© *Pharmacology & Toxicology* 2001, **88**, 159–167.
Printed in Denmark . All rights reserved

Pharmacology & Toxicology
ISSN 0901-9928

MiniReview

Aluminium Toxicokinetics: An Updated MiniReview

Robert A. Yokel and Patrick J. McNamara

College of Pharmacy and Graduate Center for Toxicology, University of Kentucky Medical Center, Lexington, KY 40536–0082, U.S.A.

(Received September 15, 2000; Accepted December 27, 2000)

Abstract: This MiniReview updates and expands the MiniReview of aluminium toxicokinetics by Wilhelm *et al.* published by this journal in 1990. The use of ^{26}Al, analyzed by accelerator mass spectrometry, now enables determination of Al toxicokinetics under physiological conditions. There is concern about aluminium in drinking water. The common sources of aluminium for man are reviewed. Oral Al bioavailability from water appears to be about 0.3%. Food is the primary common source. Al bioavailability from food has not been adequately determined. Industrial and medicinal exposure, and perhaps antiperspirant use, can significantly increase absorbed aluminium. Inhalation bioavailability of airborne soluble Al appears to be about 1.5% in the industrial environment. Al may distribute to the brain from the nasal cavity, but the significance of this exposure route is unknown. Systemic Al bioavailability after single underarm antiperspirant application may be up to 0.012%. All intramuscularly injected Al, e.g. from vaccines, may eventually be absorbed. Al distributes unequally to all tissues. Distribution and renal excretion appear to be enhanced by citrate. Brain uptake of Al may be mediated by Al transferrin and Al citrate complexes. There appears to be carrier-mediated efflux of Al citrate from the brain. Elimination half-lives of years have been reported in man, probably reflecting release from bone. Al elimination is primarily renal with ≤2% excreted in bile. The contribution of food to absorbed Al needs to be determined to advance our understanding of the major components of Al toxicokinetics.

This MiniReview will update and expand on topics covered by Wilhelm *et al.* (1990), incorporating recent reviews and original research reports. It will focus on the pharmacokinetics of aluminium (Al) that influence its potential to produce toxicity from the common sources to which humans are exposed. This will enable identification of the primary circumstances that might contribute to Al accumulation and toxicity. Research advances in the past decade include estimates of Al bioavailability under conditions that model drinking water Al consumption and from inhalation and transdermal exposure. This MiniReview will also address recent studies on the extent of Al distribution to and retention by the brain and bone and the extent of biliary Al excretion. A significant advance in Al research is the use of ^{26}Al and its analysis by accelerator mass spectrometry (AMS). Their use enables the study of Al toxicokinetics at physiologically-relevant doses/concentrations.

The toxicity, sources, speciation and analysis of Al

Al has been shown in animals and humans to have the potential to be a toxicant to the central nervous, skeletal and haematopoietic systems (Jeffery et al. 1996 & 1997; Health Canada 1998; ATSDR 1999; California EPA 2000; Cannata Andía 2000). There are suggestions of Al-induced nephrotoxicity and pulmonary fibrosis (Jeffery *et al.* 1996 &1997; ATSDR 1999). Al is a neurotoxicant. Large elevations in systemic Al from Al-contaminated dialysates and intravenous fluids, oral consumption of large amounts of Al-containing antacids/phosphate binders by people with significantly impaired or no renal function, and irrigation of the urinary bladder with massive amounts of alum to stop haemorrhaging can produce an encephalopathy. Encephalopathy from Al exposures that cause large increases in systemic Al has greatly decreased, but not disappeared, over the past two decades. It has been suggested that low level long-term exposure to Al may be a contributing factor in Alzheimer's disease and related disorders. The results of some epidemiological studies of the association between drinking water Al and Alzheimer's disease are consistent with this hypothesis while some others are not (Health Canada 1998; California EPA 1999; Yokel 2000). Similarly, only some of the studies that determined Al in bulk brain, neurofibrillary tangles and senile plaques of victims of Alzheimer's disease and related disorders are consistent with this hypothesis (Yokel 2000). A recent study investigating adverse effects on the central nervous system of Al welders found an Al-exposure-related increase in blood and urine Al concentrations, deficits in neuropsychological test performance and mild diffuse EEG abnormalities (Riihimäki *et al.* 2000). The potential for Al-induced neurotoxicity in

Author for correspondence: Robert A. Yokel, College of Pharmacy, 501b Pharmacy Building, Rose Street, University of Kentucky Medical Center, Lexington, KY 40536–0082, USA (fax +1 859 257 7585, e-mail ryokell@pop.uky.edu).

those occupationally exposed to Al fumes may be greater than previously suspected. There is developing concern about adverse effects of Al on neurobehavioural development (Golub & Domingo 1996 & 1997). This issue has not been extensively investigated. Although Al contamination of dialysates has decreased over the past two decades, Al is still a major causative agent in the low bone turnover diseases, osteomalacia and adynamic bone in those with impaired renal function (Cannata Andía 2000). An initial indicator of elevated systemic Al is often an anaemia due to decreased haemoglobin synthesis.

The primary Al sources for man are in table 1. Its presence in drinking water derives from natural sources and water treatment methods. Water treatment generally increases the percentage of dissolved, small molecular weight, chemically reactive, and possibly more readily absorbed, Al species (LaZerte *et al.* 1997; Health Canada 1998). Although water is the most extensively studied Al source, it provides only about 1% of normal daily human intake (table 1). The primary normal source of Al for man is food (table 1). The Al content of foods is highly variable (Pennington 1987; Greger & Sutherland 1997). The major contributors to the human diet are food products containing Al in food additives, such as grain products, processed cheese, and salt (Pennington 1987; Nieboer *et al.* 1995). Occupational Al exposure occurs primarily in Al processing and welding, and can significantly increase Al exposure and produce neurotoxicity (Sjögren *et al.* 1997; Riihimäki *et al.* 2000). Al exposure can result from the use of Al chlorohydrate in antiperspirants. Common iatrogenic sources are vaccines; Al hydroxide, used as both an antacid and a phosphate binder; and Al contamination in haemodialysis fluids and intravenous solutions, including total parenteral nutrition solutions (Greger & Sutherland 1997). As a result of the concern about Al in the latter, particularly to very young persons, the United States Food and Drug Administration now requires that Al concentrations be under 25 μg/l in large volume parenteral drug products used in total parenteral nutrition (US FDA 2000).

Al, as Al^{3+}, is found in various chemical species in the above sources and *in vivo*. These species have different physical, chemical and biological properties (Harris *et al.* 1996 & 1997). The solubility of Al^{3+} is lowest at pH 6.2. Acidic and alkaline solutions, as well as some complexing ligands, increase its solubility. The toxicokinetics of Al species can vary greatly. The information available on Al spe-

Table 1.

Common sources of Al for man, Al concentration in the source, resultant daily Al exposure from the source, estimated bioavailability from the source and calculated amount of Al absorbed daily.

Source	Al concentration	Daily Al exposure	Estimated percentage absorbed	Daily Al absorbed (μg/kg)[a]
Normal exposure				
Water	Average ~70 μg/l	100 μg	0.3[b]	0.005
Food		5000–10,000 μg[c]	0.1–0.3[d]	0.08–0.5
Air-rural	0.2 μg/m^3	4 μg	1.5-2 from lungs[e]	0.001
			0.1–0.3 from GI tract	0.0001
Air-urban	1 μg/m^3	20 μg	1.5-2 from lungs[e]	0.006
			0.1–0.3 from GI tract	0.0006
Antiperspirants	5–7.5%[f]	50,000–75,000 μg	up to 0.012[g]	up to 0.1
Vaccines	150–850 μg/dose	1.4–8 μg[h]	100 eventually[i]	0.07–0.4
Elevated exposure				
Antacids/phosphate Binders		up to 5,000,000 μg	0.1	80
Industrial air	25–2500 μg/m^3	250–25,000 μg per work day	1.5–2 from lungs[e]	0.6–8
			0.1–0.3 from GI tract	0.008–1
Allergy immunotherapy	150–850 μg/dose	7–40 μg[j]	100 eventually [i]	0.1–0.6
Dialysis solution	If tap water 50 μg/l	2400 μg	25[k]	9
Total parenteral nutrition solutions	Neonatal/infant 110–270 μg/l [l]	11–27 μg/kg	100	11–27
	Adult 40–135 μg/l [l]	80–270 μg	100	1.2–4.2

[a] Based on a 65 kg adult except for vaccines (20 kg child) and total parenteral nutrition solution in neonates and infants.
[b] From table 3.
[c] Pennington & Schoen (1995).
[d] Estimates based on daily urinary Al excretion/daily Al intake from food and Stauber *et al.* (1999).
[e] Based on Al exposure in an industrial setting: Gitelman *et al.* (1995); Pierre *et al.* (1995).
[f] Based on 20% Al zirconium glycine complex or 25% Al chlorohydrate in a topical product, which are typical concentrations (POISINDEX information system, Micromedex, Inc, Englewood, CO, USA).
[g] Based on Flarend *et al.* (2001), assuming that the percentage of Al absorbed does not change with repeated exposure.
[h] Based on 20 injections in the first 6 years of life and an average weight of 20 kg.
[i] Flarend *et al.* (1997).
[j] Based on a typical allergen extract treatment schedule and maintenance injections for 3.5 years of one allergen extract.
[k] Kovalchik *et al.* (1978).
[l] Based on maintenance fluids and normal neonatal/infant or adult electrolyte supplementation.

cies from thermodynamic modeling suggests there are two primary Al species in plasma and one in brain extracellular fluid (table 2). The effective equilibrium constant, a ratio of the concentration of all reaction products in solution to the concentrations of the reactants, indicates the affinity of the ligand for Al at pH 7.4. Considerations of Al distribution into tissues and out of the brain should focus on these predominant species. Even though ligand exchange reactions with Al are slow, there is very little kinetic data on pre-equilibrium Al species.

The naturally occurring isotope of Al is ^{27}Al. It was the only isotope used in Al research until the past decade. ^{27}Al is ubiquitous. Al is most commonly quantitated by electrothermal atomic absorption spectroscopy (ETAAS), which has a detection limit of $\leq$1 μg/l. Al contamination can derive from airborne particulates, reagents used to digest and dilute samples, glass labware and insufficiently cleaned labware of any composition that comes into contact with the sample. Contamination is often encountered and has rendered many studies useless, particularly those measuring Al in blood and brain at very low concentrations. Contamination can produce false elevations in the apparent Al concentration. ETAAS determines total Al. Al speciation requires a separation method prior to Al analysis when ETAAS or another destructive analytical technique is used to quantitate Al. The percentage of Al absorbed from most exposure routes is very small. Therefore, researchers had to administer amounts of Al that were >10 times the human daily Al intake in food or >1000 times the daily Al intake in water to be able to investigate the influence of oral Al intake on Al in blood, urine, or tissue. In the past decade accelerator mass spectrometry (AMS) has been applied to the quantitation of ^{26}Al (Flarend & Elmore 1998), enabling the study of extremely small Al concentrations. A disadvantage is the high cost of AMS analysis.

Al bioavailability

Al is absorbed from all routes of exposure that have been investigated. Its bioavailability is very dependent on the route of exposure. This section will review the major routes of exposure and current estimates of bioavailability.

Oral bioavailablity.

Oral exposure has been the most extensively studied route of Al absorption. It provides the greatest Al exposure for most people. However, in selected populations, it is not the route that provides the greatest risk of systemic Al accumulation and toxicity.

Methods to determine oral Al bioavailability. Bioavailability (fractional absorption) is the amount absorbed compared to the amount administered. For Al, systemic bioavailability, the fraction that ultimately reaches systemic circulation from which it has access to the target organs of its toxicity, is most relevant. Three methods to estimate Al bioavailability were discussed by Wilhelm *et al.* (1990). Method no. 1 is balance studies. In Method no. 2 absorption is based on urinary excretion/dose. Method no. 3 compares areas under the plasma Al concentration-time curve after oral and intravenous administration. A limitation of Method no. 2 to estimate bioavailability is that it does not account for the Al that is retained, excreted by non-renal routes, or excreted by the kidneys after study completion. A number of studies have used urinary Al excretion plus tissue Al to partially overcome this limitation. Another method used in recent human studies is estimation of absorption from a single blood sample × the estimated volume of distribution, to calculate the % of the dose in plasma. This method underestimates bioavailability because it does not account for Al that has been excreted prior to sample collection, Al that has distributed out of the vascular compartment, or the Al that is absorbed after sample collection. The method does not assure peak serum Al was sampled unless independently determined. It has been concluded that bioavailability estimates based on incomplete blood data have considerable error (Priest *et al.* 1996). These studies are not included in this MiniReview.

Bioavailability of the Al in drinking water. Several studies have estimated oral Al bioavailability using conditions relevant to Al consumption in drinking water. They used Al doses that reasonably compare with daily oral intake from water by man (0.1 mg, ~1.5 μg/kg, table 1) and introduced the Al as a free ion, as might be found in drinking water,

Table 2.

The predominant binding ligands for Al *in vivo*, their effective equilibrium constants with Al, their concentrations in plasma and brain extracellular fluid (based on values in cerebrospinal fluid), and the percentage of Al predicted to be associated with that ligand (all data provided by Wes Harris).

	Effective equilibrium constant with Al	Plasma		Brain extracellular fluid	
Ligand	(log)	Concentration (μmol/l)	% of A1 species	Concentration (μmol/l)	% of A1 species
Transferrin	13.7, 12.6	30	91	<0.25	4
Citrate	11.6	99	7–8	180	90
Hydroxide (free)	6.5	0.4	< 1	0.4	5
Phosphate	9.3	1100	< 1	490	1

Table 3.

Oral Al bioavailability determined in studies that model drinking water consumption.

Subject	Al administered	Oral Al bioavailability expressed as % by [method[a]]	Reference
Rat	3.8 ng ^{26}Al+63 ng ^{27}Al (total Al ~0.27 μg/kg) in distilled water	0.04 [2+bone]	Jouhanneau *et al.* (1993).
Rat	3.8 ng ^{26}Al+63 ng ^{27}Al (total Al ~0.22 μg/kg) in HCl @ pH 1.9	~ 0.1 [2+bone, liver & brain]	Jouhanneau *et al.* (1997).
Rat	3.8 ng ^{26}Al+63 ng ^{27}Al (total Al ~0.24 μg/kg) @ pH 1.6–2	0.06 [2+bone]	Drüeke *et al.* (1997).
Rat	74.5 ng ^{26}Al+552 ng ^{27}Al (total Al ~2.3 μg/kg) @ pH 5 1 & 2) in dilute HCl 3 & 4) plus 90:1 Ca:Al and 13:1 Mg:Al, as $CaCO_3$ & Mg CO_3 1 & 3) no food in stomach 2 & 4) food in stomach	1) 0.23 2) 0.21 3) 0.24 4) 0.41 [3]	Yokel *et al.* (2001).
Man	100 ng ^{26}Al+100 μg ^{27}Al (total Al ~1.4 μg/kg) as $AlCl_3$	0.1 & 0.24 in 2 subjects [2]	Hohl *et al.* (1994).
Man	141 ng ^{26}Al+12.5 μg ^{27}Al (total Al ~0.2 μg/kg) in public water from near Sydney, @ pH 6.5	0.22 [2]	Priest *et al.* (1998).
Man	224 μg ^{27}Al/day for 2 days in pH 7 alum-treated water from a municipal water treatment plant versus reconstituted soft water containing <1 μg ^{27}Al/l	0.36 [2]	Stauber *et al.* (1999).

[a] Methods, for details, see *Methods to determine oral Al bioavailability.*
2=Bioavailability based on urinary Al excretion/dose.
3=Bioavailability based on comparison of area under the serum Al concentration × time curve after oral and intravenous dosing.

or used water from municipal water suppliers. Results of these studies are shown in table 3. There are no good data to indicate if Al bioavailability from water is dose/concentration dependent. These results suggest that oral Al bioavailability from water is in the range of 0.05 to 0.4%; and most likely ~0.3%.

Recognition of Al bioavailability and neurotoxicity lead the U.S. Environmental Protection Agency to put Al on its Contaminant Candidate List (US EPA 1998). The Agency felt additional research on Al was needed as part of the consideration for development of drinking water regulations and guidance. Health Canada in conjunction with the Federal Provincial Subscommittee on drinking water established an operational guidance value of <100 μg Al/l in treated water from conventional treatment plants (Health Canada 1998). California proposed a public health goal for Al in drinking water (California EPA 2000).

Bioavailability of the Al in beverages and foods. Although food comprises the primary source of Al for the typical human being (>90%, table 1), there are very little data on oral Al bioavailability from foods, or beverages other than water. It has generally been assumed that oral Al bioavailability from food is less than from water due to Al incorporation in high molecular weight, relatively insoluble, complexes (Health Canada 1998). For example, a much lower percentage of the Al in tea was in chemically labile species, 15%, than in drinking water, 61–75% (Stauber *et al.* 1999). Reiber *et al.* (1995) suggested that a substantial portion of Al, regardless of the chemical species consumed, will be solubilized to monomeric Al in the stomach and subsequently converted to poorly soluble Al species in the near neutral pH of the upper intestine. As the stomach is not an important site of Al absorption, this implies that oral Al bioavailability should be Al species independent. Citrate and other ligands influence Al absorption, suggesting this hypothesis is an oversimplification. Stauber *et al.* (1999) estimated Al bioavailability from drinking water and food in humans and found it to be comparable from these two sources, ~0.3–0.5%. Al bioavailability from food was based on 24-hr urinary Al excretion during the second day of consumption of a controlled diet. This diet provided ~ 3000 μg Al/day, which is below typical dietary intake (table 1). Absorption of Al from food consumed prior to the study, which likely provided >3000 μg Al/day, may have contributed to the urinary Al excretion during the study. This would produce an over-estimation of Al bioavailability from the controlled diet. Others have attempted to estimate oral Al bioavailability from food by comparing 1) average daily urinary Al excretion and 2) average daily Al intake from food. Daily urinary Al excretion has been estimated to be 4–12 μg (Nieboer *et al.* 1995). Average daily Al intake by adults in the US is estimated to be 5000–10,000 μg (see table 1). This suggests an Al bioavailability from food of ~0.1%.

If Al bioavailability from the diet is indeed 0.1%, then food, not water, provides the major source of Al absorbed daily (table 1). Al bioavailability from water would have to exceed that from food by ~50 to 100 times for water to be the primary source of absorbed Al. The limited published data suggest that oral Al bioavailability from food is in the same range as from water, suggesting food provides the majority of Al that is absorbed by the typical human being.

The influence of food and dietary components on oral Al absorption. It has been assumed that the presence of food in the stomach inhibits Al absorption, due to Al association with organic ligands in food. Only a few studies directly addressed this hypothesis. Walton *et al.* (1994) conducted an ambitious study to assess the influence of beverages and foods on oral Al absorption. Their results show increased peak serum Al concentration and urinary Al excretion after co-administration with orange juice, and to a much smaller extent, coffee and wine. Meat and a carbohydrate/cereal product decreased Al absorption. However, neither the blood nor urine samples obtained hourly for 4 hr after dosing enable determination of oral Al bioavailability. Drüecke *et al.* (1997) reported 0.94% oral ^{26}Al bioavailability in 24-hr fasted rats versus 0.06% in free-feeding rats. However, rodents and rabbits recycle their faeces to increase essential nutrient absorption and usually have stomach contents 24–36 hr after food removal, suggesting the fasted rats may have had stomach contents. In contrast, we, Yokel *et al.* (2001) did not find a difference in oral ^{26}Al bioavailability in rats exposed to a procedure that resulted in no stomach contents versus rats that did have chow in their stomachs (table 3).

The addition of calcium and magnesium carbonates, modeling hard water, did not affect oral Al bioavailability from water (Yokel *et al.* 2001). There is not much evidence that food in the stomach or water quality significantly affect oral Al bioavailability. There are also no good reported data from which one can estimate the relative bioavailability of Al from beverages and food, other than Al plus citrate in solution compared to water, discussed below.

Health Canada (1998) reviewed some of the factors affecting Al absorption. They cited evidence that low pH, increased solubility of the Al species, the presence of citrate and other small organic acids, and uraemia increase Al absorption whereas phosphorus and perhaps silicon reduce Al absorption. The pH can greatly influence Al speciation, and presumably Al bioavailability. The ability of citrate to increase oral Al bioavailability has received much attention. Three proposed mechanisms; citrate enhanced Al solubility in the gut, transport of Al citrate into mucosal cells, and citrate opening of epithelial tight junctions, were reviewed by Gregger & Sutherland (1997). The different times of peak serum Al and citrate after Al citrate consumption suggest Al was not released into blood as Al citrate (Taylor *et al.* 1998). Other carboxylic acids similarly enhance Al absorption from Al hydroxide, although less effectively. It has been suggested that this is due to enhanced Al solubility. Phosphate and Al inhibit each other's absorption, due to formation of insoluble Al phosphates. Conversely, Al absorption increases as solution pH decreases from the nadir of Al solubility. Al fluoride produced higher plasma Al concentrations than Al chloride (Allain *et al.* 1996), raising concern about the presence of both Al and F in drinking water. Silicon, as monomeric silicic acid, forms soluble hydroxyaluminosilicate whereas oligomeric silica forms a more stable complex (Jugdaohsingh *et al.* 2000). Silicon reduced gastrointestinal absorption of ^{26}Al (consumed in orange juice, a source of citrate) by 85% in fasted human beings (Edwardson *et al.* 1993). Silicon may abrogate citrate-enhanced Al solubility. However, Drüeke *et al.* (1997) did not find an effect of co-administered Si on absorption of ^{26}Al given with citrate to rats after eating. Jugdaohsingh *et al.* (2000) found inhibition of ^{26}Al absorption by the poorly absorbable oligomeric, but not the absorbable monomeric silica, perhaps explaining the discrepancies in the above results.

The influence of biological factors on oral Al absorption. Uraemia appears to increase Al absorption by increasing gut permeability of the paracellular pathway (Greger & Sutherland 1997). There are suggestions in the literature that oral Al bioavailability is greater in the weanling than growing rat and increases in the aged and Alzheimer-diseased human being. In contrast, oral Al bioavailability was not found to be significantly different between adult human beings aged 36–59 versus 59–76 years old (Stauber *et al.* 1999). These studies do not provide convincing evidence to resolve the important question whether oral Al bioavailability is age-related.

Oral bioavailability from drugs. The published data on oral bioavailability of Al species relevant to drugs includes Al hydroxide; the antacid sucralfate; Al lactate, which is used in dental products for sensitive teeth; and Al in the presence of citrate. As shown in table 1, antacids/phosphate binders have the potential to produce the greatest increase of absorbed Al of all Al sources. This presents a problem when these products, which usually contain Al hydroxide, are consumed in large amounts by those who have impaired or no renal function. This practice, along with contaminated dialysate, which is largely avoided today, has produced most of the cases of Al-induced toxicity. The use of Al hydroxide by renal patients continues in some parts of the world. Citrate and other small carboxylic acids can increase Al absorption, as noted above.

Wilhelm *et al.* (1990) cited much of the work conducted with ^{27}Al, which of necessity, used large doses of Al. Priest *et al.* (1996) estimated oral Al bioavailability from 6-day urinary ^{26}Al output in 2 subjects. Both received intragastric dosing of ^{26}Al incorporated into Al hydroxide, ^{26}Al hydroxide in the presence of citrate, and ^{26}Al citrate. Estimates of the percentage of ^{26}Al absorbed from ^{26}Al hydroxide in the absence and presence of citrate averaged 0.01% and 0.14%, respectively. Al bioavailability from ^{26}Al citrate was 0.52%. These limited results mirror many reports showing very low Al bioavailability from Al hydroxide (and sucralfate) and augmentation by citrate. Oral Al bioavailability from Al hydroxide appears to be less than from food or water. However, as noted in table 1, the daily intake of Al from Al hydroxide-based antacids can greatly exceed that from the diet and water.

The site and mechanisms of absorption of ingested Al. The proximal intestine appears to be the primary site of Al ab-

sorption (Greger & Sutherland 1997). Absorption of Al was suggested to be a two-step process, uptake by mucosal cells followed by much slower release into blood (Wilhelm *et al.* 1990). Evidence that mucous in the gastrointestinal tract can bind Al, to retard and perhaps inhibit its absorption (Powell *et al.* 1999), suggests a third-step. Greger & Sutherland (1997) identified the putative mechanisms of absorption; passive (diffusion) and active (carrier- and vesicular-mediated transport) processes across intestinal cells as well as paracellular diffusion between these cells. They reviewed the evidence for absorption of Al by paracellular diffusion and active transport. The active processes that have been suggested to mediate intestinal Al absorption include mechanisms of Ca uptake such as Ca channels, Na transport processes, and a role for transferrin (Greger & Sutherland 1997; van der Voet & de Wolff 1998). The calcium and iron status of the animal inversely influence Al absorption. Transferrin addition to the vascular perfusion medium of the isolated rat intestine increased vascular Al, suggesting a role for transferrin mediating Al release from mucosal cells into blood.

Absorption of inhaled Al.

Inhalation exposure results from cosmetic, occupational and environmental Al sources. The only data amenable to Al bioavailability estimates are from occupational exposure. Occupational exposure to Al fumes, dusts and flakes can elevate serum, bone and urine Al. It is not known if the Al is absorbed from the lung or from the gastrointestinal tract after mucociliary clearance because experimental studies have not isolated the pulmonary from other absorption routes. The rapid increase of Al in the serum and urine after Al fume exposure suggested pulmonary absorption (Sjögren *et al.* 1985). Fractional Al absorption by industrial employees was $\sim$ 1.5–2%, based on the relationship between urinary Al excretion and the airborne soluble Al to which they were exposed (Gitelman *et al.* 1995; Pierre *et al.* 1995; Sjögren *et al.* 1997). Pulmonary Al absorption appears to be more efficient than gastrointestinal absorption.

Intranasal absorption.

It has been suggested that Al may directly enter the brain from the nose through olfactory neurones, which run from the roof of the nasal cavity to the olfactory bulb. Tjälve & Henriksson (1999) reviewed the anatomy of this process and the published studies with metals. Inorganic cadmium, mercury and nickel were found in the olfactory bulb after their introduction into the rat nasal cavity, but not in other brain regions. This suggests they lack the ability to cross synapses in the olfactory bulb, to distribute to other neurones. In contrast, manganese was found in numerous brain regions (demonstrating trans-synaptic distribution).

Implantation of Gelfoam® saturated with Al lactate or Al chloride solution into the nasal recess of rabbits for one month resulted in neuropathological changes and elevated Al in the brain (Perl & Good 1987). Limited results in rats exposed to Al chlorohydrate by inhalation showed Al in brain stem nuclei, also suggesting olfactory nerve uptake and trans-synaptic Al distribution (Divine *et al.* 1999). However, there are no data that could be used to estimate Al bioavailability following intranasal exposure to indicate whether this represents a significant route of exposure.

Transdermal absorption.

Al salts, such as Al chlorohydrate, are extensively used in antiperspirants. They suppress eccrine sweating by forming a hydroxide precipitate in the sweat duct or by denaturing keratin in the cornified layer that surrounds the opening of the sweat duct. Neither mechanism would suggest significant Al absorption through the sweat duct. A study of Al absorption following single underarm applications of ^{26}Al chlorohydrate to two subjects suggested up to 0.012% of the ^{26}Al might eventually be absorbed, presumably through the skin (Flarend *et al.* 2001). It is not known if comparable Al absorption would continue to occur from daily application, which would determine if this source of Al might significantly contribute to daily Al absorption (table 1). The authors suggest that interaction of Al with the sweat duct would reduce subsequent Al absorption.

Systemic appearance of Al after parenteral administration.

Intravenous Al administration creates the potential risk of Al accumulation and toxicity due to 100% bioavailability and the avid Al binding by transferrin that prevents rapid clearance. Similarly, exposure to Al-contaminated dialysate can result in diffusion of Al into plasma and its retention by transferrin. Manifestations of the resulting Al-induced toxicity are described in Health Canada (1998) and California EPA (2000). To ascertain Al bioavailability following intramuscular injection, and the potential for vaccines to contribute to Al exposure, Flarend *et al.* (1997) administered ^{26}Al hydroxide or ^{26}Al phosphate adjuvants (which did not contain allergens) to two rabbits**.** Comparison of blood ^{26}Al to one rabbit that received intravenous ^{26}Al citrate suggested that all of the injected Al may eventually be absorbed, even from these insoluble Al species. Therefore, intravenous Al exposure from dialysis, total parenteral nutrition or other solutions as well as intramuscular exposure from the 20 vaccinations given in the first 6 years of life or a typical treatment regimen of allergen extract immunotherapy could constitute significant sources of absorbed Al (table 1). The daily Al exposure to dialysis solution is based on 110 l/dialysis three times weekly and to total parenteral nutrition solution is based on 0.1 l/kg/day and 2 l/day in neonatal/infant and adult patients, respectively.

Distribution

Al distributes unequally to all tissues throughout normal and Al-intoxicated human beings (Alfrey *et al.* 1980; Di Paolo *et al.* 1997) and Al-treated experimental animals (Greger & Sutherland 1997). The volume of distribution of Al in

animals, reviewed by Wilhelm *et al.* (1990), suggests an initial distribution consistent with blood volume. Within blood, Al is ~ equally distributed between plasma and cells. The higher concentration in lung of normal humans may reflect entrapment of airborne Al particles whereas the higher concentrations in bone, liver and spleen may reflect Al sequestration. The skeletal system and lung have ~ 50 and 25% of the 30–50 mg Al body burden of the normal human (ATSDR 1999); brain has ~ 1%. Considering the Al species in plasma (table 2), it is likely that Al transferrin and Al citrate account for the majority of the Al that distributes to tissues from the vascular compartment.

Iron status negatively correlates with tissue Al accumulation. This may be due to competition between these two chemically-similar trivalent cations, enabling greater transferrin-mediated extravascular distribution and ferritin storage of Al in the presence of low iron concentrations (Greger & Sutherland 1997).

Al citrate readily distributes out of blood. The effects of citrate on brain and bone Al concentrations and uptake of Al into cells have been inconsistent. Citrate forms a small molecular weight complex with Al that appears to enhance Al distribution and elimination when compared to Al transferrin (Maitani *et al.* 1994). In the presence of renal function, citrate may enhance Al clearance; in renal impairment citrate may enhance tissue Al accumulation.

Calculations show insignificant amounts of Al fluoride species will form in the presence of normal plasma fluoride (~100 μg/l) and normal or elevated plasma Al. This suggests fluoride is unlikely to affect Al distribution or elimination, unless fluoride and Al are involved in mixed ligand complexes involving other ligands (Wes Harris, personal communication). Similarly, silicon concentrations in biological fluids are very low. It was suggested that it is quite unlikely monomeric Al silicate species play any significant role in the biological chemistry of Al (Harris *et al.* 1996 & 1997).

Distribution into and out of the brain.

The brain has lower Al concentrations than many other tissues. Increased brain Al is seen in Al-associated neurotoxicity in the human (Alfrey *et al.* 1980). Studies of AD victims inconsistently showed elevated brain Al (Yokel 2000), contributing to the controversy concerning a possible role of Al in the aetiology of this disease. Al can enter the brain from blood. This appears to occur by two processes. Roskams & Connor (1990) provided evidence that transferrin can mediate Al transport across the blood-brain barrier by transferrin-receptor mediated endocytosis (TfR-ME) of Al transferrin, the predominant Al species in plasma (table 2). Intravenous injection of ^{26}Al transferrin resulted in brain ^{26}Al concentrations (~0.001% of the injected dose/gm brain) within 4 hr (Yokel *et al.* 2000). TfR-ME could account for this appearance of Al in the brain if the rate of Al transport is similar to that reported for Fe. Transferrin increased *in vitro* Al uptake into neuroblastoma cells and oligodendroglia but not astrocytes (Golub *et al.* 1999), further suggesting transferrin-mediated distribution of Al. Allen *et al.* (1995) gave Al citrate intravenously at a rate that produced plasma concentrations in excess of the ability of transferrin to bind the Al. This presumably permitted Al citrate to be the predominant Al species in plasma. The appearance of Al in brain extracellular fluid was too rapid to be mediated by TfR-ME. This suggests a second mechanism transporting Al citrate across the blood-brain barrier into the brain that is independent of transferrin.

There appears to be a mechanism to transport Al out of the brain. When Al citrate was infused intravenously to produce constant brain and blood extracellular fluid Al concentrations, the brain extracellular fluid Al concentration was below that in blood extracellular fluid (Allen *et al.* 1995). This suggests a mechanism at the blood-brain barrier to reduce extracellular fluid brain Al by transporting it into blood. Transferrin concentration is very low in cerebrospinal fluid, and presumably brain extracellular fluid, whereas the citrate concentration is higher in brain extracellular fluid than in plasma, favoring Al citrate as the predominant Al species in brain extracellular fluid (table 2). It is therefore likely that Al citrate is the Al species transported out of the brain. Genetic differences or competing ligands for these blood-brain barrier Al influx and efflux carriers may influence brain Al concentrations.

Distribution into and out of bone.

Bone Al concentration in normal human beings is a few times greater than brain Al, on a dry weight basis (Alfrey *et al.* 1980; Di Paolo *et al.* 1997). Al increased more in bone than brain in haemodialysis patients (Alfrey *et al.* 1980; Di Paolo *et al.* 1997). Human beings with dialysis encephalopathy had brain and bone Al concentrations about 10- and 85 times higher than controls, respectively (Alfrey *et al.* 1980). Several animal studies showed ~100 times higher bone than brain ^{26}Al concentrations after a single ^{26}Al dose, suggesting greater Al entry into bone than brain. Al concentrates at the mineralization front of bone.

Elimination rates and tissue retention

Plasma Al half-lives ($t_{1/2}$s) were summarized by Wilhelm *et al.* (1990). Elimination $t_{1/2}$s of years were seen after termination of occupational Al exposure, based on urinary Al excretion (Ljunggren *et al.* 1991). An estimated terminal $t_{1/2}$ in one human being who received intravenous ^{26}Al was 7 years (Priest *et al.* 1995). This kinetic behaviour might result from retention of Al in a depot from which it is slowly eliminated. This depot is probably bone which stores ~50% of the human Al body burden. Slow Al elimination coupled with continued exposure would be predicted to produce an increasing body burden with age. Brain, serum and bone Al have been reported to increase with age (Markesbery *et al.* 1984; Zapatero *et al.* 1995; Greger & Sutherland 1997).

There is more than one compartment of Al storage. The $t_{1/2}$ of ^{26}Al in rat brain was >100 days following intravenous ^{26}Al transferrin dosing (Yokel *et al.* 2000). This is

consistent with reports suggesting little decrease of brain Al in humans after renal transplantation and termination of the Al that had been given during renal failure. As noted above, injection of ^{26}Al increased bone ^{26}Al ~100 times more than brain, yet steady-state bone Al concentration is <100 times that of brain. This suggests Al clearance from bone is more rapid than from brain, which is reasonable considering bone turnover and lack of neurone turnover. The elimination $t_{1/2}$ of Al from human brain is predicted to be very long. This is concluded from the $t_{1/2}$ of Al in the tibia of rats, 38–173 days (Greger & Sutherland 1997), compared to >100 days in brain, above, and a human ^{26}Al $t_{1/2}$ of 7 years, above, which is believed to be due to redistribution of Al out of bone.

Excretion

Urine accounts for >95% of excreted Al. Reduced renal function increases the risk of Al accumulation and toxicity in the very young, elderly and renally diseased human being (Greger & Sutherland 1997). Biliary Al accounts for ≤2% of total Al elimination in man, dog, rabbit and rat (Kovalchik *et al.* 1978; Priest *et al.* 1995; Yokel *et al.* 1996a; Yokel *et al.* unpublished results). Chelators can increase Al clearance into urine, bile and dialysate (Yokel et al. 1996b & 1997). Citrate appears to have chelation properties, to form small molecular weight Al species that can be excreted in the presence of adequate renal function, potentially protecting against the accumulation and toxicity of absorbed Al.

Summary

Studies in the past decade, particularly those using physiologically-relevant doses of ^{26}Al, have refined previous estimates of Al bioavailability from water and have provided Al biovailability estimates for inhalation, dermal and intramuscular exposure. The contribution of food to daily Al absorption, compared to other sources, needs to be determined to significantly advance the assessment of the major sources and routes of Al exposure in the human.

Acknowledgements

This journal article is based on information contained in the document "Aluminium bioavailability (a compilation and critical review)" prepared under contract to Health Canada. This journal article is the sole responsibility of the authors and does not necessarily reflect the policies or views of the Government of Canada. Health Canada will not be liable for any reliance on the information in this journal article by any person.

References

Alfrey, A. C., A. Hegg & P. Craswell: Metabolism and toxicity of aluminum in renal failure. *Amer. J. Clin. Nutr.* 1980, **33**, 1509–1516.

Allain, P., F. Gauchard & N. Krari: Enhancement of aluminum digestive absorption by fluoride in rats. *Res. Commun. Mol. Pathol. Pharmacol.* 1996, **91**, 225–231.

Allen, D. D., C. Orvig & R. A. Yokel: Evidence for energy-dependent transport of aluminum out of brain extracellular fluid. *Toxicol.* 1995, **98**, 31–39.

ATSDR (Agency for Toxic Substances and Disease Registry): *Toxicological profile for aluminum (Update).* U.S. Department of Health and Human Services, Public Health Service, 1999, 352 pp.

California EPA, Draft Public health goal for aluminum in drinking water, Office of Environmental Health Hazard Assessment, 2000, 68pp, visit: http://www.oehha.ca.gov, Water, Public Health Goal, Aluminum.

Cannata Andía, J. B.: Adynamic bone and chronic renal failure: An overview. *Amer. J. Med. Sci. 2000,* **320**, 81–84.

Di Paolo, N., A. Masti, I. B. Comparini, G. Garosi, M. Di Paolo, F. Centini, S. Brardi, G. Monaci & V. Finato: Uremia, dialysis and aluminium. *Int. J. Artif. Organs* 1997, **20**, 547–552.

Divine, K. K., J. L. Lewis, P. G. Grant & G. Bench: Quantitative particle-induced X-ray emission imaging of rat olfactory epithelium applied to the permeability of rat epithelium to inhaled aluminum. *Chem. Res. Toxicol.* 1999, **12**, 575–581.

Drüeke, T. B., P. Jouhanneau, H. Banide, B. Lacour, F. Yiou & G. Raisbeck: Effects of silicon, citrate and the fasting state on the intestinal absorption of aluminium in rats. *Clin. Sci. (Colch.)* 1997, **92**, 63–67.

Edwardson, J. A., P. B. Moore, I. N. Ferrier, J. S. Lilley, G. W. A. Newton, J. Barker, J. Templar & J. P. Day: Effect of silicon on gastrointestinal absorption of aluminium. *Lancet* 1993, **342**, 211–212.

Flarend (Flack), R. & D. Elmore: Aluminum-26 as a biological tracer using accelerator mass spectrometry. In: *Aluminum toxicity in infant's health and disease.* Eds.: P. Zatta & A. C. Alfrey. World Scientific, Singapore, London, 1998, pp. 16–39.

Flarend, R. E., S. L. Hem, J. L. White, D. Elmore, M. A. Suckow, A. C. Rudy & E. A. Dandashli: *In vivo* absorption of aluminium-containing vaccine adjuvants using ^{26}Al. *Vaccine* 1997, **15**, 1314–1318.

Flarend, R., T. Bin, D. Elmore & S. L. Hem: A preliminary study of dermal absorption of aluminum from antiperspirants using aluminum-26. *Fd. Chem. Toxicol.* 2001, in press.

Gitelman, H. J., F. R. Alderman, M. Kurs-Lasky & H. E. Rockette: Serum and urinary aluminium levels of workers in the aluminium industry. *Ann. Occup. Hyg.* 1995, **39**, 181–191.

Golub, M. S. & J. L. Domingo: What we known and what we need to know about developmental aluminum toxicity. *J. Toxicol. Environ. Health* 1996, **48**, 585–597

Golub, M. S. & J. L. Domingo: What we know and what we need to know about developmental aluminum toxicity. In: *Research issues in aluminum toxicity.* Eds:. R. A. Yokel & M. S. Golub. Taylor and Francis, Washington, D. C., USA, 1997, pp. 151–163. (Same as Golub & Domingo 1996).

Golub, M. S., B. Han & C. L. Keen: Aluminum uptake and effects on transferrin mediated iron uptake in primary cultures of rat neurons, astrocytes and oligodendrocytes. *NeuroToxicology* 1999, **20**, 961–970.

Greger, J. L. & J. E. Sutherland: Aluminum exposure and metabolism. *Crit. Rev. Clin. Lab. Sci.* 1997, **34**, 439–474.

Harris, W. R., G. Berthon, J. P. Day, C. Exley, T. P. Flaten, W. F. Forbes, T. Kiss, C. Orvig & P. F. Zatta: Speciation of aluminum in biological systems. *J. Toxicol. Environ. Health* 1996, **48**, 543–568.

Harris, W. R., G. Berthon, J. P. Day, C. Exley, T. P. Flaten, W. F. Forbes, T. Kiss, C. Orvig & P. F. Zatta: Speciation of aluminum in biological systems. In: *Research issues in aluminum toxicity.* Eds.: R. A. Yokel & M. S. Golub. Taylor and Francis, Washington, D. C., USA, 1997, pp. 91–116. (Same as Harris *et al.* 1996).

Health Canada, Environmental Health Directorate, Guidelines for Canadian Drinking Water Quality. Supporting Documentation. Part II. Aluminum. 22 pp., 1998, Visit: http://www.hc-sc.gc.ca/waterquality.

Hohl, C., P. Gerisch, G. Korschinek, E. Nolte & T. H. Ittel: Medical application of ^{26}Al. *Nucl. Instr. Meth. Physics Res.* 1994, **B 92,** 478–482.

Jeffery, E. H., K. Abreo, E. Burgess, J. Cannata & J. L. Greger: Systemic aluminum toxicity: effects on bone, hematopoietic tissue, and kidney. *J. Toxicol. Environ. Health* 1996, **48**, 649–665.

Jeffery, E. H., K. Abreo, E. Burgess, J. Cannata & J. L. Greger: Systemic aluminum toxicity: effects on bone, hematopoietic tissue, and kidney. In: *Research issues in aluminum toxicity.* Eds.: R. A. Yokel & M. S. Golub, Taylor and Francis, Washington, D. C., USA 1997, pp. 133–149. (Same as Jeffery *et al.* 1996).

Jouhanneau, P., B. Lacour, G. Raisbeck, F. Yiou, H. Banide, E. Brown & T. Drüeke: Gastrointestinal absorption of aluminium in rats using ^{26}Al and accelerator mass spectrometry. *Clin. Nephrol.* 1993, **40**, 244–248.

Jouhanneau, P., G. M. Raisbeck, F. Yiou, B. Lacour, H. Banide & T. B. Drüeke: Gastrointestinal absorption, tissue retention, and urinary excretion of dietary aluminum in rats determined by using ^{26}Al. *Clin. Chem.* 1997, **43**, 1023–1028.

Jugdaohsingh, R., D. M. Reffitt, C. Oldham, J.P. Day, L.K. Fifield, R.P.H. Thompson & J.J. Powell: Oligomeric but not monomeric silica prevents aluminum absorption in humans. *Amer. J. Clin. Nutr.* 2000, **71**, 944–949.

Kovalchik, M. T., W. D. Kaehny, A. P. Hegg, J. T. Jackson & A. C. Alfrey: Aluminum kinetics during hemodialysis. *J. Lab. Clin. Med.* 1978, **92**, 712–720.

LaZerte, B. D., G. van Loon & B. Anderson: Aluminum in water. In: *Research issues in aluminum toxicity.* Eds.: R. A. Yokel & M. S. Golub. Taylor and Francis, Washington, D. C., USA, 1997, pp. 17–45.

Ljunggren, K. G., V. Lidums & B. Sjögren: Blood and urine concentrations of aluminium among workers exposed to aluminium flake powders. *Brit. J. Ind. Med.* 1991, **48**, 106–109.

Maitani T, H. Kubota, N. Hori, K. Yoshihira & M. Takeda. Distribution and urinary excretion of aluminium injected with several organic acids into mice: relationship with chemical state in serum studied by the HPLC-ICP method. *J. Appl. Toxicol.*1994,**14**,257–261

Markesbery, W. R., W. D. Ehmann, M. Alauddin & T. I. M. Hossain: Brain trace element concentrations in aging. *Neurobiol. Aging* 1984, **5**, 19–28.

Nieboer, E., B. L. Gibson, A.D. Oxman & J.R. Kramer: Health effects of aluminum: a critical review with emphasis on aluminum in drinking water. *Environ. Rev.* 1995, **3**, 29–81.

Pennington, J. A. T.: Aluminium content of foods and diets. *Fd. Addit. Contam.* 1987, **5**, 161–232.

Pennington, J. A. T. & S. A. Schoen: Estimates of dietary exposure to aluminium. *Fd. Addit. Contam.* 1995, **12**, 119–128.

Perl, D. P. & P. F. Good: Uptake of aluminium into central nervous system along nasal-olfactory pathways. *Lancet* 1987, **1**, 1028.

Pierre, F., F. Baruthio, F. Diebold & P. Biette: Effect of different exposure compounds on urinary kinetics of aluminium and fluoride in industrially exposed workers. *Occup. Environ. Med.* 1995, **52**, 396–403.

Powell, J. J., M.W. Whitehead, C.C. Ainley, M.D. Kendall, J.K. Nicholson & R. P. H. Thompson: Dietary minerals in the gastrointestinal tract: hydroxypolymerisation of aluminium is regulated by luminal mucins. *J. Inorg. Biochem.* 1999, **75**, 167–180.

Priest, N. D., D. Newton, J. P. Day, R. J. Talbot & A. J. Warner: Human metabolism of aluminium-26 and gallium-67 injected as citrates. *Hum. Exp. Toxicol.* 1995, **14**, 287–293.

Priest, N. D., R. J. Talbot, J. G. Austin, J. P. Day, S. J. King, K. Fifield & R. G. Cresswell: The bioavailability of ^{26}Al-labelled aluminium citrate and aluminium hydroxide in volunteers. *BioMetals* 1996, **9**, 221–228.

Priest, N. D., R. J. Talbot, D. Newton, J. P. Day, S. J. King & L. K. Fifield: Uptake by man of aluminium in a public water supply. *Hum. Exp. Toxicol.* 1998, **17**, 296–301.

Reiber, S., W. Kukull & P. Standish-Lee: Drinking water aluminum and bioavailability. *Journal AWWA* 1995, **87**, 86–100.

Riihimäki, V., H. Hänninen, R. Akila, T. Kovala, E. Kuosma, H. Paakkulainen, S. Valkonen & B. Engström: Body burden of aluminum in relation to central nervous system function among metal inert-gas welders. *Scand. J. Work Environ. Health* 2000, **26**, 118–130.

Roskams, A. J. & J. R. Connor: Aluminum access to the brain: a role for transferrin and its receptor. *Proc. Natl. Acad. Sci. USA* 1990, **87**, 9024–9027.

Sjögren, B., V. Lidums, M. Håkansson & L. Hedström: Exposure and urinary excretion of aluminum during welding. *Scand. J. Work Environ. Health* 1985, **11**, 39–43.

Sjögren, B., C.-G. Elinder, A. Iregren, D. R. C. McLachlan, & V. Riihimäki: Occupational aluminum exposure and its health effects. In: *Research issues in aluminum toxicity.* Eds.: R. A. Yokel & M. S. Golub. Taylor and Francis, Washington, D. C., USA, 1997, pp. 17–45.

Stauber, J. L., T. M. Florence, C. M. Davies, M. S. Adams & S. J. Buchanan: Bioavailability of Al in alum-treated drinking water. *Journal AWWA* 1999, **91**, 84–93.

Taylor, G. A., P. B. Moore, I. N. Ferrier, S. P. Tyrer & J. A. Edwardson: Gastrointestinal absorption of aluminium and citrate in man. *J. Inorg. Biochem.* 1998, **69**, 165–169.

Tjalve, H. & J. Henriksson: Uptake of metals in the brain via olfactory pathways. *NeuroToxicology* 1999, **20**, 181–195.

US EPA, Announcement of the drinking water contaminant candidate list, *Fed Register* 1998, 63, 10273–10287; http://www.access.gpo.gov/getdoc.html

US FDA, Aluminum in large and small volume parenterals used in total parenteral nutrition, *Code of Federal Regulations* 2000, 21CFR201.323; http://wais.access.gpo.gov/nara/cfr/cfr-retrieve.html

van der Voet, G. B. & F.A. de Wolff: Intestinal absorption of aluminium: effect of sodium and calcium. *Arch. Toxicol.* 1998, **72**, 110–114.

Walton, J., G. Hams & D. Wilcox: Bioavailability of aluminium from drinking water: Co-exposure with foods and beverages. Urban Water Research Association of Australia, Research Report No. 83 Melbourne, 1994. ISBN 1875298 84 3.

Wilhelm, M., D. E. Jäger & F. K. Ohnesorge: Aluminium toxicokinetics. *Pharmacology & Toxicology* 1990, **66**, 4–9.

Yokel, R. A.: The toxicology of aluminum in the brain: A review. *NeuroToxicology*, 2000, **21**, 813–828.

Yokel, R. A., K. A. Meurer, T. L. Skinner & A. M. Fredenburg: The 3-hydroxypyridin-4-ones more effectively chelate aluminum in a rabbit model of aluminum intoxication than does desferrioxamine. *Drug Metab. Disp.* 1996a, **24**, 105–111.

Yokel, R. A., P. Ackrill, E. Burgess, J. P. Day, J. L. Domingo, T. P. Flaten & J. Savory: Prevention and treatment of aluminum toxicity including chelation therapy: status and research needs. *J. toxicol. Environ. Health* 1996b, **48**, 667–683.

Yokel, R. A., P. Ackrill, E. Burgess, J. P. Day, J. L. Domingo, T. P. Flaten & J. Savory: Prevention and treatment of aluminum toxicity including chelation therapy: status and research needs. In: *Research issues in aluminum toxicity.* Eds.: R. A. Yokel & M. S. Golub. Taylor and Francis, Washington, D. C., USA, 1997, pp. 223–239. (Same as Yokel *et al.* 1996b)

Yokel, R.A., S.S. Rhineheimer, P. Sharma, D. Elmore & P.J. McNamara: Brain aluminum clearance is slow. *Tox. Sci.* 2000, **54**, 35.

Yokel, R.A., S.S. Rhineheimer, R.D. Brauer, P. Sharma, D. Elmore, & P.J. McNamara: Aluminum bioavailability from drinking water is very low and is not influenced by stomach contents or water hardness. *Toxicology* 2001, in press.

Zapatero, M. D., A. Garcia de Jalon, F. Pascual, M. L. Calvo, J. Escanero & A. Marro: Serum aluminum levels in Alzheimer's disease and other senile dementias. *Biol. Trace Elem. Res.* 1995, **47**, 235–240.