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The Deleterious Health Effects of Aluminium: An Updated Review

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ABSTRACT

Aluminium is a frequently used metal for food processing and packaging. It is a choice of metal for food processing as it is light-weight and possesses excellent heat conductivity. In addition, it can be easily molded and therefore used in food packaging. Aluminium foils and cans are very popular for storage of food for short and long duration of time, respectively. In spite of its voluminous use in food industries, there are growing concerns of aluminium-associated health risks in human. It is reported that aluminium leach-out from the storage vessel or foil and contaminate the food material. The aluminium leaching is more during heating and in the presence of acidic contents in food. Over the course of time, aluminium accumulates and is stored predominantly in lungs, bones, liver, kidneys and brain. Researchers are investigating the level of aluminium accumulation in body and its effect in developing diseases. Several reports highlighted that aluminium increases the risk of Alzheimer's disease and other neurological disorders. In addition, the high internal concentrations of aluminium may induce convulsions, esophagitis, gastroenteritis, kidney damage, liver dysfunction, loss of appetite, loss of balance, muscle pain, psychosis, shortness of breath, weakness, fatigue and birth defects in new born. However, a systematic investigation is required to stablish the relationship between aluminium and its deleterious effects in human. The present work highlights application of aluminium in food, its route of entry in body, affected organs and developing disease. The alternatives to the aluminium in food processing and packaging are also highlighted.

KEY WORDS: ALUMINIUM, ACCUMULATION, ESOPHAGITIS, GASTROENTERITIS.

INTRODUCTION

Aluminium is the third most abundant element in the earth's crust (Stahl, 2011). In 1825, it was isolated by the Danish physicist Hans Oersted. Most aluminium is stably bound as an ore in clay, minerals, rocks and gem stones This lightweight, non-magnetic, silvery white-coloured metal can be produced from the aluminium ore—bauxite—by a high energy consuming mining process; it is this process which provides the world its main source of the metal. As a consequence of this technological progress, aluminium has become increasingly bioavailable for approximately the past 125 years. Food additives, drinking water and leaching from aluminium cooking utensils are some of the sources of exposure to aluminium. Minimal exposure of aluminum to our bodies is not a problem. Human bodies can excrete small amounts very efficiently; an aluminum tolerable daily intake of 1 mg/kg body weight /day has been established by the World Health Organization (WHO) of the United Nation (UN) (Exley 2013; Gupta, 2019).

In the medicine field, aluminium compounds are now widely used being in the composition of numerous pharmaceutical conditionings (e.g., antacids, phosphate binders, buffered aspirins, vaccines, or antiperspirants), making them a potential threat (Spencer, 1979;

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Kramer, 2014; Gupta, 2019). To date, the main known toxicological effects of aluminium included anaemia, neurodegenerative disorders such as Alzheimer disease and dementia, amyotrophic lateral sclerosis, hepatotoxicity, or diverse reproductive disorders (Jabeen, 2016, Muselin, 2016). Other symptoms that have been observed in individuals with high internal concentrations of Aluminum are colic, convulsions, esophagitis, gastroenteritis, kidney damage, liver dysfunction, loss of appetite, loss of balance, muscle pain, psychosis, shortness of breath, weakness, fatigue and birth defects in new born (Khalil, 2014).The analysis of Al is challenging because of its low concentrations in some foods and the potential for contamination during sample preparation and analysis (Saiyed, 2005; Klotz, 2017).

Figure 1: A representation of human exposure to aluminium and its impact on the body. Source: (Kramer, 2014).

Exposure of Aluminium: Aluminium has long been established in medical applications as, e.g., an adjuvant in vaccines and an agent against pathological hyperhidrosis with a low side-effect profile. It is a natural component of drinking water and foodstuffs and is a component of many manufactured materials (Stahl, 2011). Aluminium compound is used in many diverse and important industrial applications such as alums (Aluminium sulphate) in water treatment and alumina in abrasives and furnace lining (Klotz, 2017).

The internal exposure levels of those exposed in workplaces where aluminum welding is carried out, during electrolysis in aluminum production, or in the processing industries (e.g., foundries, powder production) can be significantly higher compared with individuals not exposed to aluminum at work, meaning that the reference values derived for the general population may be exceeded in these workers. Longitudinal studies on aluminum welders revealed that the aluminum content in welding fumes correlated with aluminum concentrations in blood and urine. Aluminium exposure from drinking water has been extensively investigated in relation to the development of neurological disorders, including AD, due to the proposed enhanced bioavailability of aluminium in this form (Krewski, 2007; Klotz, 2017). Aluminium in foodstuffs: Aluminium has been shown to enter the human body predominantly through the oral route, as it is present in food, food additives, pharmaceuticals, utensils, and water (Landry, 2014).

Table 2. Aluminium content of various foodstuffs and spices (n = 3) (Semwal, 2006)

Food	Al concentration (mg kg−1)
Rice (*Oryza sativa*)	0.9 ± 0.001
Wheat (*Triticum aestivum*)	1.2 ± 0.10
Bengal gram dhal (*Cicer arietinum*)	4.7 ± 0.06
Kabuli channa (*Cicer arietinum*)	5.2 ± 0.02
Red gram dhal (*Cajanus cajan*)	3.2 ± 0.009
Black gram dhal (*Phaseolus mungo*)	4.1 ± 0.03
Onion (*Allium cepa*)	0.8 ± 0.004
Garlic (*Allium sativum*)	1.1 ± 0.01
Clove (*Eugenia caryophyllus*)	0.45 ± 0.002
Cinnamon (*Cinnamomum zelyanicum*)	1.6 ± 0.03
Red chilli (*Capsicum annuum*)	0.51 ± 0.003
Turmeric (*Curcuma longa*)	0.89 ± 0.007
Cumin (*Cumimum cymimum*)	0.72 ± 0.005
Pepper (*Piper nigrum*)	3.2 ± 0.06
Coriander (*Coriandrum sativum*)	0.95 ± 0.006
Cardamom (*Elettaria cardamomum*)	0.49 ± 0.002
Black cardamom (*Amomum subalatum*)	0.84 ± 0.003
Fenugreek (*Trigonalla foenum-graecum*)	0.78 ± 0.002
Mustard (*Brassica juncea*)	0.48 ± 0.08
Mean ± SD.	

Aluminium ingestion could result from: (1) contamination of food via leaching from cooking utensils; (2) storage of food in contact with aluminium; (3) aluminium salts added to water during purification; (4) aluminium compounds added to food, e.g., aluminium in baking powder; (5) aluminium in vegetables (plants assimilate aluminium to varying degrees depending on species, the availability of aluminium in the soil, soil pH etc.); (6) use of aluminium containing drugs (Tennakone, 1992). The most recent analysis shows that to meet the current annual global demand for aluminium 11 kg of the metal must be cast for every person on Earth (Exley, 2013).

It is reported that aluminium salts can be absorbed by the gut and concentrated in various human tissues including bone, parathyroid, and brain. Aluminium bioavailability from occupational inhalation exposure

is ~ 2% whereas oral aluminium bioavailability from water has been reported to be 0.1 to 0.4% (Krewski, 2007; Bassioni, 2012). Owing to acid rain, numerous metal ions, including aluminium are escaping from mineral deposits where they had been stored for billions of years as hydroxy-aluminosilicates (HAS), increasing the biological availability of aluminium to living organisms. According to this hypothesis, acid rain is acting as a key to the lock for aluminium release, causing its appearance in polluted waters (Crisponi 2013).

Table 2. Aluminium content of various foodstuffs and spices (n = 3) (Semwal, 2006)

Source	Amount
Natural sources	2 – 5 mg/day
Tea leaves	0.1 % – 1 %
Coffee from aluminium moka	0.8 – 1.2 mg/cup
Drinking water	0.07 mg/l
Beverages in aluminium cans	0.04 – 1.0 mg/l
Cooked spinach	25 mg/kg
Unprocessed food	0.1 – 7 mg/kg
Food additives	10 – 20 mg/day
Food cooked in aluminium pots	0.2 – 125 mg/kg
Soy-based infant milk formulas	6 – 11 mg/kg
Antacids	35 – 200 mg/dose
Buffered aspirin	9 – 50 mg/dose
Antidiarrhoeal drugs	36 – 1450 mg/ dose
Antiperspirants	50 – 75 mg (daily exposure)
Vaccines	0.15 – 0.85 mg/ dose
Parenteral nutrition solutions for Adults	40 – 135 µ g/l
Parenteral nutrition solutions for Infants	10 – 270 µ g/l

European Food Safety Authority (EFSA) issued an opinion on the safety of aluminium from dietary intake in which the typical aluminium content of unprocessed foodstuffs was reported at less than 5 mg per kg food, but it also referred to higher levels of 5 to 10 mg/kg. Based on animal studies, the EFSA derived a tolerable weekly intake of 1 mg aluminium per kg body According to the EFSA assessment, the dietary intake of aluminium in the general population is between 0.2 to 1.5 mg per kilogram of body weight per week, equivalent to a daily intake of 1.7 to 13 mg of aluminium for a 60 kg adult. Human exposure is divided into two categories, "external contact" and "dietary contact"; examples of these two categories are presented in Table 5 (Stahl 2017; Sander, 2018).

The beneficial effects of aluminium-containing antacids for the treatment of peptic ulcer are well recognized. However, these antacids can cause adverse reactions. It is the aluminium which interacts in the intestine with anions, such as phosphate and fluoride, and affects the absorption of these dietary and possibly also endogenously secreted elements. Aluminium forms insoluble complexes with the dietary phosphate which becomes unavailable for absorption (Spencer, 1979). It is one of the common practices to wrap meat items in Al foil for baking and grilling. Aluminium can be toxic to bone, bone marrow and the nervous system (Kaiser, 1985; Jabeen, 2016).

Routes through which aluminium enters into the human body: Ingested metals may be considered in two categories: those soluble throughout the potential pH range of the gastrointestinal lumen (approximately pH l-s), such as Na, Mg and Ca, and those susceptible to hydroxy-polymerization, such as Al, Cu, Fe, Mn and Zn (Kaiser, 1985). The inhalation of Al via mouth may result in absorption across the lung epithelia or the deposition of Al in the lung and its subsequent passage to the gut . the mucociliary pathway may be the principal mechanism by which Al in the lung become systemic (Exley, 1996; Flarend, 2001).

The skin: The outer epidermis or stratum corneum of the skin is an enucleated layer of keratin-rich cells held within a predominantly lipid intercellular matrix. Transport of topically applied aluminium, such as an antiperspirant or a sunscreen, across this layer would involve passive diffusion by both trans- and paracellular routes and is expected to be minimal. Aluminium chlorohydrate (ACH) is a water-soluble aluminium complex (Covington, 1990) which is the active ingredient in some 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. Other antiperspirants are made from similar aluminium salts which may also contain zirconium (Laden, 1988; Robert, 2001; Flarend, 2001). It is believed that ACH acts as an antiperspirant by precipitating inside the eccrine sweat glands to produce insoluble aluminium hydroxide, which then plugs the gland and blocks the secretion of sweat (Flarend, 2001; Exley, 2013).

The Nose: It has been suggested that Aluminium may directly enter the brain from the nose through olfactory neurones, which run from the roof of the nasal cavity to the olfactory bulb. Inhalation exposure results from cosmetic, occupational and environmental Al sources (Robert 2001). The inhalation of Al via the mouth may result in absorption across the lung epithelia or the deposition of Al in the lung and its subsequent passage to the gut. This mucociliary pathway may be the principal mechanism by which Al in the lung becomes systemic (Emily 1994).The cilia of the olfactory epithelium are nonmotile and aluminium impacting upon this surface will be presented with a large surface area for association with this surface and for dissolution into the mucus layer covering the epithelium. The olfactory epithelium is essentially continuous with the olfactory nerve and olfactory bulb and presents an uptake route for aluminium, as complexes or particulates, into the brain (Exley, 2013).

The Lung: Absorption of Inhaled Aluminum Although inhalation exposure is not likely to be of concern to the general population, miners, smelters, and other metal workers can be exposed to toxic levels of aluminum through dusts and aerosols. It has been estimated that about 3% of aluminum is absorbed into the blood from the lung (Emily 1994).The lung epithelia are diverse in respect of their composition of different cell types and, in the alveolar epithelium in particular, myriad transport proteins and channels. The highly dynamic nature of the lung epithelium means that it must be a site for the accumulation of aluminium and a surface for the uptake of aluminium into lung tissues and access to the systemic circulation (Exley, 2013).

Table 4. Aluminium in foodstuffs (milligrams per kilogramme or milligrammes per litre). Source: (Stahl, 2011; Stahl 2017).

Product	Number	Minimum	Maximum	Mean value	Median value
Dates	18	1.23	6.72	3.39	2.57
Pine nuts	9	12.0	38.6	26.1	23.8
Wheat	65	1	19	4	3
Baking mixes	37	1	737	51	6
Bread	107	1	14	3	2
Spelt	28	BG	3.0	0.63	0.37
Loaf-shaped yeast fruit cakes	60	3	22	10	9
Fine pastries in aluminum trays	38	1	537	19	3
Salt pretzels and similar savory biscuits	185	2	218	13	4
Pasta	24	1	76	10	4
Herbal-teas	12	14	67	40	45
Cocoa powder	37	80	312	165	160
Chocolate	84	6	150	48	39
Confectioneries	115	1	184	17	8
Malt	50	1	12	7	7
Evaporated milk	49	0.08	0.66	0.290	0.205
Soft cheese	13	0.3	5.39	1.68	1.37
Harz cheese	22	0.15	0.78	0.400	0.438
Milk curd	53	0.03	1.73	0.224	0.109
Beer and mixed drinks containing 237	0.4	4.2	0.5	0.4	
beer, draught beer Fruit juice and fruit juice drinks	59	0.4	47	3	1
Wine and fruit wine	65	0.4	15	2	1
Mineral water, spring water and table water	171	0.1	0.07	0.01	0.006
Ready-cooked meals in aluminum tray	31	1	13	3	1
Soups	16	1	15	5	3
Pork (canned)	8	0.76	1.35	1.23	1.08
Beef (canned)	6	0.52	1.1	0.634	0.669
Game	149	<BG	1.1	0.110	0.025
Herring (canned)	32	0.16	5.99	1.99	1.60
Crustaceans	45	0.07	40.0	4.47	2.54
Flour	65	1	19	4	3

The Gut: Gastrointestinal absorption is not the only route of Al uptake. Other intake routes have been investigated including nasal, dermal, and respiratory. Some absorption of aluminum may occur in the stomach; the majority of aluminum absorption, however, is expected to occur in the intestine. In general, the two-step absorption process in the gut is 1) lumen to mucosa and 2) mucosa to bloodstream (Devoto, 1994; Peto, 2010). The reality of Al absorption in the GI tract may well be one of several mechanisms, both passive and active. The individual contributions of these processes to the net absorption of Al are dependent upon a number of factors including the chemistry of the gut lumen and the health of the individual. The rate of absorption of Al, for example, via the gut, will depend upon the route of uptake, with paracellular transport expected to proceed at a much faster rate than cellular internalization (Exley, 1996; Peto, 2010).

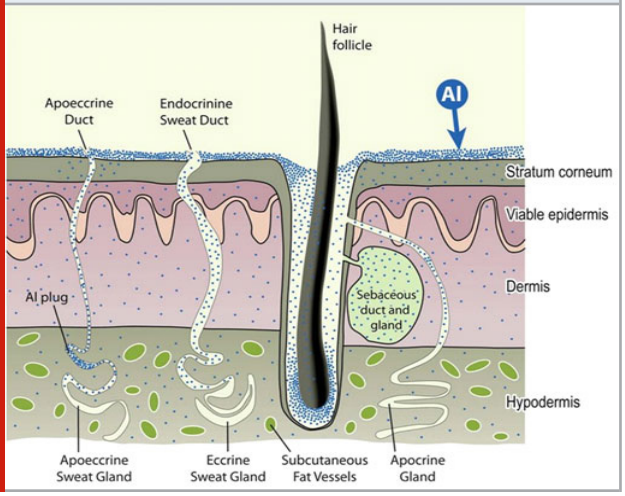
Absorption, Distribution, Metabolism, and Excretion: In humans, Al is absorbed and accumulated systemically via (1) the diet (including water and medications), with absorption occurring across the gastrointestinal tract; (2) the inhalation of partic- ulate Al through the nose

(Roberts, 1986), with absorption occurring across the olfactory epithelium; (3) the inhalation of particulate Al through the mouth, with absorption occurring via the gastrointestinal tract and, possibly, across the lung epithelia, and, controversially, the skin. The term "distribution" has been interpreted to encompass both the transport of Al and its accumulation in the various body compartments (Exley, 1996). About 90% of the Al circulating in the blood is transported bound to transferrin (iron-transporter protein), while the rest of Al binds to albumin and citrate in the blood (Igbokwe, 1919; Barr et al., 1993; Röllin et al., 1993; Ittel, 1993).

Table 5. Aluminium—external and dietary contact. Source: (Stahl 2017).

Examples of external contact	Examples of dietary contact
Construction materials, including alloys (e.g., vehicle construction, aerospace, suitcases, facades, tent construction)	Packaging and containers (beverage and food cans, coffee pots, outdoor cutlery and dishes, coffee capsules, household aluminium foil)
Electrotechnology, including alloys (e.g., electrical conductors)	Nanoparticles in sunscreens
Fuel for solid-fuel rockets (up to 30% Al) and pyrotechnics	Foodstuffs
Pigments for paints (e.g., "silver" bronze paints)	Toothpaste (e.g., AlF3: caries prophylaxis)
Metal polish (Al2O3: paste, suspension in MeOH or H_2O)	Pharmaceuticals (e.g., heartburn medicines-pH-regulation; vaccine adjuvants)
Organic syntheses (e.g., LiAlH4:reducing agent)	Vaccine adjuvant— (increases the immune reaction)
Jewellery and ornaments	Cosmetics(e.g., deodorants–antitranspirants) Food additives (e.g., as colorants or stabilizers)

Figure 3: The skin is a sink for topically applied aluminium and will act as a source of biologically reactive aluminium both to structures within the skin and to the systemic circulation (Christopher 2013).



The distribution of aluminum is better understood as accumulating mostly in bones and lungs (Krewski et al., 2007). Other affected areas are soft tissues (usually after intravenous fluid contamination), the spleen, liver, kidney, nervous tissues, muscles, and the heart (Greger, 1993). 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 (Robert, 2001). The metabolism of Al might otherwise be defined as the systemic and cellular response to the body burden of Al. The metabolism of other nonessential, potentially toxic, metals is achieved through specific cellular responses such as the metal-induced metallothionein system (Exley, 1996).

The absorbed fraction of aluminum is bound rapidly to the tissues - the remaining free aluminum is excreted through the kidneys - however, aluminum clearance is about 5% of glomerular filtration rate secondary to protein binding (Sedman, 1992). Tissue accumulation of Al is reduced by citrates and fluorides through renal excretion when the transferrin-Al binding capacity of the blood is exceeded. Al is also excreted in the milk, bile, feces, sweat, hairs, nails, sebum and semen (Igbokwe, 2019). The kidneys eliminate the absorbed aluminium in amounts of 15-55 µg/day through urine and faeces. Al excretion is lower in people with reduced renal function and this can lead to toxic effects because of the nephrotoxicity of Al.

In dialysis settings, Al is eliminated from the dialysate by reverse osmosis and deionization since the early 1980s.5 The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (KDOQI) recommends measurement of serum aluminum level (SAL) at least once per year to assess Al levels and risk for Al toxicity.6 These guidelines also recommend measurement of SAL every 3 months for patients who take Al-containing medications (Hsu, 2016; Gupta, 2019).

Blood: The blood is probably the main distribution network for systemic aluminium though this statement is made with the proviso that there are no reliable data on the aluminium content of lymph. Because of the high concentration of potential ligands relative to the concentration of the metal, aluminum is expected to be entirely soluble in blood at concentrations up to

100 ug/1. Based on more than 50 literature sources, Ganrot reported that the most credible values for serum aluminum are in the range of 1-5 pg/1, or 0.037-0.185 uM; he judged that values much higher than these stems largely from contamination (DeVoto, 1994). During hemodialysis (HD), essential kidney functions such as the elimination of water and metabolic wastes as well as the correction of the electrolyte and acid/base state, are replaced by the artificial purification system (Kazi, 2008; Khalil, 2014).

Elimination of aluminum: Minimal exposure to aluminum isn't a problem; our bodies can excrete small amounts very efficiently, a tolerable daily intake (TDI) for aluminum of 1mg/kg body weight/day has been established by an international committee of experts under the auspices of the world Health Organization (WHO) and Food and Agricultural Organization (FAO) of the United Nations. Aluminium is excreted from the body, and hence removed from the body burden, by a number of routes including via the faeces, urine, sweat, skin, hair, nails, sebum and semen. The routes of excretion are mostly from the kidneys, which accounts for 95% of elimination, and bile. 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 and Sutherland 1997; Exley, 2013; Landry, 2014; Khalil, 2014).

However, absorption of Al in the gut can easily vary by a factor of 10 or more (Edwardson et al., 1993), and this is a reflection of both dietary and physiological differences among individuals. Gastrointestinal mucus was suggested to contribute toward the effective excretion of Al (Powell et al., 1994). The mucus acted as a sink for Al, with mucus sloughing ensuring the removal of the Al in the feces (Exley, 1996; Khalil, 2014).

Leaching of Aluminum: Aluminium cooking utensils are widely used in homes, restaurants and community kitchens and in the food industry, hence the intake of aluminium from utensils is of great concern (Semwal, 2006). Nowadays, it is a common practice to wrap meat and fish prior to oven cooking. Due to the possible relation between aluminum uptake and the specific diseases mentioned in many literatures, it is important to determine the aluminum concentration in the food wrapped with aluminum foil (Khalol, 2014). It was also reported that the breast piece of chicken comprises of more aluminum level than the leg. Aluminum is found to leach out from the foil due to different stimulants; particularly in distilled water as well as in acidic and alkaline media. Rise in temperature also enhance the rate of migration of aluminum in acidic media (Jabeen, 2016).

It is well established that Al dissolution is highly dependent on pH, temperature, and the presence of complexing agents. Al exhibits a passive behavior in aqueous solutions due to the protective compact Al2O3 film on its surface. However, the solubility of this protective film increases in acidic and alkaline medium. According to Bi (1996), Al leaching in aqueous solutions may be explained by the following chemical reaction occurring on the surface of the Al cookware (Verıssimo, 2006; Juhaiman, 2010).

$$Al2O_3 + 6H+ \rightarrow 2Al_3 + 3H_2O$$

where $Al2O_3$ is a protective film. The free aluminium in solutions reacts with organic acids found in food, like citric, oxalic and acetic acids, and other complexing ligands like fluoride ion and hydroxyl. These reactions may take place simultaneously and promote each other Regardless the type of food that is being cooked, the recipe and the way of preparing the food must play an important role on the aluminium leaching levels. The interaction between food and aluminium packaging can also be a potential source of aluminium release which can contribute to aluminium ingestion. Aluminium packaging in the food industry is very popular because it is impermeable, greaseproof, non-absorptive, inert, highly formable with excellent dead fold characteristics, and easily recyclable (Verıssimo, 2006).

Aluminium in pharmaceutical products: The route of intoxications with pharmaceuticals and agrochemical sources may be through inhalation of aerosols, ingestion of medications or by parenteral administration. Humans and animals are exposed to Al-containing medications such as phosphate binders, antacids, buffered analgesics, antidiarrheal and antiulcer drugs (Lione, 1983, 1985; Yokel and McNamara, 2001). Various intravenously administered pharmaceuticalproducts were reported to contain 684–5977 µg/g of Al (Sedman et al., 1985). Many antacids contain 104–208mg of Al per tablet, capsule or 5 ml of suspension (Zhou and Yokel, 2005; Krewski et al., 2007).

The use of aluminium in non-prescription drugs has increased substantially in recent time. Aluminium containing antacids are widely used in medicinal preparations. The most common form of aluminium in these preparations is aluminium hydroxide (Rajwanshi, 1997). The beneficial effects of aluminium-containing antacids for the treatment of peptic ulcer are well recognized. However, these antacids can cause adverse reactions (Spencer, 1979). A normal therapeutic regimen of antacids contains 5 g of aluminium hydroxide per day, a dosage several hundred times higher than the amount normally ingested from food. It is the aluminium which interacts in the intestine with anions, such as phosphate and fluoride, and affects the absorption of these dietary and possibly also endogenously secreted elements. Aluminum forms insoluble complexes with the dietary phosphate which becomes unavailable for absorption. In addition to the interaction of aluminum with the dietary phosphate and fluoride, the absorption of aluminum from these antacids and the deposition of aluminum in various tissues has been reported in recent years (Spence, 1979; Crisponi, 2013).

Children seem to absorb aluminium more readily than adults and there are several reports of children with renal

failure developing aluminium toxicity from aluminium-containing phosphate binders prior to commencing dialysis. Infants given aluminium-containing antacids showed significant aluminium absorption compared to controls, as shown by blood and urine aluminium levels. Aluminium toxicity should be suspected in individuals who have had pharmacological exposure to oral aluminium or contaminated parenteral fluid. Any individual with a serum level of aluminium by tameless atomic absorption of>100 l.tg/1, who has encephalopathy, should be assumed to be aluminium toxic. Children with failure to thrive and osteopenia, who have been exposed to aluminium, should have a bone biopsy followed by quantitative histology and aluminium staining (Sedman, 1992). Parenteral nutrition solutions are contaminated with aluminium. Aluminium can cause osteomalacia in patients who receive long-term parenteral nutrition. It can also lead to encephalopathy in newborns and osteopenia in premature infants (Popinska, 2010; Mudge, 2011).

Vaccination: Aluminum is added to vaccines to help the vaccine work more effectively, but unlike dietary aluminum which will usually clear rapidly from the body, aluminum used in vaccines and injected is designed to provide a long-lasting cellular exposure (Tomljenovic, 2013). Aluminum salts are used as adjuvants in preparations for vaccines and hyposensitization. An aluminum dose of 0.1–0.8 mg is absorbed upon oneoff application of a vaccine approved in Europe (Klotz, 2017).

Some concerns have been raised in recent years regarding the possible adverse effects of aluminium in childhood vaccines on the maturation of the immune system. In fact, aluminium is used as an adjuvant in multiple childhood vaccines, including DtaP, Pediatrix (DtaP, hepatitis B, polio combination), Pentacel (DtaP, HIB, polio combination), hepatitis A, hepatitis B, Haemophilus influentiza B (HIB), human papilloma virus (HPV) and pneumococcal vaccines (Crisponi, 2013).

Toxicological effects of aluminium on humans: The toxicological effects of Aluminum (Al) might depend, between others, of administration route, the time and level of exposure, and the speciation of the metal (Bernal, 2009). Aluminium can be toxic to bone, bone marrow and the nervous system (Yang, 2014).

Aluminium toxicity has been a topic of great interest since 1976 when the metal was first associated with neurological syndrome called dialysis encephalopathy (Rajwanshi, 1997). A causal role for aluminium in human pathology has been clearly established in at least three diseases: dialysis dementia, osteomalacia and microcytic anaemia without iron deficiency (Bernal, 2009). The principal symptoms of aluminium toxicity are:– diminished intellectual function, forgetfulness, inability to concentrate;– speech and language impairment;– personality changes, altered mood, depression;– dementia;– visual and/or auditory hallucinations;– osteomalacia with fracturing;– motor disturbances;– weakness, fatigue, mainly related to microcytic anaemia;– epileptic seizures (Crisponi, 2013; Rajwanshi, 1997).

The exact mechanism of aluminum toxicity is, however, not fully understood. It is considered certain that aluminum is potentially cell- and neurotoxic. Enzyme activity may be disrupted and mitochondrial function may be impaired. Toxic effects of Al arise mainly from its pro-oxidant activity which results in oxidative stress, free radical attack and oxidation of cellular proteins and lipids (Igbokwe, 2019). Current research indicates that oxidative stress may be a factor in various neurological diseases including AD (Campbell, 2002; Stahl, 2017).

Children seem to absorb aluminium more readily than adults and there are several reports of children with renal failure developing aluminium toxicity from aluminium-containing phosphate binders prior to commencing dialysis. In 2004, the U.S. Food and Drug Administration (FDA) set a limit for aluminum from parenteral sources for individuals with impaired kidney function and premature neonates at no greater than 4 to 5 µg/kg bw/day, stating that levels above those have been associated with CNS and bone toxicity (Mudge, 2011).

In addition, according to the FDA, tissue loading may occur at even lower levels of administration. What the upper limit for “safe” aluminum exposure might be for healthy neonates is not known. In spite of these above data, newborns, infants and children up to 6 months of age in the U.S. and other developed countries receive 14.7 to 49 times more than the FDA safety limits for aluminum from parenteral sources from vaccines through mandatory immunization programs (Tomljenovic, 2011).

Affected organs

Kidney damage: The effect of renal failure on aluminium (Al) accumulation in different organs and the subsequent systemic toxicity is well known (Mahieu, 2005). Aluminium causes oxidative injuries to the kidney and liver leading to tissue degeneration and necrosis, and associated serum biochemical derangements. Although the kidney appears to be able to excrete the aluminium in healthy persons it is not known the limit of this elimination capacity and it is certain that people suffering from chronic renal failure do not possess the ability to excrete it (Merta, 2006; Igobokwe, 2019).

Al accumulation in bone: Al has also been implicated in the development of osteomalacia (bone softening), especially in hemodialysis patients who experience high Al exposure from the Al-contaminated dialysate used in dialysis procedures (Peto, 2010). The skeletal system is a target for aluminum toxicity. Aluminum incorporates into the bone and causes physiochemical mineral dissolution as well as cell mediated bone resorption (Becaris, 2010). Bone Al concentration in normal human beings is a few times greater than brain Al, on a dry weight basis. Al increased more in bone than brain in haemodialysis patients (Alfrey et al. 1980; Paolo et al.

1997). Aluminum levels in bone tissue of healthy people range from 5 to 10 mg/kg (Jabeen, 2016).

Brain: Patients exhibited elevated aluminum concentrations in plasma and brain Those affected disorientation, memory impairments, and, at advanced stages, dementia. The cause of these effects lies, firstly, in the slow—compared with other organs—removal of aluminum from the brain and, secondly, in the multitude of biological processes affected by aluminum in the brain (Klotz, 2017). Aluminium may enter the brain through multiple routes: from blood, either through choroid plexus or across the blood brain barrier (BBB) and from the nasal cavity into olfactory nerves, followed by direct distribution into the brain (Crisponi, 2013).

Liver: For orally ingested aluminum, however, the tissues mostly affected are the bones, liver and the blood itself (Landry, 2014).

Disease due to aluminum: To date, aluminum has been linked to neurological and bone abnormalities, Alzheimer's and Parkinson's diseases, and cognitive impairments (Greger and Sutherland, 1997; Greger, 1993; Krewski et al., 2007)

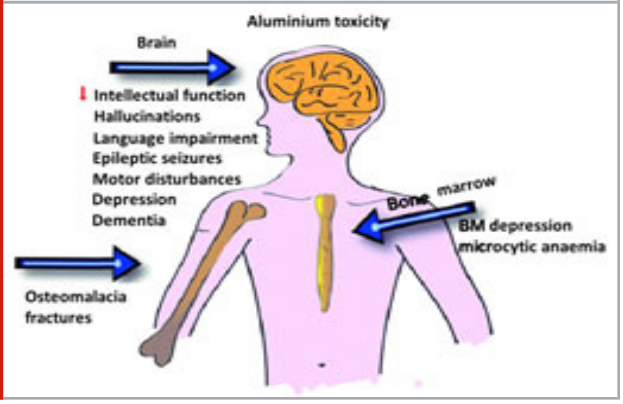
Neurodegenerative effects due to aluminium: Since aluminium is primarily excreted by the kidney, its accumulation is an important concern in patients with impaired renal functions. It can get accumulated in organs such as bones, brain and other tissues and is associated with toxic sequelae. Accumulation of aluminium in the brain appears to be a major cause in the development of a neurological syndrome called 'dialysis encephalopathy' or 'dialysis dementia' and a specific form of osteomalacia (aluminium bone disease) due to accumulation in the bone (Gupta, 2019).

Aluminum (Al^{3+}) exhibits a high affinity to proteins, which it is able to cross-link. In contrast to other ubiquitously occurring metals such as iron, manganese, and zinc, aluminum is not known to perform a physiological function in the human organism. In humans, Al accumulation in the brain and scalp hairs has been associated with neurodegenerative diseases such as dialysis-associated encephalopathy, Alzheimer's disease, Parkinson's disease (dementia), amyotropic lateral sclerosis, multiple sclerosis and autism (Exley, 2014; Klotz, 2017; Igbokwe, 2019).

As such, aluminum accumulation within the central nervous system (CNS) over the course of aging appears to reach a critical threshold in which sufficient amounts of this neurotoxin accumulates to induce proinflammatory signaling, dysregulation of gene expression (particularly in neurons), irreversible brain cell damage, and functional decline resulting in deficits in cognition, memory and behaviour. Aluminium is neurotoxic as the establishment of toxicity thresholds can result in neuronal dysfunction, neurodegeneration and ultimately neuronal cell death through a continuum of disruptive events from classical apoptosis through to sudden and violent necrosis (Exley, 2014). Cholinergic neurons are particularly susceptible to aluminum neurotoxicity, which affect synthesis of the neurotransmitter acetylcholine. In addition to these neurotoxic effects, a number of additional diseases, of which will be outlined, are being associated with aluminium as a causal relationship. However, the degree of evidence is somewhat weaker (Kramer, 2014; Klotz, 2017; Lukiw, 2019).

Oxidative stress: Oxidative stress is an event resulting from the formation of reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2) and the superoxide radical (O2¼) (Becaria, 2002). Oxidative stress is closely associated with the neuropathology of AD (Thathiah, 2009). Al-induced oxidative stress with the metabolic defects that accompanies it may incidentally be the crux of the toxicosis, to the extent that the use of antioxidant agents forms the fundamental basis for therapeutic interventions apart from chelating drugs. More generally, Al is also considered to be a mediator of oxidative stress, and efforts have been made to understand the underlying mechanisms of Al-catalyzed oxidative stress. For example, one study found that Al^{3+} ions augment iron-induced lipid peroxidation in rat liver microsomes at pH 7.4. This study also found Al^{3+} that accelerates the peroxidation of erythrocytes by hydrogen peroxide (H_2O_2). Another study found similar results (Peto, 2010; Igbokwe, 2019).

Figure 4: Principal targets of aluminium toxicity in humans (Crisponi, 2013)

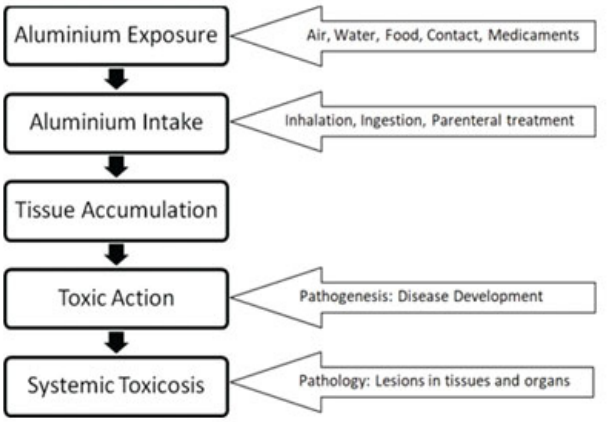


Alzheimer's disease: Alzheimer's disease (AD) is a progressive form of dementia of the elderly and the most prevalent neurodegenerative disease in the world. High concentrations of aluminum have been detected in brain tissues of patients with Alzheimer's disease (Tomljenovic, 2011). It is clinically characterized by the progressive loss of memory and other cognitive abilities and pathologically by severe neuronal loss, glial proliferation and amyloid plaques composed of β-amyloid protein (Aβ) surrounded by degenerated nervous terminations and neurofibrilar tangles. Neuropathologically, AD-afflicted brains are characterized by two proteinaceous aggregates: amyloid plaques, which are mainly composed of the β-amyloid protein (Aβ), and neurofibrillary tangles (NFTs), which are made up of hyperphosphorylated

aggregates of the tau protein (Ferrari, 2008; Thathiah, 2009; Bassioni, 2012).

Dialysis patients exhibited impaired speech, apraxia, and, in the further course, dementia syndrome as well as partly focal, partly generalized seizures. Ecological studies have suggested that concentration of aluminum in drinking water of 0.10-0.20 mg/l may increase the risk of alzheimer's disease (AD) with relative risk ranging from 1.35-2.6 (Rogers, 1991; Klotz, 2017).

Figure 5: Major themes for the literature search on aluminium toxicosis (Igobokwe, 2019).



Osteomalacia: One primary site of Al accumulation is in bone, where it contributes to the development of osteomalacia, especially in chronic hemodialysis patients (Peto, 2010). Osteomalacia, diagnosed histologically, affects about 20% of patients in terminal renal failure (Parkinson, 1981). Aluminium deposits are present at the mineralised bone front on both growing and resting bones. The association between increased aluminium bone stores in dialysed patients and the development of osteomalacia, previously known as 'renal osteodistrophy' has been well established (Crisponi, 2013).

Aluminium-related osteomalacia differs from classical vitamin-D-deficiency osteomalacia in that patients are resistant to treatment with even large doses of vitamin D, have an increased incidence of bone fractures, and are particularly likely to experience bone pain (Boyce, 1982). Hyperaluminernia and high tissue burdens of aluminum are frequently found in patients on chronic intermittent hemodialysis. It is suggested that aluminum produces chronic toxicity and that dialysis dementia and nonhypophosphatemic osteomalacic dialysis osteodystrophy are manifestations of this aluminum intoxication (Graf, 1981).

Aluminium can be detected at the interface between osteoid and calcified matrix (the mineralisation front) in bone from some patients with chronic renal failure'" after exposure to high levels of aluminium in the dialysis water or following treatment with aluminium containing phosphate-binding drugs (Boyce, 1992). The aluminium binds to the calcification front where it appears to inhibit mineralization of osteoid, and because skeletal uptake of calcium is blocked, there is a tendency to hypercalcemia and relative hypoparathyroidism. Because of low bone turnover and morbidity due to aluminium related anemia and neurotoxicity, it has been assumed that the prognosis is poor, although recently improvement in bone mineralization status has been reported after removal of aluminium from the dialysis water by reverse osmosis (Smith, 1987: Crisponi, 2013).

Figure 6: Disease caused by Aluminium

Table 6. Aluminum associated with neuronal injury (Jabeen, 2016)

Neurological findings	Neurotoxic effects
Amyotrophic lateral sclerosis Alzheimer's disease	Degenerative changes in motor neurons Loss of cognitive function
Dialysis encephalopathy	Myoclonic jerks
Hearing deficit	Cell loss in corti, spiral ganglion
Dementia	Intellectual debilitation

Anaemia induced from aluminum: Aluminum plays a role in the blood toxicity seen in patients with chronic renal failure. The usual anemia of chronic renal failure is normocytic and normochromic and is directly related to deficiency of erythropoietin Starkey, 1987) The causal relationship between anemia and aluminum intoxication was reported by Elliot et al. in 1978 (Sedman, 1992; Starkey, 1987). Anemia attributable to aluminum toxicity was first described in patients with marked aluminum overload characterized by basal serum aluminum levels over 250 pg/liter, severe bone fracturing osteomalacia and often, dialysis dementia (Bia, 1989). A microcytic anaemia is associated with dialysis encephalopathy and remits when exposure to aluminium is reduced (Parkinson, 1981; Starkey, 1987; Becaria, 2002).

CONCLUSION

Human beings are frequently exposed to Aluminium. It can be harmful if injected to living beings. At high

temperature aluminium leaching take place at higher rate and also dependent on food, salt, and pH values. In packaging of food and other related product, suppliers must be mentioned the level of aluminium in the product label. Despite its prevalence in the environment, no living organism is known to use aluminium salts metabolically, but aluminium is well tolerated by plants and animals. Because of the abundance of these salts, the potential for a biological role for them is of continuous interest and studies continue

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