Monatsh Chem (2011) 142:331–340
DOI 10.1007/s00706-011-0474-x

REVIEW

Human diseases related to aluminium overload

Guido Crisponi · Valeria M. Nurchi · Gavino Faa · Maurizio Remelli

Received: 16 December 2010 / Accepted: 21 February 2011 / Published online: 22 March 2011

Abstract In this paper attention is devoted to the role of aluminium in osteodistrophy and dialysis dementia. In fact, these diseases, in spite of the actions that have drastically reduced their occurrence, have so far constituted a cause of great medical concern. As a preliminary point, some aspects concerning the solution chemistry of aluminium are considered, then the medical problems are described and finally the chelation therapy of aluminium overload, giving some insight on the chelators recently proposed.

Keywords Aluminium overload · Ligands · Metal complexes · Chelation therapy · Bioinorganic chemistry

Introduction

Aluminium was only recently recognised as a possible source of human intoxication: it was long considered a non-essential and non-toxic metal, and aluminium products have been widely used in all human activities. It was only in the 1970s of the last century that this metal was suspected to be the cause of different diseases [1–4], especially in patients undergoing dialysis treatment. Aluminium was also suggested to be involved in Alzheimer's disease on the basis of epidemiological data [5]. This hypothesis has been extensively discussed, and it is still controversial, but its treatment is beyond the scope of this paper.

In the following, much attention will be devoted to the role of aluminium in osteodistrophy and dialysis dementia. In fact, these diseases, in spite of the actions that have drastically reduced their occurrence, up to now have constituted a cause of great medical concern. As a preliminary point, some aspects concerning the solution chemistry of aluminium will be considered, before describing the medical problems and finally the chelation therapy of aluminium overload. Some insight into the recently proposed chelators in the literature will be given.

Aluminium applications

In spite of the wide use of aluminium in all human activities (more aluminium is produced today than all other non-ferrous metals put together) and of the fact that it is the third most abundant element in the earth's crust after oxygen and silicon, and the most abundant metal, it is a very "young" metal with respect to iron, copper, lead, and tin, which have been used by humans for thousands of years [6].

H. Davy established the existence of aluminium and named it only in 1808; in 1825, H.C. Oersted was the first to produce small quantities of metallic aluminium by reacting aluminium chloride with potassium amalgam and then distilling the mercury away to leave a residue of impure aluminium. The electrolytic process, still employed nowadays, was separately patented in 1886 in France and the USA by P.L. Heroult and C.M. Hall, respectively.

G. Crisponi (✉) · V. M. Nurchi
Dipartimento di Scienze Chimiche, University of Cagliari, Cagliari, Italy
e-mail: crisponi@unica.it

G. Faa
Dipartimento di Citomorfologia, Divisione di Anatomia Patologica, University of Cagliari, Cagliari, Italy

M. Remelli
Dipartimento di Chimica, University of Ferrara, Ferrara, Italy

Aluminium production, already 8,000 tons in 1900, has continuously been increasing, as well as its applications, which completely permeate our modern life, from automotive and aeronautic transport to packaging, construction, and spatial industries [7].

This metal clearly shows a probably unrivalled, versatile chemistry, leading to myriad applications in modern living [8, 9]. Aluminium compounds are widely used in the paper industry, in dye production, in the textile industry, in processed foods, and as a component of many cosmetic and pharmaceutical preparations.

The environmental impact of aluminium directly depending on its production is negligible with respect to that depending on the incorrect use of its products, once considered completely safe, and on acid rain deriving from industrial and transportation pollution. Many epidemiological studies on industrial exposure conclude that aluminium manufacturing does not lead to any significant occupational hazard [10]. The uptake of aluminium by inhalation under normal circumstances is negligible, the estimated daily intake being 4.4 μg [11]. Occupational exposure to aluminium by inhalation has been reported in workers in bauxite mines [12] and within the aluminium production industry [13]. At the beginning of the last century, Canadian miners were deliberately exposed, at the end of each working day, to inhalation of so-called "McIntyre powder" containing ultra-fine aluminium powder, which was believed to prevent lung silicosis [14]. This "preventive" treatment was then demonstrated to be the cause of aluminium intoxication and brain damage.

Aluminium, naturally present at low concentrations in staple foods, is also used as a food additive: sodium aluminium phosphate is an approved emulsifying agent frequently incorporated in cheese [15].

Moreover, aluminium salts are currently utilised as anticaking agents for baked goods, to emulsify cheese, to bind meats, to thicken prepared sauces, to colour desserts, and for buffering, stabilising, curing, and giving texture to foods [16].

Aluminium compounds are used in water purification as well as in brewing and sugar refining [17]. They are also frequently utilised as pharmaceutical drugs in human and veterinary medicine [18]. Among them, buffered aspirin containing aluminium glycinate has been used as a common analgesic for years [19].

Solution aluminium chemistry

Until some decades ago, the content of aluminium in waters was usually insignificant, with the exception of waters in specific areas such as volcanic regions. Any free native Al(III) was immobilised in the soil as insoluble hydroxide. However, more recently, the environmental pollution caused by different human activities has caused acid rains. These modify the pH of water coming in contact with soils, thus being responsible for the solubilisation of aluminium-containing minerals. When the metal is no longer bound by its mineral deposits, it flows into fresh water. Thus, aluminium concentrations became noticeable in rivers and lakes where the pH is lower than 6 (the pH ranges of aluminium solubility will be discussed below). As reported by Martin [20] "Al^{3+} is more damaging to fish than increased acidity; even 5 mM Al^{3+} kills fish…", and "given adequate nutrients, the presence of Al(III) is the main limiting factor in plant productivity in acidic soils".

In order to understand the behaviour of aluminium in natural waters, the speciation and the solubility of Al(III) compounds as a function of different parameters, like pH, total concentration of the metal, and the presence of coordinating anions, must be considered on the basis of hydrolysis and complex-formation constants available in the literature. This kind of knowledge can be applied to completely dissimilar environments, such as:

- water from a municipal treatment plant, after a clarifying treatment
- dialysate water purified by inverse osmosis treatment.

In order to calculate the aluminium speciation in the above systems, the most important equilibria acting in solution have to be taken into account, i.e. the formation equilibria of the different hydroxo compounds and the competitive equilibria with some anions (above all fluoride) that can be found in relevant amounts in natural waters.

Municipal drinking water

Aluminium salts are widely used in water treatment as coagulants to reduce organic matter, colour, turbidity, and also microorganism levels. The process consists of proper addition of an aluminium salt (usually sulfate) under defined pH conditions, followed by flocculation, sedimentation, and filtration. The slow precipitation of gelatinous $Al(OH)_3$, which forms around any solid particle of whatever origin, like dust particles and bacteria, purifies and clarifies the water. The resulting purified water is thus a saturated solution of aluminium hydroxide. Many chemical parameters, such as the amount of inorganic ligands in solution (F^-, Cl^-, SO_4^{2-}, and SiO_4^{2-}) and pH, determine the total aluminium and its species present in water. According WHO Guidelines for Drinking-water Quality (Geneva 2004, http://www.who.int/water_sanitation_health/dwq/GDWQ2004web.pdf) typical coagulant doses are 2–5 mg/dm^3 as aluminium, but effective operation of the coagulation process depends on selection of the optimum

coagulant dose, which has to keep pace with changes in raw water quality. Assuming the worst raw water quality we took into consideration a dose of about 50 mg/dm^3 of aluminium, added to water in the form of different salts, i.e. a concentration of added aluminium about 2×10^{-3} M.

We take two kinds of water into consideration, one with a low content of dissolved salts with a dry residue of about 0.3 g/dm^3 and the second with a high content of dissolved salts with a dry residue of about 3.0 g/dm^3; these concentrations may be considered the extreme situations for municipal waters. Being the main dissolved salt bicarbonates and sulfates of alkaline earths, the corresponding ionic strengths can be roughly estimated as 0.01 and 0.1 M. Furthermore, we also take into consideration a third ionic strength, 0.16 M, corresponding to that of human blood plasma. The stability constants used in the present speciation study, reported in Table 1, are those derived from the data of Baes and Mesmer [21] for different ionic strengths at 25 °C and those reported by B. Martin for $\mu = 0.16$ M [22] and by Martell et al. [23] at the same temperature. It is worth noting that the three sets of constants are not in perfect agreement.

In Fig. 1 the distribution plots at the ionic strength 0.16 M, calculated with the Baes and Mesmer values (right plot) and with those of Martin (left) are reported. They look somewhat different, even though it can be summarised that the $Al(OH)_3$ precipitation starts at a pH that is a bit higher than 4, and it is the unique species at neutral pH. $Al(OH)_3$ dissolves above pH 8 or above pH 9 according to whether the constant of Baes and Mesmer or of Martin is used, with the deprotonation of a water molecule in the first coordination sphere of aluminium and the formation of the negatively charged species $Al(OH)_4^-$. To observe in detail the existence of soluble species in the pH range 6–8, we calculated their concentrations at pH 6, 7, and 8, and the results are reported in Table 2, both in mol/dm^3 and in mg/dm^3, at the three different ionic strengths, using the Baes and Mesmer constants, and in the case of $\mu = 0.16$ M also those of Martin. Some considerations can be made:

1. Being a solution in contact with a $Al(OH)_3$ solid phase, the obtained results do not obviously depend on the amount of added flocculant;
2. The polynuclear species do not contribute at all to the total amount of soluble species, which are at $\mu = 0.01$ and pH 6 $Al(OH)_2^+$ and soluble $Al(OH)_3$, with a total soluble concentration of about 9 μg/dm^3. At pH 7 the total soluble concentration decreases to 7 μg/dm^3, because of $Al(OH)_3$ and in a negligible quantity to $Al(OH)_2^+$ and $Al(OH)_4^-$; at pH 8 the soluble aluminium increases to 13 μg/dm^3, with a similar contribution of $Al(OH)_3$ and $Al(OH)_4^-$; a similar behaviour is presented at higher μ values, and only at pH 8 is the contribution of $Al(OH)_4^-$ higher;
3. Different results are obtained when the values of Martin are used: the concentration of soluble aluminium at pH 6 goes from 9.1 to 15.6 μg/dm^3, at pH 7 from 7 to 35 μg/dm^3, and above all at pH 8 from 17 to 305 μg/dm^3. These last data appear more reasonable compared to the findings of various authors on aluminium concentrations in pipe water, measured with atomic absorption spectroscopy or ICP-AES, which determines the total soluble aluminium.

The concentrations of total soluble aluminium were furthermore calculated in the same conditions as above for $\mu = 0.16$ M, but in the presence of about 5 mg/dm^3 of fluoride, to take into account the influence of the presence of a strong complexing anion on the solubility of aluminium. The WHO Guidelines for Drinking-water Quality specify a guideline value for fluoride of 1.5 mg/dm^3, but nonetheless report that in areas with high natural fluoride levels the guideline value may be difficult to achieve in some circumstances; for this last reason we chose the higher value of 5 mg/dm^3. The equilibrium constants taken into consideration are from references [23–25], reported in Table 3. In this situation the contribution of hydroxo species is almost equal to that previously calculated, but the fluoride complexes AlF_2^+, AlF_3, and AlF_4^- strongly contribute at pH 6 (717 μg/dm^3 total soluble aluminium when the Baes and Mesmer constants are used, and 1116 μg/dm^3 with Martin constants). Fluoride complexes contribute to a lesser amount at pH 7 and do not form in measurable quantities at pH 8.

Table 1 Equilibrium constants for Al(III) hydrolysis reactions

Species	$\mu = 0.01$ M[a]	$\mu = 0.1$ M[a]	$\mu = 0.16$ M[a]	$\mu = 0.16$ M[b]	$\mu = 0.10$ M[c]
$Al(OH)^{2+}$	−5.15	−5.41	−5.47	−5.5	−5.31
$Al(OH)_2^+$	−9.57	−9.98	−10.09	−11.3	−10.76
$Al(OH)_3$	−15.27	−15.69	−15.80	−17.3	−16.64
$Al(OH)_4^-$	−23.18	−23.45	−23.53	−23.5	−23.62
$Al_2(OH)_2^{4+}$	−7.7	−7.7	−7.7	–	
$Al_3(OH)_4^{5+}$	−13.85	−13.69	−13.65	–	
$Al_{13}(OH)_{24}^{15+}$	−100.4	−102.8	−103.41	–	
$Al(OH)_{3\ SOL}$	8.77	9.19	9.30	10.7	7.84

[a] [21], [b] [22], [c] [23]

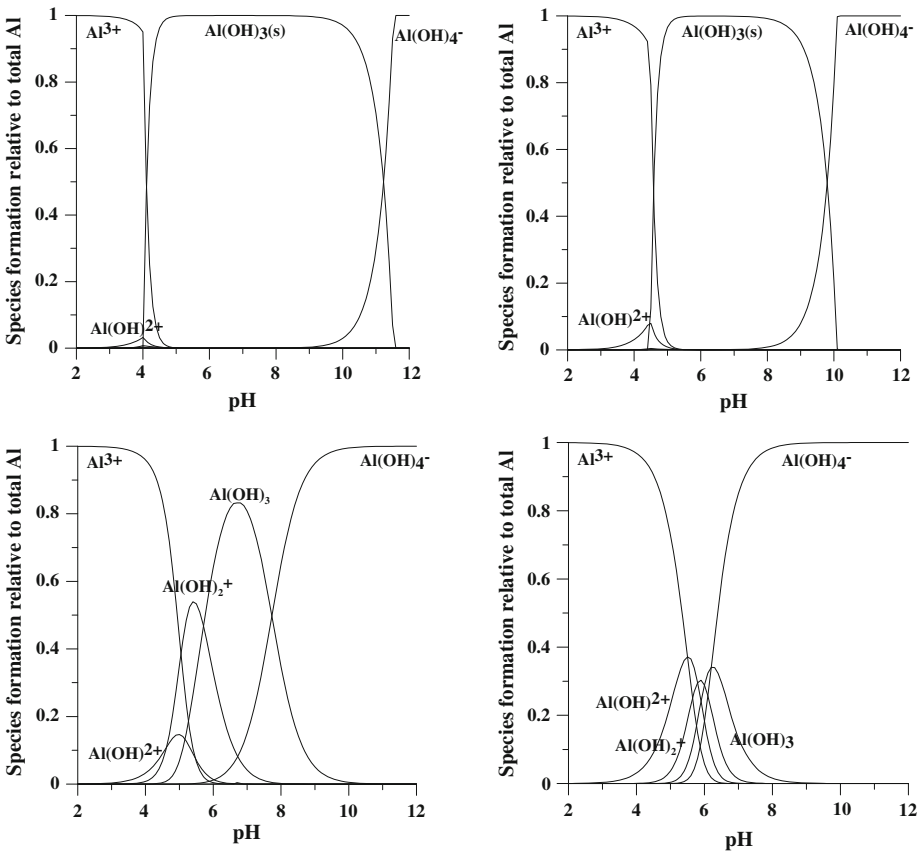

Fig. 1 Aluminium hydroxo-species distribution plots at 0.16 M ionic strength calculated with the Baes and Mesmer [21] hydrolysis constants at a total aluminium concentration of 0.002 M (*left upper plot*) and 5×10^{-7} M (*left lower plot*), and calculated with the Martin [22] hydrolysis constants at a total aluminium concentration of 0.002 M (*right upper plot*) and 5×10^{-7} M (*right lower plot*)

Table 2 Aluminium concentration in water after addition of aluminium salts as flocculant at three different pH values

	pH = 6	pH = 7	pH = 8	pH = 6	pH = 7	pH = 8
	Water 0.01 μ = 0.2 g/dm^3 [a]			Water 0.1 μ = 2 g/dm^3 [a]		
	Flocculants 0.002 M = 50 mg/dm^3			Flocculants 0.002 M = 50 mg/dm^3		
$Al(OH)_2^+$	1.58×10^{-7}	1.58×10^{-8}	1.58×10^{-9}	1.61×10^{-7}	1.61×10^{-8}	1.61×10^{-9}
	3.0	0.3	–	3.0	0.3	–
$Al(OH)_3$	3.16×10^{-7}	3.16×10^{-7}	3.16×10^{-7}	3.16×10^{-7}	3.16×10^{-7}	3.16×0^{-7}
	6.0	6.0	6.0	6.0	6.0	6.0
$Al(OH)_4^-$	3.89×10^{-9}	3.89×10^{-8}	3.89×10^{-7}	5.43×10^{-9}	5.43×10^{-8}	5.43×10^{-7}
	–	0.7	7.0	0.1	1.0	10.3
Total soluble Al	9.0	7.0	13.0	9.1	7.3	16.3
	Water 0.16 μ = 3 g/dm^3 [a]			Water 0.16 μ = 3 g/dm^3 [b]		
	Flocculants 0.002 M = 50 mg/dm^3			Flocculants 0.002 M = 50 mg/dm^3		
$Al(OH)^{2+}$	–	–	–	1.58×10^{-7}	1.58×10^{-9}	1.58×10^{-11}
				3.0	–	–
$Al(OH)_2^+$	1.63×10^{-7}	1.63×10^{-8}	1.63×10^{-9}	2.51×10^{-7}	2.51×10^{-8}	2.51×10^{-9}
	3.1	0.3	–	4.8	0.5	–
$Al(OH)_3$	3.13×10^{-7}	3.13×10^{-7}	3.13×10^{-7}	2.51×10^{-7}	2.51×10^{-7}	2.51×10^{-7}
	5.9	5.9	5.9	4.8	4.8	4.8
$Al(OH)_4^-$	5.94×10^{-9}	5.94×10^{-8}	5.94×10^{-7}	1.58×10^{-7}	1.58×10^{-6}	1.58×10^{-5}
	0.1	1.1	11.3	3.0	30.0	300
Total soluble Al	9.1	7.3	17.2	15.6	35.3	304.8

The upper values are in mol/dm^3, the lower values in μg/dm^3. Total soluble aluminium in μg/dm^3

[a] Hydrolysis constants from reference [21]

[b] From reference [22]

Table 3 Complex formation constants for Al(III) reaction with fluoride at 25 °C

Species	$\mu = 0.1$ M[a]	$\mu = 0.16$ M[b]
HF	2.94	–
AlF^{2+}	6.42	6.37
AlF_2^+	11.63	11.55
AlF_3	15.5	15.38
AlF_4^-	18.1	18.48

[a] From reference [23]

[b] From reference [25], interpolating data at $\mu = 0.1$ and 0.2 M

To sum up, judging the Martin constants more reliable, a water treated with aluminium as flocculant contains noticeable amounts of soluble aluminium, above all at a pH equal to or greater than 8; non-negligible amounts of complexing inorganic ligands, such as fluoride, can seriously increase the amount of soluble aluminium at pH 6 and 7 (Table 4).

Dialysate water purified by inverse osmosis treatment

Deionised water such as what is nowadays available in dialysis centers has an aluminium content of 0.6×10^{-7} M, corresponding to the upper suggested value of 10 μg/dm^3 by the UE recommendations. We evaluated the speciation of aluminium hydroxides at this concentration using both the Martin constants and those of Baes and Mesmer for $\mu = 0.16$, disregarding the ionic strength effects. The relative plots are presented in the lower part of Fig. 1: it can be remarked that in both cases no solid precipitate is formed, and all aluminium is in the form of soluble species, at pH 6, with prevailing $Al(OH)_2^+$ and $Al(OH)_3$, whereas at pH 8 $Al(OH)_4^-$ becomes the principal species.

Aluminium overload diseases

Prior to the recognition that aluminium in dialysate and in oral medications is extremely toxic for human health, for a long time aluminium salts were the unique phosphate chelators commercially available in clinical practice and were widely utilised to treat hyperphosphataemia, an important mortality risk in haemodialysis patients [26, 27]. As a consequence, uncontrolled aluminium accumulation led to serious toxicity in subjects affected by chronic kidney disease [28] and in subjects on total parenteral nutrition

Table 4 Aluminium concentration in water containing fluoride after addition of aluminium salts as flocculant at three different pH values, using the complex formation constants for fluoride from reference [23]

	pH = 6	pH = 7	pH = 8	pH = 6	pH = 7	pH = 8
	Water 0.16 $\mu = 3$ g/dm^3 [a]			Water 0.16 $\mu = 3$ g/dm^3 [b]		
	Flocculant 0.002 M = 50 mg/dm^3			Flocculant 0.002 M = 50 mg/dm^3		
	F^- 0.00025 M = 4.75 mg/dm^3			F^- 0.00025 M = 4.75 mg/dm^3		
$Al(OH)^{2+}$	6.76×10^{-9}	–	–	1.58×10^{-7}	1.58×10^{-9}	1.58×10^{-11}
	0.1			3.0	–	–
$Al(OH)_2^+$	1.62×10^{-7}	1.62×10^{-8}	1.62×10^{-9}	2.51×10^{-7}	2.51×10^{-8}	2.51×10^{-9}
	3.1	0.3	–	4.8	0.5	–
$Al(OH)_3$	3.16×10^{-7}	3.16×10^{-7}	3.16×10^{-7}	2.51×10^{-7}	2.51×10^{-7}	2.51×10^{-7}
	6.0	6.0	6.0	4.8	4.8	4.8
$Al(OH)_4^-$	5.88×10^{-9}	5.89×10^{-7}	5.94×10^{-7}	1.58×10^{-7}	1.58×10^{-6}	1.58×10^{-5}
	0.1	11.1	11.3	3.0	30.0	300
AlF^{2+}	7.13×10^{-7}	–	–	6.67×10^{-6}	2.32×10^{-8}	2.91×10^{-11}
	13.5			127	0.4	–
AlF_2^+	1.65×10^{-5}	4.41×10^{-8}	4.42×10^{-11}	2.79×10^{-5}	1.03×10^{-6}	1.11×10^{-9}
	313	0.8	–	530	19.6	–
AlF_3	1.68×10^{-5}	7.37×10^{-8}	7.41×10^{-11}	2.18×10^{-5}	1.66×10^{-6}	1.86×10^{-9}
	319	1.4	–	414	31.5	–
AlF_4^-	3.29×10^{-6}	2.36×10^{-8}	2.37×10^{-11}	1.58×10^{-6}	5.14×10^{-7}	5.96×10^{-10}
	62.5	0.4	–	30.0	9.8	–
Total soluble Al	717.3	20.0	17.3	1,116	96.6	304.8

The upper values are in mol/dm^3; the lower values and the total soluble aluminium in μg/dm^3

[a] Hydrolysis constants from reference [21]

[b] From reference [22]

[29]. The toxicity of aluminium related to its accumulation in different organs in dialysis patients was a serious problem for haemodialysis units in the 1970s and 1980s [30]. The first time that aluminium was reported to be toxic in patients affected by chronic kidney diseases was in 1976 [31]. Subsequently, aluminium overload was implicated in disturbances of cerebral function and identified as the major risk factor in dialysis-induced encephalopathy [32], in microcytic anaemia in dialysis patients [33], and in osteomalacia [34]. Moreover, aluminium overload has been considered responsible for frequent fractures in dialysis patients [35]. All these data clearly indicate aluminium exposure as an environmental risk factor in patients undergoing dialysis, contributing to the development and progression of several human degenerative disorders, grouped under the definition of dialysis encephalopathy [31, 36]. Patients affected by dialysis encephalopathy present with mental confusion, speech alterations, dementia, myoclonias, and convulsions, often occurring after haemodialysis sessions, associated with a typical electroencephalogram [37]. Dialysis encephalopathy generally shows a poor prognosis, resulting in death in the majority of cases. Fatal cases of aluminium overload-related encephalopathy have been occasionally described even in patients affected by chronic kidney disease not on dialysis [38].

Approximately 70% of the aluminium body burden in humans is localised in the skeletal system, with a bone aluminium concentration of 5–10 mg/kg [39]. The storage of a major fraction of the body burden of aluminium in bone together with the apparent long half-life of bone aluminium may easily explain the high frequency of osteomalacia in patients on dialysis [40]. In dialysis patients, monitoring of serum aluminium levels has been demonstrated to have a predictive value for the diagnosis of aluminium-related bone disease when reaching values of 60 μg/dm^3 [41]. When aluminium accumulates in bones, the process of bone formation is disrupted, and a osteodistrophy [42], subsequently better defined as "adynamic bone disease" [43] or "aluminium-induced bone disease" (AIBD), develops, ending with spontaneous fractures. In these patients, a bone biopsy shows classical histological features of osteomalacia, characterised by a marked increase in non-mineralised osteoid tissue surrounding calcified bone [44]. Aluminium delivered to bone tissue exerts an antiproliferative effect on osteoblasts, cells specialised in new bone deposition, followed by a low bone turnover, eventually leading to osteomalacia [45]. In rare cases in which serum aluminium levels are not clearly indicative for aluminium-related bone disease and in which the test for desferoxamine (DFO) is not suggestive of aluminium toxicity, a bone biopsy may be diagnostic, revealing aluminium deposits in bone cells [46].

Although the use of aluminium hydroxide is no longer recommended in dialysis units, aluminium, given its high potency binding to phosphate, is still being used in clinical practice with limitations [26]. But the risk of aluminium overload is not restricted to subjects affected by chronic kidney diseases undergoing dialysis: general populations may be exposed to aluminium toxicity when aluminium sulfate is used as a sedimentation agent for treating city water (see above) [26]. Moreover, food is considered to provide the majority of aluminium absorbed by humans, with the daily exposure to aluminium from food products being estimated between 3 and 10 mg [47]. In particular, tea infusions have been discovered to be a major source of dietary aluminium exposure to humans [48]. It has been shown recently that the aluminium content can reach the values reported for tea even in coffee infusions, generally considered a poor source of aluminium intake [49], when prepared using moka pots [50]. Contamination of food during processing, cooking, and storage has been shown to result in high aluminium intakes among consumers [51]. Leaching of relevant amounts of aluminium has been demonstrated especially when acidic foods are cooked in aluminium pots, reaching concentrations as high as 50 mg/dm^3 [52].

Regarding the bioavailability of aluminium contained in food, some associations have been discovered to interfere with the percentage of the absorbed trace metal: in particular, adding milk to tea infusions has been shown to significantly decrease the bioavailability of aluminium [53]. On the other hand, the concomitant administration of aluminium-rich compounds and citrate has been shown to markedly increase aluminium absorption [54]. It should be emphasised that some widely used pharmaceutical products, such as antacids and antidiarrheic drugs, which are non-prescription medications containing high quantities of aluminium compounds, have been administered for many years for the treatment of peptic disorders [55]. Among the classes at risk of aluminium intoxication are patients affected by Down syndrome, a genetic disease caused by trisomy of chromosome 21, who show a higher frequency of Alzheimer's disease compared to the normal population. In Down syndrome subjects, gastrointestinal absorption of aluminium has been shown to be markedly increased [56], suggesting a connection between the aluminium burden and human dementia.

Human exposure to aluminium takes myriad forms, including the use of illicit drugs, with aluminium being both biologically accumulated in plant-based products and a processing contaminant of such products. Elevated concentrations of aluminium have been reported in users of illicit heroin [57], indicating an increase in the body's burden of the metal. Different clinical symptoms related to aluminium toxicity have been reported in subjects

undergoing inhalation of cocaine vaporised on aluminium foil [58], in tobacco and cannabis smokers [59], after ingestion of oral methadone solutions [60], and after intravenous injection of boiled methadone [61].

Aluminium chelators

The discovery of the the toxicity of aluminium overload was at the basis of many studies aimed at identifying aluminium chelators, which are able to mobilise aluminium deposits, reduce the body burden of the metal, and reverse dialysis encephalopathy and osteomalacia. Management of aluminium intoxication initially involves discontinuation of aluminium exposure by removal of all parenteral and oral exposures to the metal. The introduction of water treatment systems in all dialysis centres in the last 20 years has greatly contributed to managing the aluminium concentration in the water used for dialysis, and this has led to a drastic decrease in aluminium overload diseases [26]. The quality standards for treated dialysis water before 1990 were much weaker than those in use today: in 1977 deionisers were installed for aluminium concentrations exceeding 100 μg/dm^3, and in 1978 when greater than 50 μg/dm^3, and reverse osmosis was not used in that period [62]. The current quality standard in European countries for aluminium in treated water for dialysis is 10 μg/dm^3, and for input water is 200 μg/dm^3. Some authors describe aluminium levels in the dialysis fluid lower than 2 μg/dm^3, using a double system of reverse osmosis, in their dialysis centres [26]. The same authors correlate the amount of aluminium in the intake water with the amount of aluminium sulfate used as a sedimentation agent for treating city water: we remember, as shown previously, that the amount of dissolved aluminium depends on various factors (pH, ionic strength, nature of anions, etc.), but does not depend on the amount of added aluminium salts. At any rate the use of double reverse osmosis devices, allowing very low aluminium concentrations in dialysate, has different beneficial effects: not only does it avoid toxic aluminium passing from the dialysate to plasma, but it also allows aluminium removal from plasma by haemodialysis: the extent of removal depends on the concentration gradient between the free diffusible plasma aluminium and the dialysate aluminium concentration [63].

Patients who do not show clinical improvement following the interruption of exposure to aluminium should undergo chelation therapy [44]. Deferoxamine was the first aluminium chelator to be introduced in clinical practice for the treatment of aluminium-related osteomalacia [64, 65], and it was shown to be equally effective when given intramuscularly or intraperitoneally [66, 67]. Treatment of aluminium bone toxicity with deferoxamine requires a prolonged therapeutic protocol, which should be continued for at least 6 months [68]. Long-lasting deferoxamine therapy might reduce not only bone aluminium deposits, but also the aluminium burden in the brain in humans [69]. Deferoxamine treatment has been successful even in cases of acute encephalopathy due to severe aluminium intoxication following aluminium bladder irrigation [70]. Therapy with deferoxamine is not without some risk: patients with marked aluminium overload may develop acute neurological toxicity following deferoxamine administration [44]. Given the relevant possible side effects of deferoxamine treatment, DFO therapy may be indicated only for patients showing serum aluminium levels higher than 200 μg/dm^3 and for subjects whose aluminium bone concentration is ten times greater than normal values [71]. The hazards of deferoxamine treatment justify the performance of a bone biopsy in order to ensure the diagnosis of aluminium-related adynamic bone disease before starting a long and complex therapeutic protocol [72]. Among the multiple side effects of deferoxamine therapy for aluminium-related bone disease, the precipitation of dementia is the most severe, leading to death in a high percentage of affected patients [73]. In recent years, other aluminium chelators have been developed and progressively introduced in clinical settings. Among them ascorbate and Feralex-G have been used, either alone or in combination with deferoxamine, to remove aluminium overload [74]. Recently "metal-targeted strategies" have been proposed, whose major goal is brain metal redistribution rather than brain metal scavenging and removal. The up to date developments in metal-targeted strategies are discussed by Hedge et al. [75] using, as useful examples, clioquinol, curcumin, and epigallocatechin.

Different new ligands for aluminium have been synthesised in the last 10 years; for most of them, the complex formation equilibria were thoroughly studied, and in some cases also biological evaluation was made. Inside these molecule families, particular attention has to be paid to 3-hydroxy-4-pyridinone (3,4-HP) derivative ligands. The 3,4-HPs are mono-anionic N-heterocyclic bidentate {O,O}-chelators with high affinity for hard metal ions. They can be easily extra-functionalised to modify their properties, above all in view of improving the bioavailability. Hider et al. [76, 77] in their studies for the treatment of iron overload introduced a large amount of bidentate or polydentate 3,4-HP chelators. Some analogues were also taken into account for the removal of other hard metal ions, in particular aluminium, by Santos et al. [78, 79] and plutonium by Fukuda [80].

The strategy of functionalising the bidentate mono-3,4-HP unit with carbohydrate moieties to improve the cell transport of the ligand for aluminium mobilisation has been used by two different research groups: Kruck and Burrow

[81] described the procedures for the synthesis of the mentioned Feralex-G, a glucopyranose derivative of deferiprone (2-deoxy-2-[[2-(3-hydroxy-2-methyl-4-oxo-1(4*H*)-pyridinyl) acetyl]amino]-D-glucose), and Chaves et al. [82] proposed two *N*-glycosyl-mono-3,4-HP derivatives.

Different tetradentate 3,4-HP chelators have been proposed by the group of Santos [82, 83]; in particular two 3,4-HP chelating moieties were appended to an iminodiacetic acid (IDA) scaffold, with a 1,4-disubstituted arylpiperazine *N*-attached.

The same group has also proposed

- two hexadentate ligands, the tris-hydroxypyridinone-based compounds KEMPPr(3,4-HP)$_3$ and MPBu(3,4-HP)$_3$. Their structure is based on the KEMP acid scaffold to which three 3-hydroxy-4-pyridinone chelating moieties are attached via two differently sized spacers [84]. These hexadentate ligands proved to be strong sequestering agents for the group III metal ions, with potential pharmacological applications in metal-chelation therapy.
- two new tripodal tris(3-hydroxy-4-pyridinone) hexadentate chelators NTA(BuHP)$_3$ and NTP(PrHP)$_3$, (NTA, nitrilotriacetic acid; NTP, nitrilotripropionic acid; HP, hydroxypyridone). Their iron and aluminium binding affinity have been studied in solution and their capacity to remove metals from overloaded animals assayed in vivo. These chelators share important properties such as a mildly hydrophilic character and a very strong chelating affinity for Fe and Al [pFe = 27.9 and pAl = 22.0 for NTA(BuHP)$_3$; pFe = 29.4 and pAl = 22.4 for NTP(PrHP)$_3$] [85].

Piyamongkol et al. [86] synthesised and studied the physicochemical properties of a set of 2- and 6-amido-3-hydroxypyridin-4-ones. All these exhibit lower pK_A values than 1,2-dimethyl-3-hydroxypyridin-4-one (deferiprone) because of the inductive effect of the amido group. The decreased proton competition leads to better chelating properties of these molecules with respect to the parent deferiprone.

Different families of chelating agents have been taken into consideration as aluminium chelators. Biaso et al. [87] studied two tripodal molecules, O-TRENSOX, containing three 8-hydroxy-5-sulfonate-quinoline and as anchor tris(2-aminoethyl)amine (TREN), and the analogous tris-catechol TRENCAMS. The authors found the impressive pAl values 20.0 and 26.2 for O-TRENSOX and TRENCAMS, respectively.

A number of studies on the synthesis and the aluminium-ligand solution chemistry of hydroxypyridinecarboxylic acids has been presented. These ligands have the two coordinating –OH and –COOH groups in different positions (2,3; 3,2; 3,4; 4,3) and are variously methylated [88–93].

Our group has found that bisphosphonate ligands are very efficient chelating agents for aluminium, with pAl values higher than that of deferiprone and similar to that of deferoxamine [94]. With the aim of improving bisphosphonate chelating properties the strategy of conjugating them with other effective coordinating groups was proposed. Catechol-bisphosphonate conjugates were synthesised by Ding et al. [95] and mixed bisphosphonate-hydroxypyridinonate compounds by Bailly et al. [96]. The shortness of the linker prevented simultaneous tetradentate coordination both in catechol-bisphosphonate and in pyridinone-bisphosphonate ligands [97, 98]. An interesting aluminium chelator, 2,2′-methylenebis[3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one], synthesised from two kojic acid units linked by a methylene group, was proved by Fox and Taylor [99] to be an efficient ligand for the in vitro mobilisation of ferritin-bound iron. In a recent study we found that it forms very stable iron and aluminium dinuclear complexes [100].

Two interesting studies on aluminium interactions with natural substances were also presented:

- Cornard and Merlin [101] examined the interaction of quercetin (3,3′,4′,5,7-pentahydroxyflavone), one of the most common flavanols present in nature, with aluminium and found two different complexes with 1:2 and 2:1 Al/L stoichiometries.
- Kobayashi et al. [102] recognised an aluminium-binding substance (ABS) secreted by *Saccharomyces cerevisiae* able to solubilise Al(III) at neutral pH. ABS was identified to be 2-isopropylmalic acid (2-iPMA). The aluminium complexation was supported by ^{27}Al NMR spectrometry on a solution containing 10 mM Al(III) and 20 mM 2-iPMA at pH 6.6, where four Al(III) species were evident.

References

1. Savory J, Exley C, Forbes WF, Huang Y, Joshi JG, Kruck T, McLachlan DRC, Wakayama I (1997) In: Yokel RA, Golub MS (eds) Research issues in aluminium toxicity, Taylor and Francis, Washington, p 185
2. Flaten TP, Alfrey AC, Birchall JD, Savory J, Yokel RA (1997) In: Yokel RA, Golub MS (eds) Research issues in aluminium toxicity, Taylor and Francis, Washington, p 1
3. Reuche E (1997) Acta Neuropathol 94:612
4. Klein GL (2005) Curr Opin Pharmacol 5:637
5. Yokel RA (2000) Neurotoxicology 21:813
6. Gourier-Fréry C, Fréry N (2004) EMC Toxicologie-Pathologie 1:79
7. Yokel RA, Florence RL (2006) Toxicology 227:86
8. Exley C (2003) J Inorg Biochem 97:1
9. Macdonald TL (1988) Trends Biochem Sci 13:15
10. Bertholf RL, Wills MR, Savory J (1988) Aluminum. In: Seiler HG, Sigel H, Sigel A (eds) Handbook on the toxicity of inorganic compounds. Marcel Dekker Inc, New York, p 55

11. Priest ND (2004) J Environ Monit 6:375
12. de Kom JFM (1997) Clin Toxicol 35:645
13. Sjogren B (1983) Br J Ind Med 40:301
14. McDonald B (1996) Neurobiol Aging 17:S122
15. Yokel RA (2008) Food Chem Toxicol 46:2261
16. Humphreys S, Bolger PM (1997) A public health analysis of dietary aluminium. In: Zatta PF, Alfrey AC (eds) Aluminium toxicity in infants' health. World Scientific, Singapore, p 226
17. Martin RB (1986) Clin Chem 32:1797
18. Greger JL (1997) Crit Rev Clin Lab Sci 34:439
19. Lione AJ (1985) Gen Pharmacol 16:223
20. Martin RB (1994) Acc Chem Res 27:204
21. Baes CF, Mesmer RE (1976) The hydrolysis of cations. Wiley, New York
22. Martin RB (1991) J Inorg Biochem 44:141
23. Martell AE, Hancock RD, Smith RM, Motekaitis RJ (1996) Coord Chem Rev 149:311
24. Martin RB (1996) Coord Chem Rev 141:23
25. Agarwal R, Moreno E (1971) Talanta 18:873
26. Arenas MD, Malek T, Gil MT, Moledous A, Nunez C, Alvarez-Ude F (2008) Nefrologia 2:168
27. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM (2004) J Am Soc Nephrol 15:2208
28. Tonelli M, Wiebe N, Hemmelgarn B, Klarenbach S, Field C, Manns B, Thadani R, Gill J (2009) BMC Med 7:25
29. Muller M, Manfred A, Illing-Gunther H (1997) Z Lebensm-Unters Forsch 205:170
30. Report from the Registration Committee of the European Dialysis and Transplant Association (1980) Lancet 316:190
31. Alfrey AC, LeGendre GR, Kaehny WD (1976) N Engl J Med 294:184
32. Altmann P, Dhanesha U, Hamon C, Cunningham J, Blair J, Marsh F (1989) Lancet 334:7
33. Swartz R, Dombrouski J, Burnatowska-Hledin M, Mayor G (1987) Am J Kidney Dis 9:217
34. Ward MK, Feest TG, Ellis HA, Parkinson IS, Kerr DN (1978) Lancet 311:841
35. Parkinson IS, Ward MK, Feest TG, Fawcett RW, Kerr DN (1979) Lancet 313:406
36. Rozas VV, Port FK, Rutt WM (1978) Arch Int Med 138:1375
37. Alfrey AC (1986) Kidney Inter 29(S18):53
38. Zatta P, Zambenedetti P, Reusche E, Stellmacher F, Cester A, Albanese P, Meneghel G, Nordio M (2004) Nephrol Dial Transplant 19:2929
39. Ganrot PO (1986) Environ Health Perspect 65:363
40. Finch JL, Bergfeld M, Martin KJ, Chan YL, Teitelbaum S, Slatopolsky E (1986) Kidney Int 30:318
41. D'Haese PC, Clement JP, Elseviers MM, Lamberts LV, Van de Vyver FL, De Broe ME (1990) Nephrol Dial Transplant 5:45
42. Nebeker HG (1986) Ann Rev Med 37:79
43. Malluche HH (1992) Kidney Int 42:S62
44. Alfrey AC (1991) Aluminium intoxication recognition and treatment. In: Nicolini M, Zatta PF, Corain B (eds) Aluminium in chemistry, biology, and medicine. Cortina International, Verona & Raven Press, New York, p 73
45. Kasai K (1991) Am J Physiol Endocrinol Metab 260:E537
46. Modelli Andrade LG, Duarte Garcia F, Santos Silva V, Ponce Gabriel D, Goncalves Rodrigues A Jr, Nascimento GVR, Teixeira Caramori J, Cuadrado Martin L, Barretti P, Balbi AL (2005) Nephrol Dial Transplant 20:2582
47. Yokel R (2004). In: Merian E, Auke K, Inhad M, Stoeppler (eds) Elements and their compounds in the environment, Wiley-VCH, Weinheim, p 635
48. Flaten TP (2002) Coord Chem Rev 228:385
49. Malik J, Szakova J, Drabek O, Balik J, Kokoska L (2008) Food Chem 111:520
50. Frankova A, Drabek O, Havlik J, Szakova J, Vanek A (2009) J Inorg Biochem 103:1480
51. Jorhem L (1992) Z Lebensm-Unters Forsch 194:38
52. Liukkonen-Lilja H (1992) Food Addit Contam 9:213
53. Milacic R (2005). In: Cornelis R, Caruso J, Crews H, Heumann K (eds) Handbook of elemental speciation II. Species in environment, food, medicine, and occupational health, Wiley, New York, p 20
54. Froment DH, Molitoris BA, Buddington B, Miller N, Alfrey AC (1989) Kidney Int 36:978
55. Domingo JL (1995) Neurotoxicol Teratol 17:515
56. Moore PB (1997) Biol Psychiatry 41:488
57. Exley C, Ahmed U, Polwart A, Bloor RN (2007) Addict Biol 12:197
58. de los Bueis AB, Vega AP, Ramos JLS, Perez JAM, Garcia RA, Jimenez DG, de la Llave EP (2002) Chest 121:1223
59. Exley C, Begun A, Woolley MP, Bloor RN (2006) Am J Med 119:276
60. Friesen MS, Purssell RA, Gair RD (2006) Clin Toxicol 44:307
61. Yong RL, Holmes DT (2006) N Engl J Med 354:1210
62. Platts MM, Owen G, Smith S (1984) Br Med J 288:969
63. Graf H, Stummvoll HK, Meisinger V, Kovarik J, Wolf A, Pinggera WF (1981) Kidney Int 19:587
64. Brown DJ, Dawborn JK, Ham KN, Xipell JM (1982) Lancet 320:343
65. Nebeker HG, Milliner DS, Ott SM, Sherrard DJ, Alfrey AC, Abuelo JG, Wasserstein A (1984) Kidney Int 25:173
66. Molitoris BA, Alfrey PS, Miller LN, Hasbargen JA, Kaehney WD, Alfrey AC, Smith BJ (1987) Kidney Int 31:986
67. Ciancioni C, Poignet JL, Narel C, Delons S, Mauras Y, Allain P, Man NK (1984) Proc EDTA-ERA 21:469
68. Yokel RA, Ackrill P, Burgess E, Day JP, Domingo JL, Flaten TP, Savory J (1996) J Toxicol Envl Health 48:667
69. Yokel RA, Rhineheimer SS, Sharma P, Elmore D, McNamara PJ (2001) Toxicol Sci 64:77
70. Nakamura H, Rose PG, Blumer JL, Reed MD (2000) J Clin Pharmacol 40:296
71. Wang G, Zhu P, Wang S (1996) Zhonghua Nei Ke Za Zhi 35:36
72. Ghitu S, Oprisiu R, Benamar L, Said S, Tataru Albu A, Arsenescu I, Esper N, Morinière P, Fournier A (2000) Nephrologie 21:413
73. Sherrard DJ, Walker JV, Boykin JL (1988) Am J Kidney Dis 12:126
74. Kruck TP, Cui J-G, Percy ME, Lukiw WJ (2004) Cell Mol Neurobiol 24:443
75. Hegde ML, Bharathi P, Suram A, Venugopal C, Jagannathan R, Poddar P, Srinivas P, Sambamurti K, Rao KJ, Scancar J, Messori L, Zecca L, Zatta P (2009) J Alzheimer's Dis 17:457
76. Liu ZD, Hider RC (2002) Med Res Rev 22:26
77. Hider RC, Liu ZD (2003) Curr Med Chem 10:1051
78. Santos MA (2002) Coord Chem Rev 228:187
79. Santos MA, Gil M, Gano L, Chaves S (2005) J Biol Inorg Chem 10:564
80. Fukuda S (2005) Curr Med Chem 12:2765
81. Kruck TPA, Burrow TE (2002) J Inorg Biochem 88:9
82. Chaves S, Dron PI, Danalache FA, Sacoto D, Gano L, Santos MA (2009) J Inorg Biochem 103:1521
83. Gama S, Gil M, Gano L, Farkas E, Santos MA (2009) J Inorg Biochem 103:288
84. Grazina R, Gano L, Šebestík J, Santos MA (2009) J Inorg Biochem 103:262
85. Chaves S, Marques SM, Matos AMF, Nunes A, Gano L, Tuccinardi T, Martinelli A, Santos MA (2010) Chem Eur J 16:10535
86. Piyamongkol S, Ma YM, Kong XL, Liu ZD, Aytemir MD, van der Helm D, Hider RC (2010) Chem Eur J 16:6374

87. Biaso F, Baret P, Pierre JL, Serratrice G (2002) J Inorg Biochem 89:123
88. Di Marco VB, Tapparo A, Bertani R, Bombi GG (1999) Ann Chim (Rome) 89:535
89. Di Marco VB, Yokel RA, Ferlin MG, Tapparo A, Bombi GG (2002) Eur J Inorg Chem 10:2648
90. Di Marco VB, Dean A, Ferlin MG, Yokel RA, Li H, Venzo A, Bombi GG (2006) Eur J Inorg Chem 2006:1284
91. Bombi GG, Di Marco VB, Marton D, Moro S, Reheman A, Tapparo A, Viero L (2007) Polyhedron 26:3419
92. Dean A, Ferlin MG, Brun P, Castagliuolo I, Badocco D, Pastore P, Venzo A, Bombi GG, Di Marco VB (2008) Dalton Trans 53:1689
93. Dean A, Ferlin MG, Brun P, Castagliuolo I, Yokel RA, Badocco D, Pastore P, Venzo A, Bombi GG, Di Marco VB (2009) Dalton Trans 10:1815
94. Gumienna-Kontecha E, Silvagni R, Lipinski R, Lecouvee M, Cesare Marincola F, Crisponi G, Nurchi VM, Leroux Y, Kozlowski H (2002) Inorg Chim Acta 339:111
95. Ding H, Xu G, Wang J, Zg Y, Wu X, Xie Y (2004) Heteroatom Chem 15:549
96. Bailly T, Burgada R, Prange T, Lecouvey M (2003) Tetrahedron Lett 44:189
97. Crisponi G, Nurchi VM, Pivetta T (2008) J Inorg Biochem 102:209
98. Crisponi G, Nurchi VM, Pivetta T, Gałezowska J, Gumienna-Kontecka E, Bailly T, Burgada R, Kozłowski H (2008) J Inorg Biochem 102:1486
99. Fox RC, Taylor PD (1998) Bioorg Med Chem Lett 8:443
100. Nurchi VM, Crisponi G, Lachowicz JI, Murgia S, Pivetta T, Remelli M, Rescigno A, Niclós-Gutíerrez J, González-Pérez JM, Domínguez-Martín A, Castiñeiras A, Szewczuk Z (2010) J Inorg Biochem 104:560
101. Cornard JP, Merlin JC (2002) J Inorg Biochem 92:19
102. Kobayashi A, Edo H, Furihata K, Yoshimura E (2005) J Inorg Biochem 99:1260