any subject being 0.00294%. No clear differences in  
219 bioavailability were seen between healthy volunteers and dialysis patients, i.e. the target population for  
220 phosphate binding treatment with lanthanum carbonate (Damment and Pennick 2008; Pennick et al.  
221 2006;).

#### 222 ***Ingestion and gastrointestinal absorption of aluminium***

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

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

### 236 ***Lanthanum in blood/plasma***

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

### 244 ***Aluminium in serum/plasma***

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

249  $< 30 \mu\text{g/L}$ : aluminum-related bone disease is unlikely but possible particularly when patients are iron-  
250 overloaded

251  $30-60 \mu\text{g/L}$ : aluminum-related bone disease is quite possible, especially if serum parathyroid hormone  
252 (PTH) levels are low or low-normal

253  $> 60 \mu\text{g/L}$ : aluminum-related bone disease is probable, but not invariably present, especially if serum  
254 PTH levels are high, iron-transferrin saturation is low.

255  $> 100 \mu\text{g/L}$ : aluminum-related bone disease is most probable unless patients are iron deficient.

256 Neurologic disorders should be checked for by taking the patients' electroencephalogram.

257 Whilst in the past values up to  $>500 \mu\text{g/L}$  were seen in uremic patients treated with aluminium-  
258 containing phosphate binders either in combination with aluminium-contaminated dialysis fluids or not,  
259 nowadays with the introduction of aluminium-free medication and high performance water treatment  
260 systems concentrations above  $10 \mu\text{g/L}$  are rarely seen. The majority (80-90%) of aluminium in serum  
261 is bound to transferrin which can accommodate two aluminium ions, the first at the C-lobe and the  
262 second at the N-lobe (Mujika et al. 2012), and is considered the most important, if not the sole, carrier  
263 protein of the element in plasma (Van Landeghem et al. 1994, 1998) with the remainder fraction  
264 bound to low molecular mass compounds. Hence, it is not surprising that the protein bound fraction is  
265 influenced by the iron status; i.e. iron-transferrin saturation, as both elements compete for binding to  
266 transferrin (Van Landeghem et al. 1997). This implies that when iron-transferrin saturation is high there  
267 is less binding of aluminium to transferrin, hence, more non-protein bound aluminium, i.e. free  
268 aluminium in circulation which thus becomes available (i) for being deposited in the calcified bone  
269 compartment thereby impairing bone mineralisation, (ii) to pass the blood brain barrier by which it may  
270 induce deleterious neurological effects. On the other hand when iron transferring saturation is low,  
271 more aluminium will bind to transferrin which however may be taken up by the parathyroid gland  
272 through transferrin-mediated endocytosis which in turn may lead to a decreased PTH  
273 secretion/synthesis, hence hypoparathyroidism ensuing in the so-called adynamic or low turn-over  
274 bone disease (D'Haese 1988; Smans et al., 2000; Van Landeghem et al., 1997 & 1998a).  
275 Once bound to transferrin, studies from Mujika et al. (2012) revealed that conformational changes  
276 under conditions where Tyr188 is protonated permit aluminium release from the protein.

#### 277 ***Tissue distribution of lanthanum***

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

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

### 293 ***Tissue distribution of aluminium***

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

### 308 ***Elimination of lanthanum***

309 The kidneys are responsible for eliminating only a very small fraction of systemic lanthanum which  
310 also explains the lack of appreciable plasma lanthanum concentrations over time in uremic patients.  
311 Following intravenous administration of lanthanum chloride to rats, biliary excretion was the  
312 predominant route of elimination, with 85.6% of recovered lanthanum collected from bile over a period  
313 of 5 days. Experimental studies presented evidence for lanthanum to be transported and eliminated by  
314 the liver via a transcellular, endosomal-lysosomal-biliary canicular transport route (Bervoets et al.  
315 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  $\pm 10\%$  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

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

### 354 ***Aluminium***

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

375 much attention has been paid to the potential neurotoxic effects of aluminium in humans and  
376 numerous groups assessed the aluminium content in the brain of subjects with various neurological  
377 disorders, in particular those with Alzheimer disease as well as non-affected individuals. Most of these  
378 data have been summarized by Exley and House (2011) reporting a normal range between 0.1 and  
379 4.5  $\mu\text{g/g}$  dry weight with the higher values ( $>2$   $\mu\text{g/g}$  dry weight) in brains of non-demented elderly,  
380 Alzheimer patients (up to 11.5  $\mu\text{g/g}$  dry weight), dialysis encephalopathy (up to 14.1  $\mu\text{g/g}$  dry weight –  
381 see below also), congophilic amyloid angiopathy (up to 23.0  $\mu\text{g/g}$  dry weight) and other  
382 encephalopathies (up to 47.4  $\mu\text{g/g}$  dry weight). Despite these numerous data the question as to  
383 whether in the general population, aluminium exposure is either the cause, a potential contributor to  
384 the onset, progression and aggressiveness, or increased concentrations in the brain are the  
385 consequence of the neurological condition itself, with exception to dialysis encephalopathy, has been  
386 a matter of debate for many years (Kawahara et al. 2011; Martyn et al. 1989; Willhite et al. 2014).

### 387 ***Therapeutic use***

#### 388 ***Lanthanum***

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

405 bone, lanthanum could be localized at sites of active as well as non-active bone  
406 remodeling/mineralization with no association between histological deposition sites and the typical  
407 bone pathologies observed in renal failure (Behets et al. 2005c). As mentioned above, in the liver the  
408 localization of the element is lysosomal whilst lanthanum treatment during 20 weeks at a daily 1000  
409 mg/kg/day dose was not accompanied by an increased concentration of liver enzymes (Yang et al.  
410 2006; Bervoets et al. 2009). Following gavage (863 mg/kg/day during several weeks) or intravenous (a  
411 route enabling >300-fold higher plasma lanthanum concentrations) administration (0.03 mg/kg/day) of  
412 lanthanum, median brain concentrations remained near the lower limit of quantification (2.4 ng/g). This  
413 together with data from ultrastructural studies thus provide strong evidence that lanthanum does not  
414 cross the blood-brain barrier (Damment et al. 2009). In patients, lanthanum carbonate monotherapy  
415 was effective and well tolerated for up to 6 years with no evidence of safety concerns or increased  
416 frequency of adverse events (Hutchison et al. 2008). A 2-year follow up study in hemodialysis patients  
417 indicated that lanthanum carbonate as a phosphate binder did not adversely affect cognitive function  
418 compared with standard therapy (Altmann et al. 2007) whilst a bone-biopsy based study in dialysis  
419 patients receiving a median daily dose of 1250 mg elemental lanthanum/day showed an evolution  
420 towards normal bone histology and absence of aluminium-like effects (see below) on bone after 1-year  
421 treatment (D'Haese et al., 2003).

## 422 ***Aluminium***

423 Being widely used in the past, aluminium hydroxide has proven to be a highly effective phosphate  
424 binder. Its substantial gastrointestinal absorption and renal route of elimination however posed its  
425 target population for therapeutic use to an increased risk of accumulation. In the past aluminium-  
426 phosphate binder treatment, in particular when used in combination with aluminium-contaminated  
427 dialysis fluids (see below) led to the development of severe side-effects, mainly in the bone and brain.  
428 In bone, aluminium accumulates at the osteoid calcification front, a critical site of bone mineralization  
429 which at high exposure leads to the so-called aluminium-induced osteomalacia, a disease manifested  
430 by recurrent fractures and resistance to vitamin D therapy (Goodman 1985; Verbueken et al. 1984).  
431 This type of bone disease is characterized by an increased amount of osteoid due to a defective  
432 mineralization. Another type of aluminium-related bone disease is adynamic bone characterized by a  
433 dramatically reduced bone turn-over, and absence of osteoblasts, osteoclasts and osteoid (Goodman  
434 1985). Aluminium is unquestionably neurotoxic in patients treated by dialysis. The so-called dialysis



435 encephalopathy syndrome, the result of acute intoxication of aluminium caused by the use of an  
436 aluminium-containing dialysate, was a common occurrence prior to 1980 (Rob et al. 2001; Ward et al.  
437 1978). Although with the introduction of modern techniques of water purification, acute intoxication can  
438 now be avoided, occurrences of aluminium intoxication may still occur (D'Haese and De Broe, 1996;  
439 Simoes et al., 1994;), and chronic moderately elevated concentrations may still be seen in dialysis  
440 centres in particular regions (Hou et al. 2010). The neurologic symptoms may be precipitated by  
441 concomitant ingestion of aluminium-containing phosphorus binders and citrate (D'Haese and De Broe,  
442 2007). Onset or exacerbation of neurological disorders has been observed during deferoxamine  
443 therapy, presumably because of redistribution of mobilized deferoxamine-bound aluminium into the  
444 brain (Barata et al. 1996). Main symptoms are speech disturbances, tremor, epilepsy and an altered  
445 electroencephalopathic pattern while the serum aluminium concentrations usually exceed 100 µg/L  
446 (Van Ginkel 1991). The disease progresses and ends mostly with the death of the patient within one  
447 year of initial symptoms. Although with the replacement of aluminium-based phosphate binders and  
448 adequate monitoring of dialysis fluids the major clinical manifestations have now disappeared,  
449 aluminium has also been implicated in more subtle diseases, such as microcytic hypochromic anemia,  
450 resistance to erythropoietin treatment and suppression of parathyroid hormone secretion. With regard  
451 to the latter, an increased effect of aluminium has been reported in the presence of a relative iron  
452 deficiency (Smans et al. 2000; Van Landeghem et al. 1997). Comparing different tissues of aluminium-  
453 intoxicated uremic patients, however, the relation between aluminium overload and toxicity is not  
454 straightforward. Whilst bone aluminium concentrations in aluminium-related bone disease, are  
455 distinctly elevated, comparable or even higher liver aluminium concentrations are seen without any  
456 apparent toxicity in humans. On the contrary, aluminium toxicity has been demonstrated in the brain at  
457 concentrations below 3 µg/g wet weight. This discrepancy points to the importance of the  
458 ultrastructural/subcellular localization of the element which determines its potential interference with  
459 physiological processes (Verbueken et al. 1984).

#### 460 **Potential exposure routes in water treatment**

##### 461 ***Lanthanum exposure and toxicity***

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

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

480 Data from experimental studies where lanthanum was given as lanthanum chloride in drinking water to  
481 rats and mice suggested neurobehavioral impairment, although a clear dose-response relationship is  
482 often lacking (Briner et al. 2000; Damment 2007a; Feng et al. 2006, 2006a; He et al. 2008; Yang et al.  
483 2013; Zarros et al. 2013). Given (i) the maximal amounts at which lanthanum is leached into the water  
484 following application of LMB to surface waters either as filterable lanthanum (nominally  $<0.2$  or  $0.45$   
485  $\mu\text{m}$ ), or total lanthanum or predicted 'free' (uncomplexed) ionic lanthanum ( $0.026$  mg/L to  $2.30$  mg/L;  
486  $0.002$  mg/L to  $0.14$  mg/L and  $<0.0004$  mg/L to  $0.12$  mg/L respectively) (Spears et al. 2013), (ii) the  
487 duration and magnitude of exposure to lanthanum-treated water, (iii) the ability of 'free' lanthanum to  
488 directly bind phosphate and other oxyanions in the intestine resulting in a low bioavailability and, (iv)  
489 the absence of significant toxic effects when used therapeutically during years at doses up to 3000 to  
490 5000 times higher than those seen in lanthanum-treated water, one may reasonably accept that  
491 exposure to lanthanum via the drinking water or leisure activities will pose no increased risk for toxicity  
492 in humans even in patients with impaired renal function as biliary excretion is the major route of  
493 elimination of lanthanum. Nevertheless, when using lanthanum treated water to prepare dialysis fluids,  
494 even in dialysis centers equipped with the highest standards of water purification (carbon filtration,

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

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

#### 504 ***Aluminium exposure and toxicity***

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

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

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

524 risk of Alzheimer's disease, with relative risks or odds ratios ranging from 1.35 to 2.67 (Gauthier et al.  
525 1999; Martyn et al. 1989; Rondeau et al. 2000).

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

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

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

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

### 555 **Importance of chemical speciation and effects on toxicity**

#### 556 ***Lanthanum***

557 Substantial information exists on the aqueous chemistry and speciation of the REE/lanthanides.  
558 Geochemical modelling with the chemical equilibrium model MINEQL+ indicated that dissolved  
559 lanthanides (Ln) are complexed mainly to carbonates and dissolved organic matter. In the aqueous  
560 phase, the relative abundance of the free ion,  $\text{LnCO}_3^{2+}$ , and humic complexes decreases from  
561 lanthanum to lutetium, whereas the relative abundance of  $\text{Ln}(\text{CO}_3)_2^+$  increases (Moermond et al.  
562 2001). As is the case for any element, the toxicity of lanthanum primarily depends on the inorganic salt  
563 (anion) with which it occurs, with  $\text{LD}_{50}$  values for oral doses in rats and mice varying between 2354  
564 and  $> 10.000$  mg/kg body weight for lanthanum chloride ( $\text{LaCl}_3$ ) and lanthanum oxide ( $\text{La}_2\text{O}_3$ )  
565 respectively (Shimomura et al. 1980; Cochran et al. 1980). With regard to the use of LMB, concern  
566 has been raised regarding the potential for release of filterable lanthanum in lakes and surface waters  
567 and the potential unintended ecological implications of this release (Lüring and Tolman 2010; Spears  
568 et al. 2013). The speciation of filterable lanthanum ions is also important when considering the  
569 ecotoxicological impact and of all filterable lanthanum species (i.e.  $\text{La}^{3+}$ ,  $\text{La}(\text{OH})_2^+$ , and  $\text{La}(\text{OH})_2^+$ ). The  
570  $\text{La}^{3+}$  cation carries the greatest risk of biological effects (Das et al. 1988). In humans, once absorbed,  
571 lanthanum circulates  $>99.7\%$  protein bound in plasma (Damment and Pennick 2007, 2008). High  
572 protein binding, to a certain extent, may explain (i) the low toxicity profile of lanthanum, as it is unlikely  
573 for the lanthanum-protein complex to cross the blood-brain barrier, incorporate in the calcified bone  
574 matrix or interfere with the various ionized calcium-regulated cell biological functions, and (ii) the  
575 almost unique biliary elimination of the element after transferrin-mediated endocytosis by the  
576 hepatocyte (Bervoets et al. 2009).

#### 577 ***Aluminium***

578 In the environment as well as in the human body aluminium occurs in various chemical species which  
579 have different physical, chemical and biological properties (Harris et al. 1996; Van Landeghem et al.  
580 1998; Yokel and McNamara 2001). The chemical speciation of aluminium in drinking water is of  
581 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  $\text{Al}(\text{OH})_2^+$ ,  $\text{Al}(\text{OH})_2^{2+}$  and  $\text{Al}(\text{H}_2\text{O})_6^{3+}$  - often abbreviated as  $\text{Al}^{3+}$  and sometimes referred to in  
589 the literature as 'free' aluminium. The solid  $\text{Al}(\text{OH})_3$  is the predominant species between pH 5.2 and  
590 8.8, whereas the soluble  $\text{Al}(\text{OH})_4^-$  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<sup>2</sup> (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<sup>2</sup> (range 0.3-33.3) or 1.74 mg lanthanum/cm<sup>2</sup>. Using the data  
645 presented by Reitzel et al. (2013) applied aluminium concentrations in bed sediments may reach 54 g  
646 aluminium/m<sup>2</sup>, although Wauer and Teien (2010) report sediment aluminium concentrations of up to  
647 200 g aluminium/m<sup>2</sup>. Assuming a specific density of 1 g/cm<sup>3</sup> 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<sup>2</sup>).

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  $0.12 \pm 0.05$  µg lanthanum/g dry-weight before application to  $89 \pm 42$  µg lanthanum/g dry weight in  
662 animals caught 4 months after application and  $37 \pm 13$  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<sup>2</sup> 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



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

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

## 677 **Fish**

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

699 exposed fish was  $0.03 \pm 0.02 \mu\text{g}$  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 ( $0.81 \mu\text{g}$   
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  $100 \mu\text{g}$  aluminium/g dry weight and  $401 \mu\text{g}$   
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  $7.03 \mu\text{g}$  lanthanum/g dry weight at pond Dongen and between  $0.14$  and  
727  $13.53 \mu\text{g}$  lanthanum/g dry weight at pond Eindhoven, the stocking plant material at the start of the

728 experiment contained on average 7.50  $\mu\text{g}$  lanthanum/g dry weight. The mean lanthanum  
729 concentration of *E. nuttallii* from the LMB treated compartments reached up to 380  $\mu\text{g}$  lanthanum/g at  
730 pond Dongen and 871  $\mu\text{g}$  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

- 757 • The extent of lanthanum leached into LMB-treated water reported so far, do not exceed  
758 concentrations that might be considered harmful, however, considerable care in manufacture  
759 and quality control needs to be exercised to minimize risk to receiving aquatic environments.
- 760 • Regular monitoring of both aluminium and lanthanum concentrations in lanthanum-  
761 /aluminium-treated water by the responsible authorities is recommended to avoid accidental  
762 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
<b>Water column</b>						
	0.4 mg FLa/L	< 12 months	Spears et al., 2013	Low	Mod-High	Low
	0.2 mg FAI/L	>30 days	Scmeltzer et al., 1999	Low	Mod-High	Low
<b>Bed sediments</b>						
	33.3 g La/m <sup>2</sup>	Unknown	Spears et al., 2013	Low	Mod-High	Low
	200 g Al/m <sup>2</sup>	Unknown	Wauer and Teien, 2010	Low	Mod-High	Low
<b>Crustacea</b>						
<i>Orconectes limosus</i>	131 µg La/g DW	>14 months		Low	Mod-High	Low
<i>Asellus aquaticus</i>	2400 µg Al/g DW	< 1 month	Elangovan et al., 1999	Low	Mod-High	Low
<b>Fish</b>						
<i>Perca fluviatilis</i>	0.56 µg La/g DW	5 years	Waajen et al., 2017	Low	Mod-High	Low
<i>Gymnocephalus cemuus</i>	401 µg Al/g DW	Unknown	Wauer and Teien, 2010	Low	Mod-High	Low
<b>Plants</b>						
<i>Elodea nuttallii</i>	871 µg La/g DW	Unknown	Waajen et al., 2017	Low	Mod-High	Low
<i>Lemna minor</i>	17 mg Al/g DW	Unknown	Goulet et al., 2005	Low	Mod-High	Low

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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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1169 **Legend to Figure**

1170

1171 Effect of pH on the aqueous chemistry of lanthanum and aluminium. The speciation of lanthanum and  
1172 aluminium was evaluated by chemical equilibrium modelling using the program CHEAQS Pro (release  
1173 P2013.1; Verweij, 2013) in the pH range 1 – 14 with 1  $\mu\text{M}$  La or Al and 1 mM NaCl. The five most  
1174 prominent species are presented.

ACCEPTED MANUSCRIPT

Figure 1. Lanthanum and aluminium speciation as a function of pH in the systems La-H<sub>2</sub>O and Al-H<sub>2</sub>O.

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## 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.



