The 28th INAUGURAL LECTURE

DEMYSTIFYING ALUMINIUM TOXICITY: To Eat or Not to Eat

Delivered by

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COURTESIES

All praises and Salutations are due Allah (SWA) alone, the Beneficent, the most Merciful. The Creator, Provider and Sustainer of the Universe. May the Peace and Blessings be upon our noble Prophet Muhammad bn Abdullah (SAW), his household, companions and those who follow his righteous path till the day of resurrection.

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My tutors

Greatest Danfodites

Members of my family

Invited guests

Gentlemen of the press

I greet you with the best and noble greetings; Assalamu alaikum warahmatullahi wabarakatuh

Preamble

Inaugural lecture is an essential vehicle that provides opportunity for academics to advertise and share their gradual achievements in research, innovation, engagement and teaching activities before members of the University community and the general public. The new professor seizes the opportunity of celebrating an important milestone with his/her family, friends, colleagues and general public. It is also an avenue for the University to recognise and showcase the academic achievements of its staff. Most importantly colleagues can hear about researches that are going around the University.

Despite widely documented toxicity of Aluminium, its usage is becoming unavoidably in present day life. Researchers and general population tend to ignored its devastating effects probably due to difficulty in its determination. Hence, virtually aluminium is present in every shiny indoors and outdoors materials, food, drugs, cosmetics and pharmaceutical preparations. These among other things prompted me to choose this particular topic to showcase the dangerous interaction between aluminium and humanity.

APPENDIX III: ABBREVIATIONS

AD	Alzheimer's disease
ADI	Adult Dietary Intake
Al	Aluminium
ALS	Amyotrophic Lateral Sclerosis
APP	Amyloid Precursor Protein
ATP	Adenine-triphosphate
ATSDR	Agency for Toxic Substances and Disease Registry
CDCP	Centre for Disease Control and Prevention
COT	Committee on Chemicals Toxicity
DE	Dialysis Encephalopathy
EFSA	European Food Safety Authority
ETC	Electron Transport Chain
FAO	Food and Agricultural Organisation
FEHD	Food and Environmental Hygiene Department
FIRA	Federal Institute for Risk Assessment
FSA	Food Standard Agency
GIT	Gastrointestinal Tract

GPx	Glutathione peroxidise
GST	Glutathione S-transferase
GSTM	Glutathione S-transferase mu
GSTP	Glutathione S-transferase pi
HIF-1α	Hypoxia Inducible Factor-1α
IPAI	International Primary Aluminium Institute
JECFA	Joint Expert Committee on Food Additives
LMW	Low Molecular Weight
MS	Multiple Sclerosis
PD	Parkinson's disease
PHD	Prolyl Hydroxylase
ROS	Reactive Oxygen Species
SOD	Superoxidase Dismutase
TBARS	Thiobarbituric Acid Reactive Substances
TWI	Tolerable Weekly Intakes
US	United State
VLDL	Very Low-Density Lipoprotein
WHO	World Health Organisation

INTRODUCTION

Aluminium is the most abundant metallic element, and the third most abundant chemical element in the earth's crust (Exley, 2003; Krewski *et al.,* 2007; ATSDR, 2008; Gupta *et al.,* 2013). About 8.8% (88 g/kg) of its weight (Frederick and Edward, 2000) is found in the environment as silicates, oxides and hydroxides and as complexes with organic matter (Nayak, 2002). It exists as aluminosilicate composed of aluminium, silicon, oxygen, and in combination with other elements such as sodium and fluorine in rocks (particularly igneous rocks), soil, clays, and gems (Whitney, 2002; Lide, 2005). Aluminium was first produced commercially by Sainte-Claire Deville (1856). The aluminium production process is much more complex and required huge amounts of electricity. The bauxites that contain aluminium are extracted from the ground and processed into alumina or aluminium oxide. Pure aluminium is produced using electrolytic reduction. This electrolytic process was patented by Heroult and Hall (1886). The global production of aluminium has been increased from 8,000 tons in 1900 to about 50 million tons in 2006 (Exley, 2009). The production began to shift from developed to the developing nations and the World production had increased up to 58,500, 000 metric tons in 2015.

Plants, animals and humans are experiencing increased exposure to biologically reactive aluminium and is strongly influenced by atmospheric acidification, especially acid rains which have an adverse effect on the environment (plants, animals, and humans) (Kopacek *et al.,* 2009). Aluminium commodities permeated all human activities until the second half of the twentieth century, when the aluminium was recognized as the main cause of serious diseases, like dialysis, osteodystrophy and dementia (Berthon, 2002; Bodor *et al.,* 2002; Yokel, 2002; Crisponi *et al.,* 2012). Consequently, the chemical and biomedical research on aluminium dramatically increased,

and many research articles, reviews and books are now available in the literature on its biological role, speciation and toxicokinetics.

ALUMINIUM IDENTITY

The existence of aluminium was ascertained and named after alumina (aluminium oxide) by Humphry Davy (1808). The name, aluminium is derived from the Latin name for alum, 'alumen' meaning bitter salt. Aluminium was discovered in 1825 by the Danish chemist and Hans Christian Oersted, who successfully separated some impure metallic aluminium by reacting its chloride salt with potassium amalgam and then distilling the mercury off. Pure aluminium is characterized by some distinctive chemical identities, as shown in Table 1 below.

Table 1: Chemical Identity of Aluminium

CHARACTERISTICS	
CHARACTERISTIC	**INFORMATION**
Chemical name	Aluminium (U.S., Canada)
Synonym(s)	Aluminium; alumina fibre; metana; aluminium bronze; aluminium dehydrated; aluminium flake; aluminium powder; aluminium-27; Noral aluminium; PAP-1
Chemical formula	Al
IDENTIFICATION NUMBERS	
CAS Number	7429-90-5
EINECS	231-072-3
NIOSH RTECS	BD330000
EPA Pesticide	000111
CHEMICAL CODE	
DOT/UN/NA/IMCO	UN 1309; UN 1396; IMO
Shipping	4.1; IMO 4.3; NA 9260
HSDB	507

(Soni *et al.*, 2001; Meija *et al.*, 2016)

CHEMISTRY OF ALUMINIUM

Aluminium is a soft, silvery-white, ductile, and malleable metal with atomic number and atomic mass 13 and 26.9815, respectively (Table 2). Aluminium has one stable isotope ^{27}Al, and one long-lived radioactive isotope ^{26}Al, a beta and gamma emitter with a half-life of 7.2 x 10^5 years. The electronic configuration of aluminium is $1s^2$, $2s^2$, $2p^6$, $3s^2$ $3p^1$, and it belongs to Group 13 (IIIA), Boron family and found in period 3 of the periodic table (O'Neil *et al.,* 2001). Aluminium has a melting point of 933.47 K (9660.32 ^oC, 1220.58 ^oF), and boiling point 2743 K (2470^oC, 4478^oF). The density of aluminium is approximately 2.7 g/cm^3, and soluble at pH 6.2 (Table 3). The solubility increases with acidic or alkaline solutions and some ligand complexes (Soni *et al.,* 2001). In compounds, aluminium typically occurs in its +3 oxidation state (O'Neil *et al.,* 2001; Lide 2005). Aluminium is an amphoteric oxide with different ionization energies, and its atomic properties are presented in Table 4.

Aluminium reacts with water to produce hydrogen gas and aluminium hydroxide bayerite ($Al(OH)_3$), aluminium hydroxide boehmite (AlO(OH)), and aluminium oxide (Al_2O_3) in the following reactions, respectively.

$$2Al + 6H_2O \longrightarrow 2Al(OH)_3 + 3H_2 \quad (1)$$

$$2Al + 4H_2O \longrightarrow 2AlO(OH) + 3H_2 \quad (2)$$

$$2Al + 3H_2O \longrightarrow Al_2O_3 + 3H_2 \quad (3)$$

All the reactions are thermodynamically favourable at room temperature and highly exothermic (Digne *et al.,* 2002; Andersen *et al.,* 2004). From room temperature to 280 ^oC, $Al(OH)_3$ is the most stable product, while from 280-480 ^oC, AlO(OH) is most stable. Above 480 ^oC, Al_2O_3 is the most stable product (Digne *et al.,* 2002; Andersen *et al.,* 2004). However, aluminium hydroxide bayerite

(Al $(OH)_3$) in solid state reacts with water to produce hydroxide (OH^-) and hydroxonium (H_3O^+) ions.

$$Al(OH)_3 + 6H_2O \longrightarrow [Al(H_2O)_6]^{3+} + 3OH^-$$

$$Al(OH)_3 + 4H_2O \longrightarrow [Al(H_2O)_2(OH)_4]^- + H_3O^+$$

Table 2: Periodic Properties of Aluminium

PROPERTY	**INFORMATION**
Atomic number	13
Atomic mass	26.9815
Group	3
Period	3
Block	p-block
Element category	Post-transition metal (Metalloid)
E.C.	[Ne] $3s^2$ $3p^1$
Electrons per shell	2, 8, 3

(Whitten *et al.,* 2014)

Table 3: Physical Properties of Aluminium

PROPERTY	**INFORMATION**
Appearance	silvery grey metallic
Phase at STP	Solid
Melting point	933.47 K (9660.32 ^oC, 1220.58 ^oF)
Boiling point	2743 K (2470 °C, 4478 °F)
Density	~ 2.7 g/cm^3
Heat of fusion	10.71 $kJmol^{-1}$
Heat of vaporization	284 kJmol-1
Molar heat of capacity	24.20 $Jmol^{-1}K^{-1}$

(O'Neil *et al.,* 2001; Cox, 2004; Lide, 2005)

Table 4: Atomic Properties of Aluminium

PROPERTY	INFORMATION
Oxidation states	−2, −1, +1, +2, +3 (an amphoteric oxide)
Electronegativity	Pauling scale: 1.61
Ionization energies	1st: 577.5 $kJmol^{-1}$
	2nd: 1816.7 $kJmol^{-1}$
	3rd: 2744.8 $kJmol^{-1}$
Atomic radius	empirical: 143 pm
Covalent radius	121±4 pm
Van der Waals radius	184 pm

(O'Neil *et al.,* 2001; Cox, 2004; Lide, 2005)

SOURCES OF ALUMINIUM

Aluminium is naturally found in air, water and soil (ATSDR, 2010). Surprisingly, some reasonable amounts of aluminium are found in different antiperspirants, vaccines, antacids and cosmetics (Table 5). Some foodstuffs are also considered as important sources of aluminium (Yokel and McNamara, 2001), these include; potatoes, spinach, tea, coffee, beans, marjoram and thyme (Malik *et al.,* 2008; Giddings *et al.,* 2010), very low aluminium levels were reported in tomatoes (Giddings *et al.,* 2010). Crayfish have been shown to accumulate aluminium from contaminated water, mostly found in their hepatopancreas (Woodburn *et al.,* 2011). Products containing aluminium as food additives include; processed cheese, baked goods, jellyfish, fried twisted cruller, or microalgal supplements (Rzymski *et al.,* 2015; Zhang *et al.,* 2016; Rzymsk *et al.,* 2018).

Aluminium was also found in some consumer products such as antacids (aluminium hydroxide), astringents, food additives (aluminium oxides), antiperspirants, fuel additives, explosives, propellants and cosmetics (Krewski *et al.,* 2007; ATSDR, 2008). Aluminium is used in the process

of making cooking pots, pans, utensils and foil, most baking powders, toothpaste, dental amalgam, bleached flour, grated cheese, table salt, and chokes and beers (especially when they are in aluminium cans) (Rzymski *et al.,* 2015; Zhang *et al.,* 2016; Rzymsk *et al.,* 2018)

Table 5: Sources of Aluminium

SOURCE	AMOUNT	REFERENCE
Natural sources (Rivers, Sea etc.)	2–5 mg/day	Jorhem and Haegglund (1992); Woodburn *et al*. (2011);
Tea leaves	0.1%–1%	Koch *et a*l. (1988); Matsumoto *et al.* (1978)
Coffee from aluminium moka	0.8–1.2 mg/cup	Malik *et al*. (2008)
Drinking water	0.07 mg/l	Crisponi *et al*. (2011)
Beverages in aluminium cans	0.04–1.0 mg/l	Duggan *et al.* (1992); Liukkonen and Piepponen (1992)
Cooked spinach	25 mg/kg	Liukkonen and Piepponen (1992)
Unprocessed food	0.1–7 mg/kg	Malik *et al*. (2008)
Food additives	10–20 mg/day	Jorhem and Haegglund (1992)
Food cooked in aluminium pots	0.2–125 mg/kg	Liukkonen and Piepponen (1992)
Soy-based infant milk formulas	6–11 mg/kg	Burrell and Exley (2010)
Antacids	35–200 mg/dose	Simon *et al*. (1990)
Buffered aspirin	9–50 mg/dose	Simon *et a*l. (1990)
Anti-diarrhoeal drugs	36–1450 mg/dose	Simon *et al*. (1990)
Antiperspirants	50–75 mg	Burrell and Exley (2010)
Vaccines	0.15–0.85 mg/dose	Malik *et al*. (2008)
Marjoram and thyme	500 - 1000 μg/g	Burrell and Exley (2010)
Tomatoes	0.2 - 1.1 μg/g	Burrell and Exley (2010)

ALUMINIUM CYCLE

Aluminium has an important biogeochemical cycle, at high concentrations can have widespread environmental effects and cause toxicity in a variety of living organisms; including microbes, plants, fishes, and mammals (Bruins *et al.,* 2000; Exley, 2003; Lemire *et al.,* 2010; Delhaize *et al.,* 2012). Aluminium from industrial and mining processes, food packaging, and cooking utensils is released into the environment; mainly into the atmosphere (Soni *et al.,* 2002). Acid rain causes changes in the pH of the soil and water, resulting in mobilization of toxic aluminium ions leading to increase in atmospheric acidification (Exley, 2003; Kopacek *et al.,* 2009). This causes the release of aluminium into the soil solution, underground and surface waters where absorbable cationic aluminium species come in contact with plants, animals and humans causing many adverse effects (Kopacek *et al.,* 2009). All these phenomena are conceptualized in the form of a cycle, as presented in Figure 1 below.

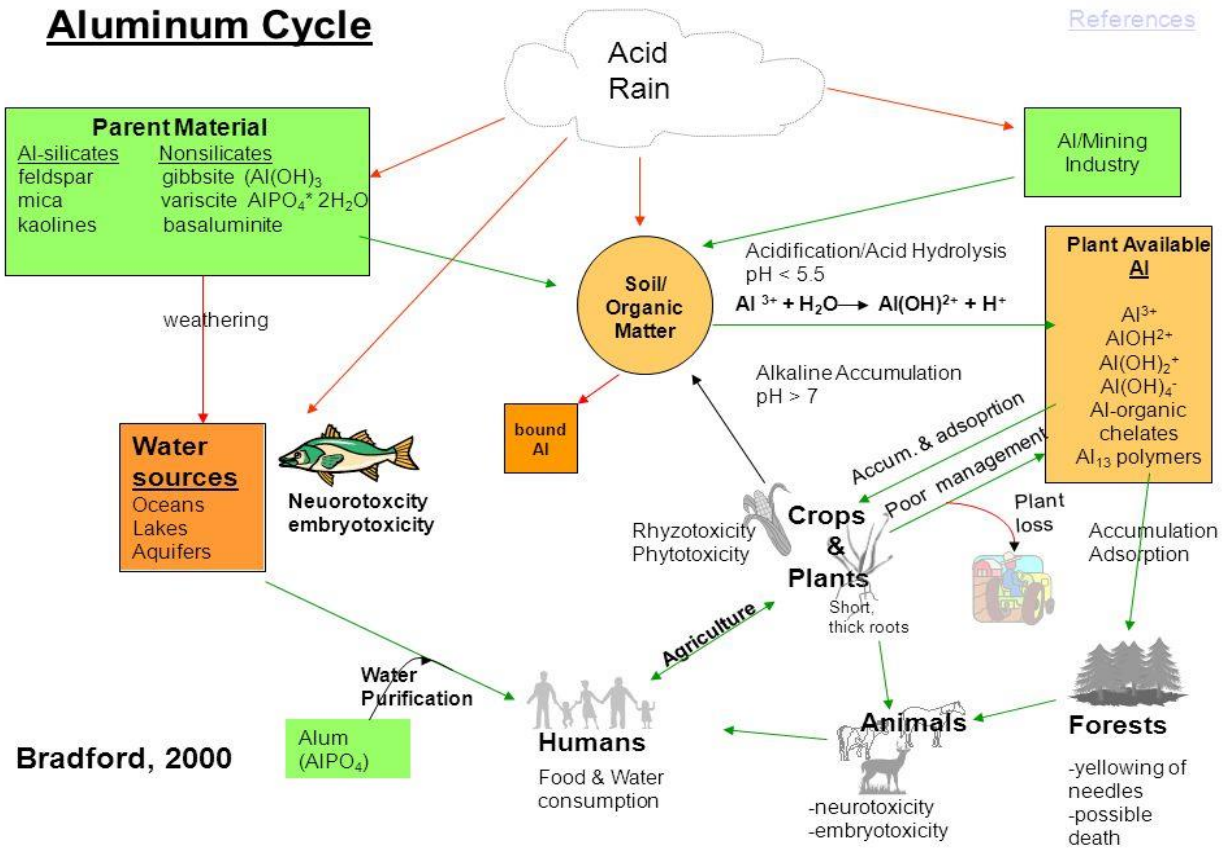

Figure 1: Aluminium Cycle (*Source:* Bradford, 2000)

The adverse effects of aluminium in the environment include drying of forests, plant poisoning, crop decline or failure, death of aquatic animals, and the various imbalances in the function of human and animal systems (Barabasz *et al.*, 2002). The common manifestations in plants are root growth inhibition, cellular modification in leaves, small and dark green leaves, yellowing and death of leaves, chlorosis, purpling and foliar necrosis (Gupta *et al.*, 2013). Aluminium in high concentrations is very toxic for aquatic animals, especially for gill breathing organisms such as fish, causing osmoregulatory failure by destructing the plasma and hemolymph ions.

USES OF ALUMINIUM

Aluminium is widely used in the fields of medicine, pharmacy, food technology, and cosmetics (Aronson, 2006). Aluminium is used for various purposes in the following industries:

Pharmaceutical industries (Reinke *et al.*, 2003)

- antacids
- phosphate binders
- buffered aspirins
- adjuvant
- vaccines or antiperspirants

Cosmetics industries (Aronson, 2006)

- antiperspirants

Food industries (Yokel *et al.*, 2008)

- food packaging
- food additive
- emulsifying cheeses
- binding meats

Aluminium is also used in automotive aircraft and industries, construction and spatial industries, cooking utensils, and water treatment (Exley, 2003; WHO, 2003). Aluminium compounds are widely used in paper and dye production; in the textile industry; as a catalyst in oil refining; in the glass industry; in paints and pigments industry; as anti-caking agents; for leaving baked goods; thickening prepared sauces; colouring agents; and for buffering, stabilizing, curing and texturing

foods (IPAI, 2000; Soni *et al.*, 2001; Hem, 2002; Yokel *et al.*, 2008). Moreover, some aluminium salts are used in water purification, as well as in brewing and sugar refining (WHO, 2003).

ORGANOLEPTIC PROPERTIES OF ALUMINIUM

Aluminium flexible packaging is used to keep the organoleptic properties of food and to isolate the product from oxygen and other environmental phenomena which may alter its physicochemical properties (Nayak, 2002). The use of aluminium-containing additives in processing certain types of food such as grain-based products and processed cheese may change the colour, taste or odour of the processed food products (Nayak, 2002).

The use of aluminium salts as a coagulating agent (promoting particle collision by neutralizing charge) in the purification of drinking water and wastewater treatment plants may lead to increased concentration of aluminium in finished water resulting in undesirable colour and turbidity (Kvech and Edwards, 2002; GHEF, 2007).

Aluminium sulphate is used as a mordant in dyeing and printing textiles. Aluminium sulphate when dissolved in a large amount of neutral or slightly alkaline water, produces a gelatinous precipitate of aluminium hydroxide, $Al(OH)_3$ which is used in dyeing and printing cloth, helps the dye adhere to the clothing fibres by rendering the pigment insoluble. The use of aluminium sulphate to reduce the pH of garden soil results in a change in the colour of flowers (*Hydrangea*) to blue (Kari, 2013).

DIETARY INTAKE OF ALUMINIUM

The total aluminium content of foods comprises naturally present aluminium, aluminium from food additives and aluminium leaching into foods from food contact materials like aluminium foil, trays, cans, cookware, utensils and food packaging (Zhou and Yokel, 2005). Dietary intake of

aluminium considerably varies; it depends on the country, place of residence, and diet composition (Vargel, 2004). Humans consume about 10 mg of aluminium on a daily basis of which 9.6 mg is taken from foods, 0.1–0.4 mg is taken from kitchen utensils and packaging, and 5 µg is taken from the air (Vargel, 2004). However, dietary intake of aluminium from foods and drinking water is low compared with that consumed by people taking aluminium-containing medicinal preparations (Zhou and Yokel, 2005).

In order to address the safe limits for aluminium in the human diet, tolerable weekly intakes (TWI) of aluminium were established by some regulatory authorities. In 2008, the 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 less than 5 mg per kg food (EFSA, 2008). 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 (EFSA, 2008). Based on animal studies, EFSA has established a Tolerable Weekly Intake (TWI) of 1 mg aluminium per kg of body weight (EFSA, 2011).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has recently given a scientific opinion on the safety of aluminium from dietary intake (JECFA 74th Meeting, Rome June 14– 2 3, 2011). In the JECFA report, the TWI for aluminium was determined and corresponded to 2 mg aluminium per kg of body weight per week (FAO/WHO, 2011). This value is twice that established by EFSA. The JECFA affirms in their report that ‘The Committee noted that estimates of the contribution to overall mean dietary exposure from all sources (including natural sources, water consumption, food contact materials and food additives) were in the range of 10 – 140 mg/week in adult populations (0.2 – 2.3 mg/kg bw per week as aluminium, assuming

a bodyweight of 60 kg). The estimated dietary exposures are related to average adult populations, and high dietary exposures are generally assumed to be 2 times higher than the reported average.

It also noted that children generally have higher food intake than adults when expressed on a body weight basis and therefore represent the highest potential exposure to aluminium per kilogram of body weight (Joint FAO/WHO, 2006). These demonstrated that in many countries, a considerable number of people, especially children, are under high aluminium exposure and are at risk of aluminium intoxication (Krewski *et al.,* 2007).

The dietary intakes of aluminium of the adult population from the overall diet including additives, varied among different countries; this ranged from 1.6 mg/day in most French studies (Leblanc *et al.,* 2004) to more than 34 mg/day in Mainland China (Zhang and Gao, 2003) (which contributed to about 20 – 400% of PTWI, assuming a bodyweight of 60 kg). In fact, the dietary intakes of aluminium of some population groups were found to exceed the Population tolerable weekly intake (PTWI) in some countries such as the UK (1.3 mg/kg bw/week for toddlers (1.5 – 4.5 years) (FSA, 2009), Sweden (1.5 mg/kg bw/week for 60-kg females) (WHO, 1997), and Mainland China (4.0 mg/kg bw/week for 60-kg adults) (Zhang and Gao, 2003). Adult dietary intakes of aluminium have been reported in several countries, including Nigeria (Table 6).

Table 6: Adult Dietary Intakes of Aluminium

COUNTRY	ADULT DIETARY INTAKE (mg/day)	REFERENCE
France	1.6	Leblanc *et al*. (2004)
Australia	1.9 - 2.4	WHO (1997)
Netherlands	3.1	WHO (1997)
Switzerland	4.4	WHO (1997)
Japan	4.5	WHO (1997)
Hong Kong	5.1	FEHD (2009)
UK	5.4	FSA (2009)
Finland	6.7	WHO (1997)
USA	7.1 – 8.2	WHO (1997)
Germany	8 - 11	WHO (1997)
Sweden	13	WHO (1997)
Mainland China	34	Zhang and Gao (2003)
Nigeria	9.9 - 14.4	Ekanem *et al*. (2009)

Dietary intake studies in Mainland China and UK showed that cereals and cereal products were the main dietary sources of aluminium, contributed 79.5% and 49% of total dietary intakes, respectively. The relatively high aluminium intake from the cereal products might be attributed to the use of aluminium-containing food additives (Zhang and Gao, 2003; FSA, 2009).

ALUMINIUM SPECIATION

Aluminium can be found in water, based on aquated positive ions or hydroxylated aluminates in different forms including monomeric and polymeric hydroxy species, colloidal polymeric solutions and gels, and precipitates. Aluminium speciation is a complex problem in the biological system, due to the wide variety and complexity of aluminium hydrolytic species, their low solubility and their spectroscopic silence (Sarpola, 2007). Aluminium speciation in biological

systems exist in various aluminium hydrolytic species that could be formed in aqueous solution as a function of pH which implies the study of different protonation states, tautomers and oligomers that aluminium can form in solution (Bogatko *et al.,* 2010). It also includes the interaction of aluminium with biomolecular building blocks, low molecular weight (LMW) species, or high molecular weight (HMW) ligands such as proteins (Bogatko *et al.,* 2013).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Aluminium is found in the environment; mainly released by natural and anthropogenic processes. It is released into the environment by natural processes through the weathering of rocks and minerals (Soni *et al.,* 2002). Acidification of the environment caused by acid mine drainage or acid rain can cause an increase in the dissolved aluminium (Al^{3+}) content of the aquatic systems (WHO, 1997; Soni *et al.,* 2002; ATSDR, 2008). Aluminium is also released into the environment in the form of air emissions, wastewater effluents, and solid waste primarily associated with industrial and mining processes as captured by Likens (2001) in Figure 2.

However, aluminium content in food packaging and cooking utensils is an important route of aluminium release into the environment (Soni *et al.,* 2002). Residues of aluminium-containing drugs, cosmetics and food additives can also release aluminium into the environment. Several factors influence aluminium mobility and subsequent transport within the environment. These include chemical speciation, hydrological flow paths, soil-water interactions and the composition of the underlying geological materials (WHO, 1997; ATSDR, 2008).

It is abundant in the biosphere and widespread in the air (150 mg/m^3), water (0.8 mg/l), and plants (up to 200 mg/kg) (Kabata, 2011). The routes of human exposure to aluminium include the

digestive tract, skin, and occupational inhalation (Krewski *et al.,* 2007; ATSDR, 2008; Shaw *et al.,* 2014).

Air

In 2005, 586 metric tons of aluminium was released (fume or dust) to the atmosphere from 329 domestic manufacturing and processing facilities. This accounted for about 2.8% of the estimated total aluminium released into the environment (EFSA, 2008). Air concentrations vary between rural and urban settings, with higher levels in industrial areas. Exposure from this source could contribute up to 0.04 mg/day (EFSA, 2008).

The air we breathe is an important contributor to the body burden of aluminium. In a clean environment (air) of 100 ng/m^3 aluminium content, human exposure to aluminium through normal breathing is approximately 1.4mg per day (Goncharuk *et al.,* 2012). This is essentially the lowest possible exposure to aluminium from breathing, and the majority of this aluminium is retained in the lungs and olfactory epithelia (Goncharuk *et al.,* 2012). This value could easily be increased one thousandfold to 1.4 mg per day in many industrialised regions (Polizzi *et al.,* 2007).

Exposure to aluminium through breathing can be significantly influenced by natural soil erosion, volcanic eruptions, coal combustion or specific activities including agricultural activities, industrial and mining activities or workplace exposure (Polizzi *et al.,* 2002) and habitual exposure such as smoking of cigarettes and cannabis (Exley, 2006) and use of cocaine (Pechansky *et al.,* 2007) and heroin (Exley, 2007). Aluminium is an essential component of many aerosol formulations of cosmetics, and particularly antiperspirants, and these, especially through regular use, will contribute significantly to exposure to aluminium through breathing (Exley, 2007).

Diets

Measurements of the intake of aluminium in whole diets have varied from about 1 to more than 20 mg per day (Bratakos *et al.*, 2012). These are conservative estimates of mean daily intake and do not account for compounding factors such as contamination from cooking and cooking wares (Bassioni and Mohammed, 2012), specific products with unusually high burdens of aluminium (Stahl *et al.*, 2011), or individual eating patterns (Lopez *et al.*, 2002). Dietary supplements, such as vitamins, whether 'natural' products or otherwise are never included in these estimates of aluminium intake despite being regular components of many people's diets and despite being widely contaminated with aluminium (Shafer and Seifert, 2006). Dietary exposure of humans to aluminium can be through water (FIRA, 2008), foods (Saiyed and Yoke, 2005), food additives (Krewski *et al.*, 2007), and aluminium contaminated equipment/utensils (Domingo, 2003).

Water

Drinking water is one of the common forms of human exposure to aluminium. The aluminium concentration in natural waters varies according to numerous physicochemical, mineralogical and geochemical factors (EFSA, 2008). Aluminium based coagulants, such as aluminium sulfate (Al-sulf) and polyaluminium chloride (PACl), are widely used in water treatment plants to remove particulate, colloidal, and dissolved substances via coagulation process (Kvech and Edwards, 2002; GHEF, 2007). A residual quantity of this aluminium is then present in the drinking water. The concentration of aluminium in natural waters (e.g., ponds, lakes, streams) is generally below 0.1 milligrams per litre (mg/L). Several cities have reported concentrations as high as 0.4– 1 mg/L of aluminium in their drinking water (EFSA, 2008).

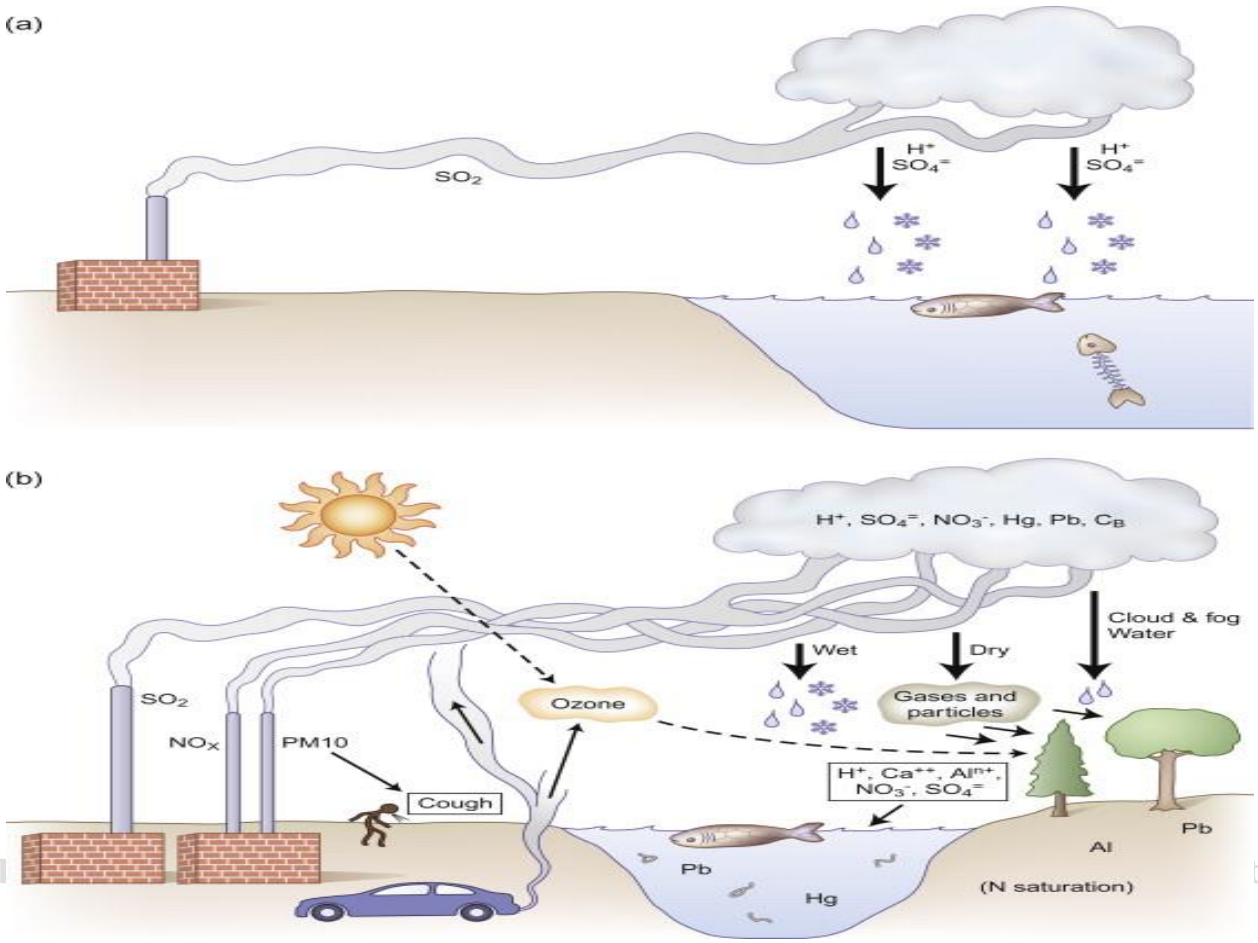

Figure 2: Atmospheric and Soil Acidification (a). The "simple" view of the early 1960s to early 1970s. (b).The increasingly complex view currently (Likens, 2001).

Foods and Food Products

Foods or food products are the primary sources of dietary aluminium exposure to humans with estimated daily exposure between 3 and 10 mg (Yokel and Florence, 2008). Tea and coffee infusions are recognized as a significant source of dietary aluminium exposure to humans (Milacic, 2005; Malik *et al.,* 2008). Some studies suggest that aluminium exposure in humans is associated with utilization of cookware and food packaging materials made from aluminium (Ai-Ashmawy, 2011; Weidenhamer *et al.*, 2014).

Aluminium is used as a food packaging material because it is lightweight and highly resistant to most forms of corrosion (Marsh and Bugusu, 2007). Migration of aluminium from foil into food depends on several factors, including the composition of the raw food, the duration and temperature of heating, the pH of the food, and the presence of other substances (e.g. organic acids, salt, sugar and other ions) (Ranau *et al.,* 2001; Turhan, 2006). Cooking of acidic foods in aluminium saucepans or foil can result in leaching of the metal (Ranau *et al.,* 2001).

Antiperspirants containing aluminium chlorohydrate are another source of exposure. Vaccines, antacids, phosphate binders, dialysis, and total parenteral nutrition solutions are common and can result in a significant increase in aluminium exposure (Yokel and McNamara, 2001).

ACUTE EXPOSURE

Acute exposures to aluminium cause adverse effect in human bones (Hongve *et al.,* 1996; Zioła *et al.,* 2015), brain (Abubakar *et al.,* 2008; Mold *et al.,* 2018) and uterus (Rzymski *et al.,* 2016; Rzymski *et al.,* 2018), as well as in fluids including urine (Ogawa and Kayama, 2015), serum (Röllin *et al.,* 2018), breast milk (Poniedziałek *et al.,* 2018), and semen (Klein *et al.,* 2016). Studies showed an association between acute human exposures to aluminium and cognitive impairment, such as agitation, confusion, or myoclonic jerk (Bakir *et al.,* 2002, Nayak, 2002), while occupationally exposed subjects revealed disruption in memory and concentration (Riihimäki *et al.,* 2000; Giorgianni *et al.,* 2003).

Acute exposure to aluminium in humans is significantly increased by various activities which include specific industrial and agriculture occupations, first-hand and second-hand smoking, and the use of recreational drugs; such as heroin or cocaine (Rzymski *et al.,* 2015; Zhang *et al.,* 2016; Rzymski *et al.,* 2018). Aluminium phosphide, a potent pesticide utilised for the protection of stored

products and crops has been shown to be severely toxic to humans (Bogle *et al.,* 2016). Individuals that underwent acute exposure to aluminium phosphide have been presented with nausea, vomiting, acute respiratory distress syndrome and altered sensorium (Sudakin, 2005). The oral median lethal dose (LD_{50}) of the aluminium compounds (bromide, nitrate, chloride and sulphate) is moderate to low (1000 – 200 mg/kg b.wt) (FAO/WHO, 2007; EFSA, 2008; and 2012).

CHRONIC EXPOSURE

Prolong aluminium exposure induces oxidative stress and pathological alterations in diverse areas of the brain of neonatal rats (Yuan *et al.,* 2012). It has been demonstrated that chronic exposure to aluminium not only causes neurologic signs, which mimic progressive neurodegeneration but also results in neurofilamentous changes in the hippocampus, cerebral cortex and biochemical changes (Savor *et al.,* 2006). It has been reported that prolong administration of aluminium compounds (including aluminium nitrate, aluminium sulphate and potassium aluminium sulphate) in rats produced various effects, including the decreased gain in body weight, and mild histopathological changes in the spleen, kidney, liver and primary cortical astrocyte of the rat's brain(FAO/WHO, 2007; Abubakar *et al.*, 2008).

Chronic aluminium exposure disrupts normal development in baby rats (Nehru and Anand, 2003). It was also reported that chronic aluminium exposure increased the weights of the maternal spleen and liver, and decreased foetal top-to- heel lengths in pregnant mice (Golub *et al.,* 1987). However, it has been shown that chronic aluminium exposure causes significant morphologic and ultrastructural damage to the rat kidney, liver and testis (Kutlubay and Oguz, 2007).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Absorption

The absorption of dietary aluminium, distribution, metabolism and excretion are presented in Figure 3 and 5. Gastrointestinal tract (GIT) absorption of Aluminium is poor, accounting for only about 0.1 - 0.3% of the total intake (Moore *et al.,* 2000). The process of absorption depends on the intraluminal speciation, the intraluminal quantity, the presence of competing (iron, calcium) or complexing (citrate) substances and the intraluminal pH (Sjögren *et al.*, 2007; Fernández-Maestre, 2014) and is also promoted by many factors which include parathyroid hormone, dihydroxy vitamin D, zinc deficiency and citrate ingestion. Under sustained exposure of the gastrointestinal tract, or/and under certain conditions, particularly renal failure, increased aluminium accumulation in the body can occur (Yokel and Namara, 2001).

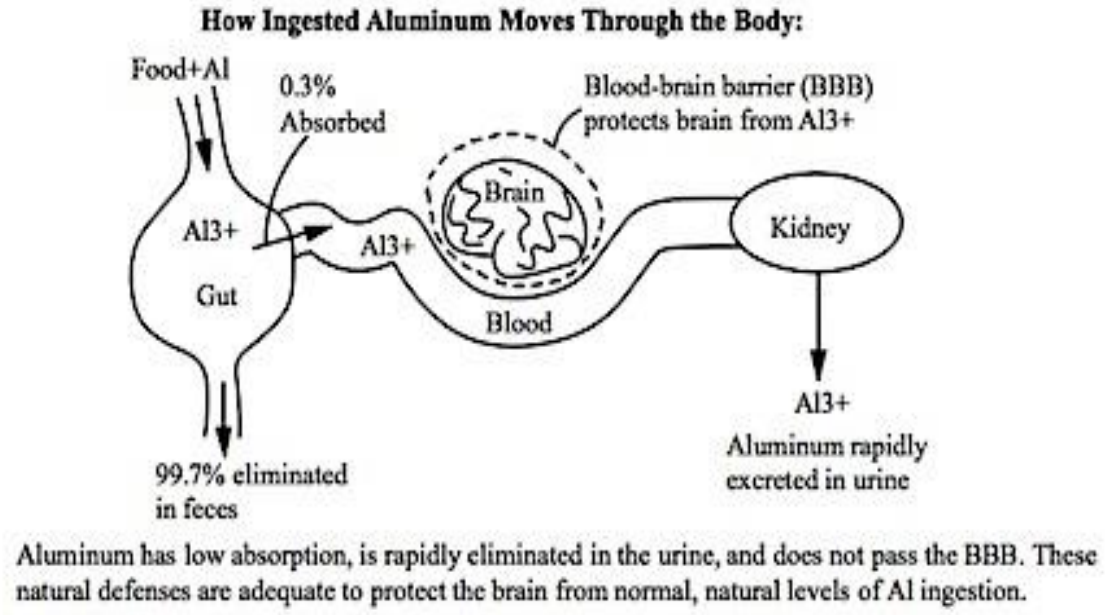

Figure 3: Absorption of Dietary Aluminium (Kramer and Heath, 2014)

Absorption of dietary aluminium is affected by several factors including; gastric pH levels (for aluminium speciation and solubility), bioavailability, diet or presence of organic acids (citrate, lactate) (Sjögren *et al.,* 2007; Giddings *et al.,* 2010; Kumar and Gill, 2014).

The citric acid in fruit juices markedly increases aluminium absorption in the gastrointestinal tract (GIT) (Glynn *et al.,* 2001). Other short-chain carboxylic acids such as acetate, oxalate, lactate, malate, tartrate, gluconate, ascorbate, and carbonate have also been shown to increase aluminium absorption in animal studies (Domingo *et al.,* 1994; Krewski *et al.,* 2007). Dietary intake of vitamin D increases aluminium absorption resulting in more amount of aluminium in the muscles and hearts (Moon *et al.,* 1992). The parathyroid hormone can also increase the absorption of aluminium by stimulating renal synthesis of 1, 25-dihydroxy vitamin D3 (Moon *et al.,* 1992).

Fluoride has been reported to decrease aluminium absorption (Nayak, 2002; Sjögren *et al.,* 2007; Fernández, 2014) and eliminates aluminium in the urine and faeces (Glynn *et al.,* 2001). It has been reported that dietary intake of silicon decreases the absorption of aluminium and facilitates its excretion (Krewski *et al.,* 2007). Calcium and phosphate have been shown to decrease the absorption of aluminium due to the formation of insoluble products with aluminium (Fernández, 2014). High levels of iron decrease the intestinal absorption of aluminium by competing with aluminium bind to the transferrin (Fernández, 2014). Adding milk to tea infusions has been shown to significantly decrease the bioavailability of aluminium (Milacic, 2005).

Distribution

Following the absorption of aluminium, it is subsequently distributed throughout the human body. Aluminium has been shown to accumulate in all tissues of mammals, preferentially in kidneys, liver, heart, bones and brain (Abubakar *et al*., 2002; Gonzalez *et al.,* 2009; Bondy, 2014). The

brain is a vital organ that accumulates aluminium in terms of exposure and contains less aluminium than the other tissues (Nayak, 2002; Priest, 2004; Krewski *et al.,* 2007). The total body load of aluminium is approximately 30–50 mg (Yokel and McNamara, 2001; Priest, 2004).

The highest levels of aluminium are found in the bone and liver (Exley, 2001; Hellstrom *et al.,* 2008) with only 1% of the total body aluminium in the brain (Yokel and McNamara, 2001; Priest, 2004). Accumulation of aluminium in tissues and organs has been reported to result in their toxicity and dysfunction (Walton, 2006). By overcoming the body barriers, aluminium can infiltrate the blood and promote toxic effects in the liver, bone and the central nervous system (Klein, 2005).

Metabolism

Aluminium is not essential for the growth, reproduction, and sustainability of humans and animals (Domingo, 2003; Exley, 2003). Its exclusion from successful biochemical pathways is mainly due to its very low natural availability (Yokel and McNamara, 2001; Exley, 2009; Aspenstrom *et al.,* 2009). Aluminium is present in four different forms in the body; free ions, low molecular-weight complexes, physically bound macromolecular complexes and covalently bound macromolecular complexes (EFSA, 2008). Free Al^{3+} binds easily to many substances and structures, and its metabolism is determined by its affinity to each of the ligands and their relative amounts and metabolism (ATSDR, 2008; EFSA, 2008).

Aluminium can form low-molecular-weight complexes with organic acids, amino acids, nucleotides, phosphates and carbohydrates (ATSDR, 2008; EFSA, 2008). These complexes are metabolically active, particularly the non-polar ones and may be very stable. Much of the aluminium in the body may exist as physically bound macromolecular substances such as proteins,

polynucleotides and glycosaminoglycans. However, metabolically, these macromolecular complexes are expected to be less active than the smaller low-molecular-weight complexes (ATSDR, 2008; EFSA, 2008).

The mechanisms of how aluminium enters the brain are not fully known (Yokel, 2002). Aluminium may enter the brain from the blood, either through choroid plexuses or the blood-brain barrier (BBB); from the nasal cavity into olfactory nerves followed by direct distribution into the brain (Abubakar *et al.,* 2002; Yokel, 2002). Other routes through which aluminium enters the brain and gets metabolized include; via transferrin-iron transporter, ferritin transport systems, and displacement of magnesium (Figure 4).

When aluminium is absorbed, it reaches the blood where it is immediately bound by the iron transporter transferrin molecule to its oxidative state (Al^{3+}) which is the same as the iron (Fe^{3+}) (Crichton *et al.,* 2002), and circulates across the blood-brain barrier (Yokel and McNamara, 2001; Bondy, 2016). Transferrin has been shown to bind about 90 % of circulating aluminium, ranging from 80 to 94 % (Milacic *et al.,* 2009). Aluminium bound to the transferrin molecule enters the cell and accumulates in the area of the brain cortex that is rich in transferrin receptors (Sjogren *et al.,* 2007; Martinez *et al.,* 2017). Inside the cytosol, Al^{3+} is released from the complex due to a decrease in pH level at 5.5 (Crichton *et al.,* 2002).

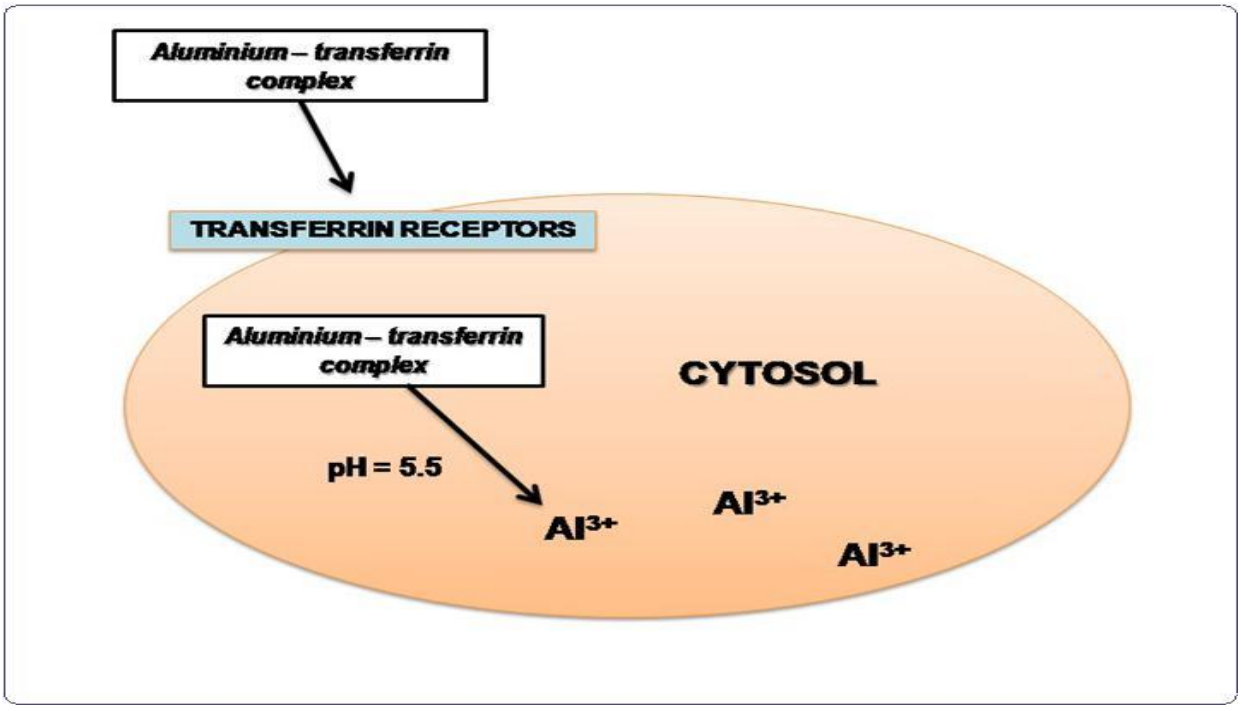

Figure 4: Transferrin-transferrin Pathway (Crichton *et al.*, 2002)

Excretion

Aluminium is excreted from the human body through the faeces and urine (ATSDR, 2008), though, the main route of aluminium elimination is renal clearance (Stoehr *et al.*, 2006). Individuals with kidney malfunction or immature kidneys, such as nephropathy patients or neonates, might experience toxic accumulation of aluminium in the body (Yuan *et al.*, 2011). Excretion of aluminium in man is primarily renal, with less than 2 % excreted in bile (Drueke, 2002). The amount of aluminium excreted per day is extremely variable (Ezomo *et al.*, 2009). In many studies, 1.8 - 12 mg per day has been reported according to the variations in the volume of urine excreted by different individuals (Ezomo *et al.*, 2009).

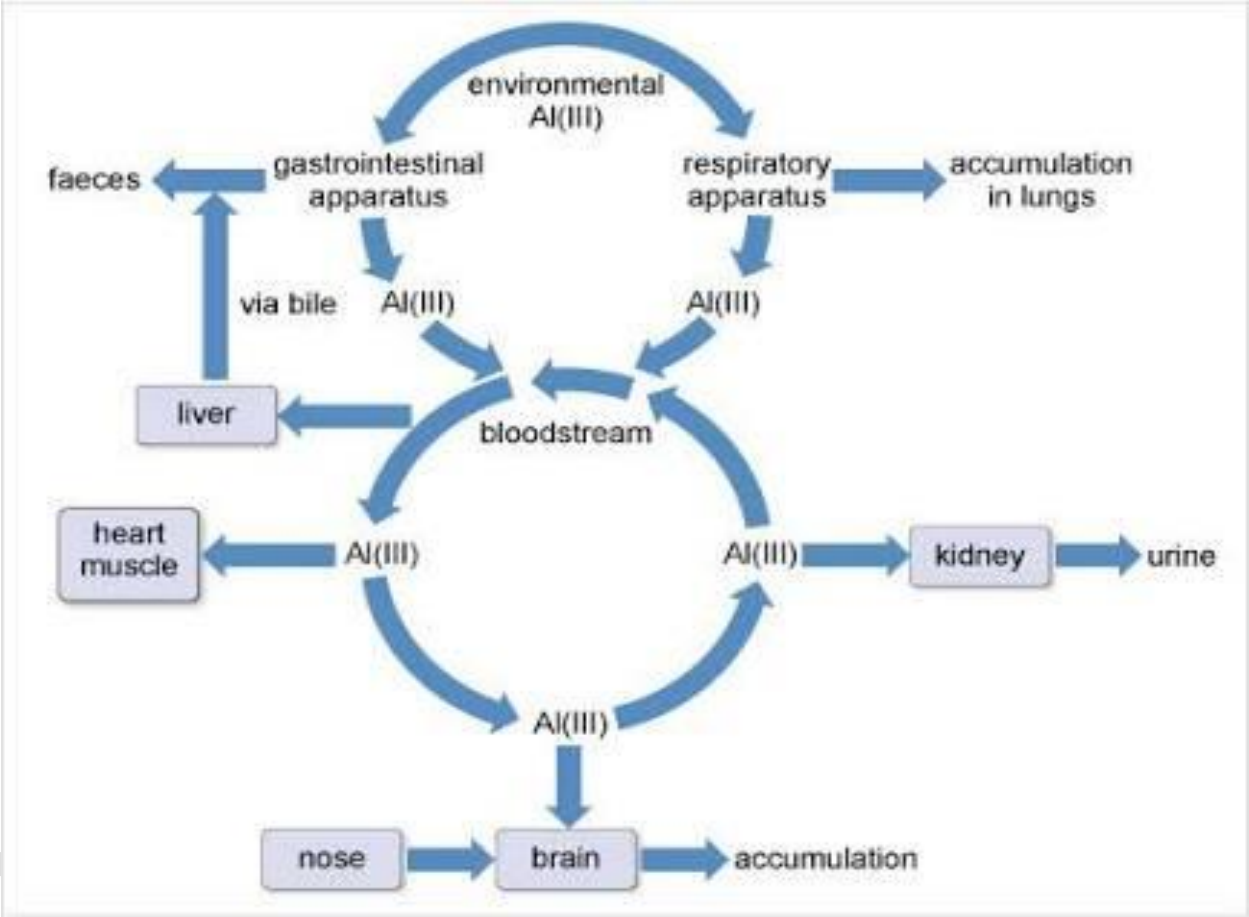

Figure 5: Absorption, Distribution, Metabolism and Excretion of Aluminium (WHO, 2017).

ALUMINIUM TOXICITY

Aluminium is very harmful to nervous, osseous and hemopoietic cells (Barabasz *et al.*, 2002; Kochian *et al.*, 2005). The main symptoms of aluminium toxicity in humans include; diminished intellectual function, forgetfulness, inability to concentrate, speech and language impairment, personality changes, altered mood, depression, dementia, visual and/or auditory impairment, hallucinations, osteomalacia with fracturing, motor disturbances, weakness, fatigue, mainly related to microcytic anaemia, epileptic seizures etc. (Campbell, 2000; Rengel, 2004; Bogle *et al.*, 2006).

Aluminium toxicity is associated with various pathological conditions including anaemia (Farina *et al.*, 2002; Osinska *et al.*, 2004; Lambert *et al.*, 2010), osteomalacia (COT, 2005), obesity (Paolo

et al., 2002; Becaria *et al.,* 2002; Exley, 2004; Jaffe *et al.,* 2005; Mailloux *et al.,* 2007; Peto, 2010), neurodegenerative disorders such as encephalopathy, Alzheimer's disease, Parkinson's disease, and multiple sclerosis (Nakamura *et al.,* 2000; Rondeau *et al.,* 2000; Mold *et al.,* 2018), amyotrophic lateral sclerosis (He *et al.,* 2000; Roos *et al.,* 2006) hepatotoxicity (Abubakar *et al*., 2001; Bogdanovic *et al.,* 2008; Türkez *et al.,* 2011; Geyikoglu *et al.,* 2013), or various reproductive disorders (Sharma *et al.,* 2003; Guo *et al.,* 2005; Yousef *et al.,* 2005; Yousef *et al.,* 2007; Guo *et al.,* 2009; Yousef and Salama, 2009).

NEUROTOXICITY OF ALUMINIUM

The most significant complications of aluminium toxicity are neurotoxic effects such as neuronal atrophy in the locus ceruleus (Exley, 2012), substantia nigra and striatum (Filiz and Meral, 2007), neuronal apoptosis in the brain (Walton, 2007; Ribes *et al.,* 2008), and impair learning and memory functions (Miu *et al.,* 2003; Jing *et al.,* 2004), problems with balance and loss of coordination (Krewski *et al.,* 2007). Neurotoxicity potential of aluminium has received particular attention due to a speculated link to neurodegenerative disorders including; Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), dialysis encephalopathy (DE) and amyotrophic lateral sclerosis (ALS) (Kawahara, 2005; WHO, 2013). The neurotoxicity of aluminium has also been demonstrated in humans, animal models and tissue and cell culture (Bondy, 2010; Exley and House, 2011).

DISORDERS LINKED TO ALUMINIUM NEUROTOXICITY

Alzheimer's disease (AD)

Alzheimer's disease is characterized by a progressive neurological impairment affecting several cognitive domains, behaviour, and personality (Wang *et al.,* 2016). Alzheimer's disease is accompanied by changes in cerebral functions as a result of biochemical incidents, each of which is related to each other. Typical neuropathological signs of the disease are intracellular neurofibrillary tangles (hyperphosphorylation of tau protein), deposition of extracellular senile plaques (hyperphosphorylation of AβP, optimal losses of synapses and neurons in hippocampal) and cerebral cortical regions, cortical and subcortical atrophy, and cerebrovascular amyloids (Gupta *et al.,* 2005; Kawahara, 2005; Sjögren *et al.,* 2015) as in Figure 6.

Aluminium has long been implicated in the pathogenesis of Alzheimer's disease, but the precise mechanism of aluminium toxicity in this disease remains unknown (Gupta *et al.,* 2005). Deposition can occur throughout the brain, as aluminium can cross the blood-brain barrier (Roig *et al.,* 2005; Sanchez-Iglesias *et al.,* 2007). It is thought that genetic factors, oxidative stress, infectious factors, and environmental factors are playing a role in AD (Gupta *et al.,* 2005). As there is no sufficient genetic information about AD, it is thought that environmental factors including aluminium interact with other factors and provide a basis for the formation of the Alzheimer's disease (Yokel, 2013).

The hypothesis, stating that aluminium was one of the environmental factors in the pathogenesis of AD, was named as "Al hypothesis," based on various neurotoxicological, analytical, and epidemiological data found in the 1960s (Klato *et al.,* 1965; Crapper *et al.,* 1973; Martyn *et al.,* 1989). The beginning of the hypothesis, stating that aluminium was included in the aetiology of

AD, is revealed by observing the neurofibrillary degeneration after the intracerebral injection of Al into rabbit's brain (Klato *et al.*, 1965).

A meta-analysis of cohort studies showed a significant correlation between Al exposure and AD risk (Neri and Hewit, 1991; Flaten, 2001). McLachlan *et al*. (1996) found a dose-response correlation between an increasing concentration of Al in the drinking water (100 mg/L or greater Al) and a higher risk of developing AD. There are several epidemiological studies of drinking water and AD risk that have also shown dose-response effects.

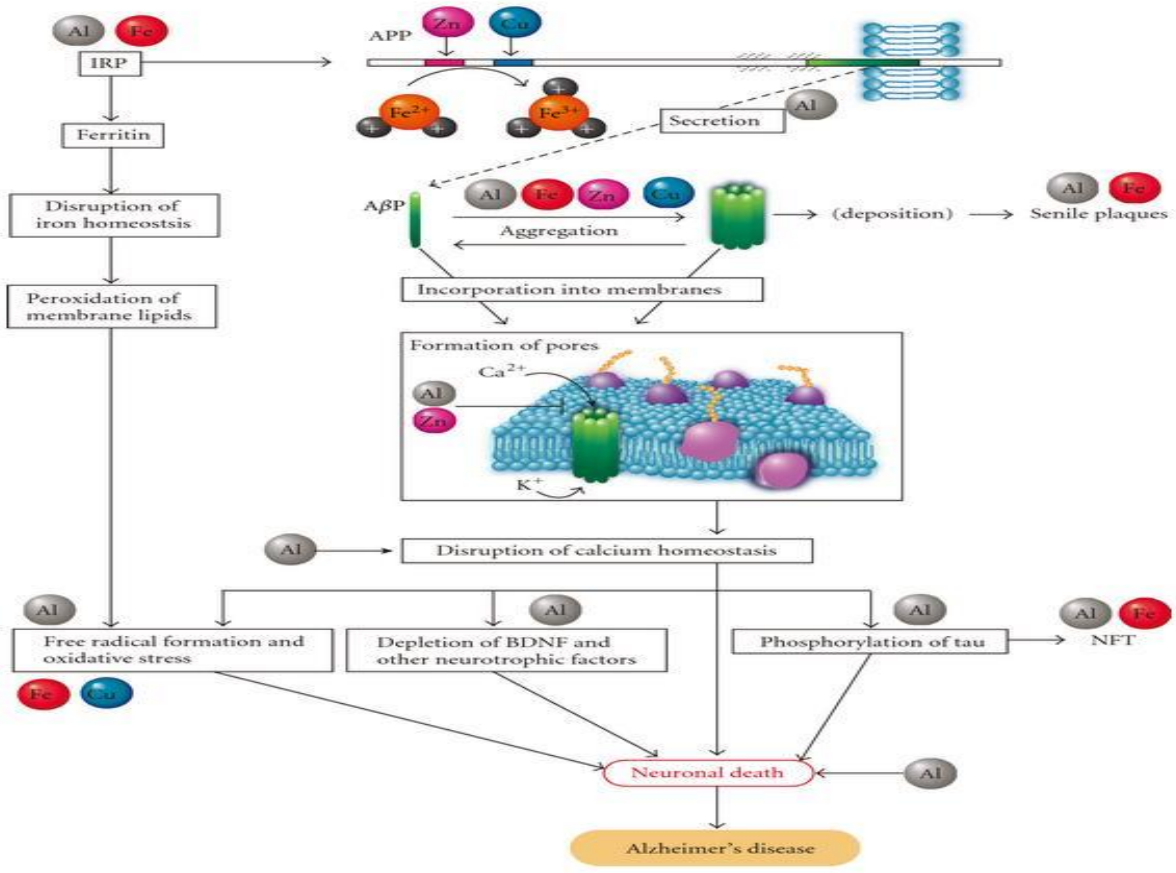

Figure 6: Mechanism of Aluminum Toxicity in Alzheimer Disease (Andrasi *et al.*, 2005)

Parkinson's disease (PD)

Parkinson's disease is a neurodegenerative disorder characterized by selective death of neurons in substantia nigra, tremors in the face, hands and jaw, muscle rigidity, and slow physical activities (Chan *et al.,* 2015). Parkinson's disease occurs as a result of the decrease of stimuli by basal ganglia in the motor cortex, depending on the death of neurons in globus pallidus and substantia nigra, which normally synthesizes and releases epinephrine and dopamine (Chin-Chan *et al.,* 2015).

The relationship between PD and Al has been demonstrated in gastric ulcer patients due to the use of aluminium-containing antacids (Altschuler, 2000). Indirect evidence between Al and PD is the ability of Al to activate the monoamine oxidase B; the enzyme increases with age and PD (Zata *et al.,* 2000). Activation of the NF-kB transcription factor and triggering of inflammatory processes have been found to occur synergistically after simultaneous treatment of experimental animals with a low level of Al in drinking water (Bondy, 2016). Yasui *et al*. (1991) found that Al concentration in the substantia nigra, caudate nucleus, and globus pallidus was higher in PD brains and significantly higher in gray matter and the basal ganglia.

Multiple sclerosis (MS)

Multiple sclerosis is a chronic, immune-mediated, demyelinating disease of the central nervous system of unknown aetiology (Exley, 2013). Human exposure to aluminium is identified as a possible contributor to multiple sclerosis (Exley, 2013). Individuals with relapsing-remitting (RRMS) and secondary progressive (SPMS) were shown to excrete large amounts of aluminium in their urine (Exley *et al.,* 2006), an observation recently built upon and confirmed in individuals with SPMS (Jones *et al.,* 2017). Many studies indicate that aluminium can be an environmental

factor in the aetiology of MS (Mirza *et al.,* 2017; Mold *et al.,* 2018). Also, the use of Al adjuvant containing vaccines has been associated with an increased incidence of MS (Álvarez *et al.,* 2011; Shoenfeld *et al.,* 2011).

Dialysis encephalopathy (DE)

Dialysis encephalopathy, first described in 1972, has emerged as a complication of prolonged hemodialysis exposure (Alfrey *et al.,* 1996). Patients with dialysis encephalopathy have difficulty in speaking (dysarthria), movement planning disorder (dyspraxia), unconsciousness and psychosis following ataxia, personality changes, myoclonic movements, electroencephalographic abnormalities, convulsions, and dementia (Murphy *et al.,* 1992).

In many studies, the aluminium content of the dialysis fluids of patients with encephalopathy was found higher than 200µg/L (WHO/IPCS, 1997). However, high levels of aluminium were reported in brain, muscle, and other tissues of dialysis encephalopathy patients (Priest, 2005). Cerebral cortical aluminium concentrations of patients with dialysis encephalopathy were reported as 10–25 µg/g dry brain weight (Priest, 2005). Nowadays, the exposure of dialysis patients to Al is the minimum, as the Al level of dialysis fluid in the majority of dialysis centres is <10 µg/L (CDCP, 2007).

Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis is a neurodegenerative disease characterized by selective motor neuron death (Ludolph *et al.,* 2015). Patients develop a progressive muscle phenotype characterized by spasticity, hyperreflexia, fasciculations, muscle atrophy, paralysis, and damages of upper and/or lower neurons (Ludolph *et al.,* 2015).

The deleterious effect of aluminium was firstly reported 40 years ago in an animal model with several studies linking its presence in serum, cerebrospinal fluid (CSF) and central nervous system (CNS) to Amyotrophic Lateral Sclerosis (ALS) (Lord *et al.,* 2000; Kamel *et al.,* 2005; Qureshi *et al.,* 2008; Roos *et al.*, 2013).

OTHER TOXIC EFFECTS OF ALUMINIUM

Reproductive and Developmental Toxicity

Soluble aluminium compounds have demonstrated reproductive toxicity (including histopathological changes in the testes and effect on gestation length) and developmental toxicity (including increased pup mortality, decreased growth, delayed maturation, and impaired neurodevelopment) in experimental animals (WHO, 2003; WHO, 2007). However, it has been reported that the developmental toxicity of aluminium by the oral route would be highly dependent on the form of aluminium and the presence of organic compounds that influence bioavailability (WHO, 2003; WHO, 2007).

Studies of reproductive toxicity in male mice (intraperitoneal or subcutaneous administration of aluminium nitrate or chloride) and rabbits (administration of aluminium chloride by gavage) have demonstrated the ability of aluminium to cause testicular toxicity, decreased sperm quality and reduced fertility (EFSA, 2008; FAO/WHO, 2012). Exposure to higher aluminium concentrations significantly reduced the body weight and the weight of testes, and epididymal in mice (Mayyas, *at al.,* 2005) and rats (Hichem *et al.,* 2013). These can be explained by the finding that aluminium concentrations higher than 200 mg/l are correlated with lower levels of testosterone, the primary androgen controlling reproductive tissue development in males (Abu-Taweel *et al.,* 2007; Sun *et*

al., 2011). Sun and collaborators (2011) found lower testosterone levels in male rats exposed to 256.72 mg/kg Al, so it is possible that testosterone disorders occurred in the 200 mg/l of the aluminium exposure.

Spermatogenic activity, spermatogenesis, and spermiogenesis are mainly under the control of testosterone (McLachlan *et al.,* 2002). Their negative effect on sexual intercourse, sperm quality, and quantity may be due to the effect of 200 mg/l dose and disturbing testosterone homeostasis (McLachlan *et al.,* 2002). Guo *et al*. (2009) suggested that aluminium induces production of nitrogen monoxide (NO), a suppressor of circulating and testicular testosterone. Zhu *et al*. (2014) also suggested that the main reason for reduced spermatogenesis in male rats was a decline in testicular enzyme activity and an imbalance in the concentrations of other trace elements (Zn, Fe, Cu) in the testes.

It was reported that oral administration of high doses of aluminium compounds in mice and rats induced signs of embryotoxicity including; reduced fetal body weight or pup weight at birth and delayed ossification (EFSA, 2008). In developmental toxicity studies, oral administration of aluminium chloride in pregnant rats showed evidence of fetotoxicity (FAO/WHO, 2012). Poirier *et al*. (2011) reported that administration of aluminium citrate in Sprague-Dawley rats, showed signs of reproductive toxicity including; renal damage, resulting in high mortality in the male offspring (Poirier *et al.,* 2011).

Mutagenicity

Aluminium compounds (including aluminium chloride, sulphate, nitrate, lactate, fluoride and pigments composed of potassium aluminium silicate) have been non-mutagenic when assessed in bacterial and mammalian cell systems and by an in vivo rat bone marrow micronucleus test (WHO,

2003). However, aluminium chloride produced some DNA damage and aluminium hydroxide, aluminium sulphate and aluminium chloride produced effects on chromosome integrity and segregation in vitro (EFSA, 2008; FAO/WHO, 2012).

Carcinogenicity and Genotoxicity

The available studies do not indicate the carcinogenic potential of aluminium for human exposure (EFSA, 2008; FAO/WHO, 2012). Several indirect mechanisms of genotoxicity have been proposed, which are considered unlikely to be of relevance for humans exposed to aluminium via the diet. However, no reports have indicated that aluminium is genotoxic to human following oral exposure (EFSA, 2008; FAO/WHO, 2012).

MECHANISM OF ALUMINIUM TOXICITY

The mechanisms of aluminium toxicity are not fully understood (Yokel *et al.,* 2001; Krewski *et al.,* 2007). The toxic effects associated with aluminium are due, in most situations, to the generation of reactive oxygen species (ROS) (Abubakar *et al*., 2001; Türgut *et al.,* 2006; Yuan *et al.,* 2012), disrupting biological membranes (Becaria *et al.,* 2004; Exley, 2006; Kuma *et al.,* 2009) and/or DNA oxidative deterioration (El-Demerdash *et al.,* 2004; Sargazi *et al.,* 2006).

Cytological changes

Aluminium toxicity can result from the interaction between aluminium and various cells including; plasma membrane, apoplastic and symplastic targets (Kochian *et al.,* 2005). In humans, Mg^{2+} and Fe^{3+} are replaced by Al^{3+}, which causes many disturbances associated with intercellular communication, cellular growth and secretory functions. The changes that are evoked in neurons by aluminium are similar (Figure 7) to the degenerative lesions observed in Alzheimer patients (Krewski *et al.,* 2009).

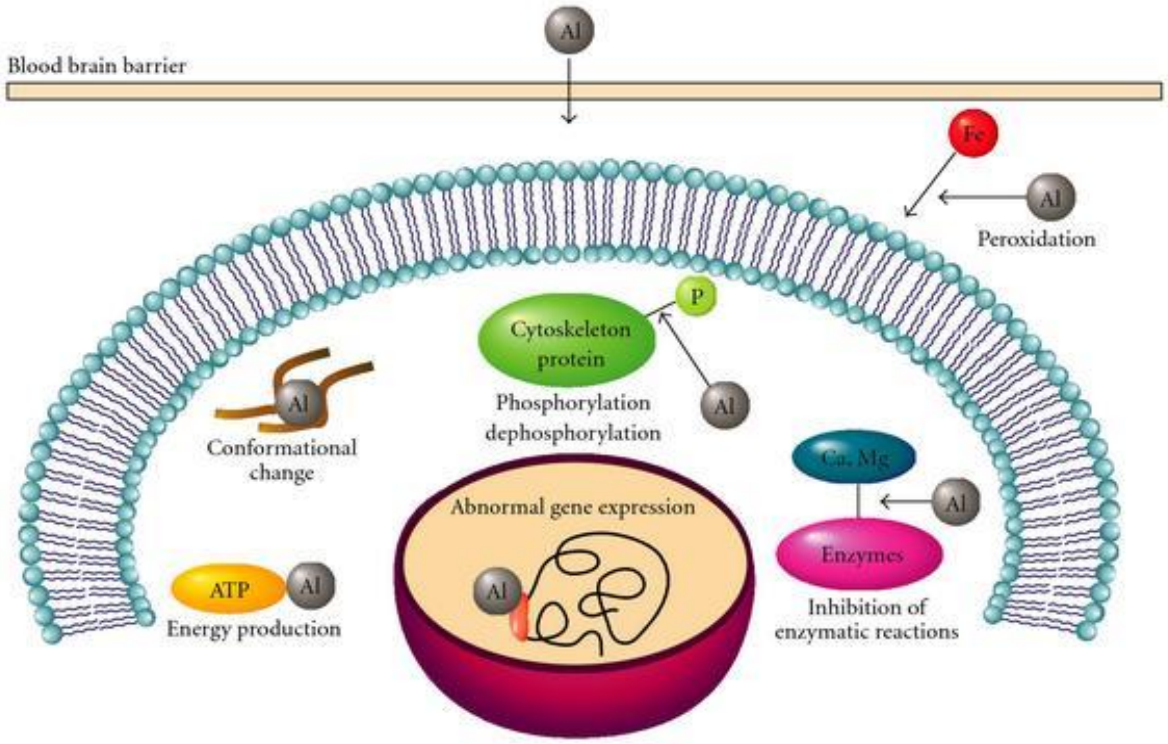

Figure 7: Mechanism of Aluminum Toxicity in the Central Nervous System (Shaw *et al.*, 2013)

Aluminium can interfere with enzymatic activities in key metabolic pathways causing changes in cellular functions (Zatta *et al.*, 2000). It can inhibit the activity of hexokinase, phosphofructokinase, and glucose-6-phosphate dehydrogenase and causing mitochondrial dysfunction and depletion of adenosine triphosphate (ATP) (Socorro *et al.*, 2000; Kumar *et al.*, 2008; Lemire *et al.*, 2009).

Aluminium toxicity disrupts mitochondrial metabolism. Aluminium toxicity also decreases the activity of α-ketoglutarate dehydrogenase, which leads to a decrease in the activity of prolyl hydroxylase (PHD). This results in stabilization of hypoxia-inducible factor-1α (HIF-1α), a transcriptional protein required for the induction of glycolytic genes.

The Al-induced perturbation of mitochondrial function leads to the subsequent diversion of metabolized carbohydrates towards lipid biosynthesis and triglyceride accumulation. Perturbation of the TCA cycle prompts the accumulation of citrate, which is then exported into the cytosol and acted upon by lipogenic enzymes to generate fatty acyl moieties. Following the esterification of fatty acyl groups with glycerol, the triglyceride is either stored in the cytosol or exported into the surrounding extracellular environment as VLDL. Aluminium toxicity also causes a decrease in L-carnitine diminishing fatty acid oxidation (Figure 8).

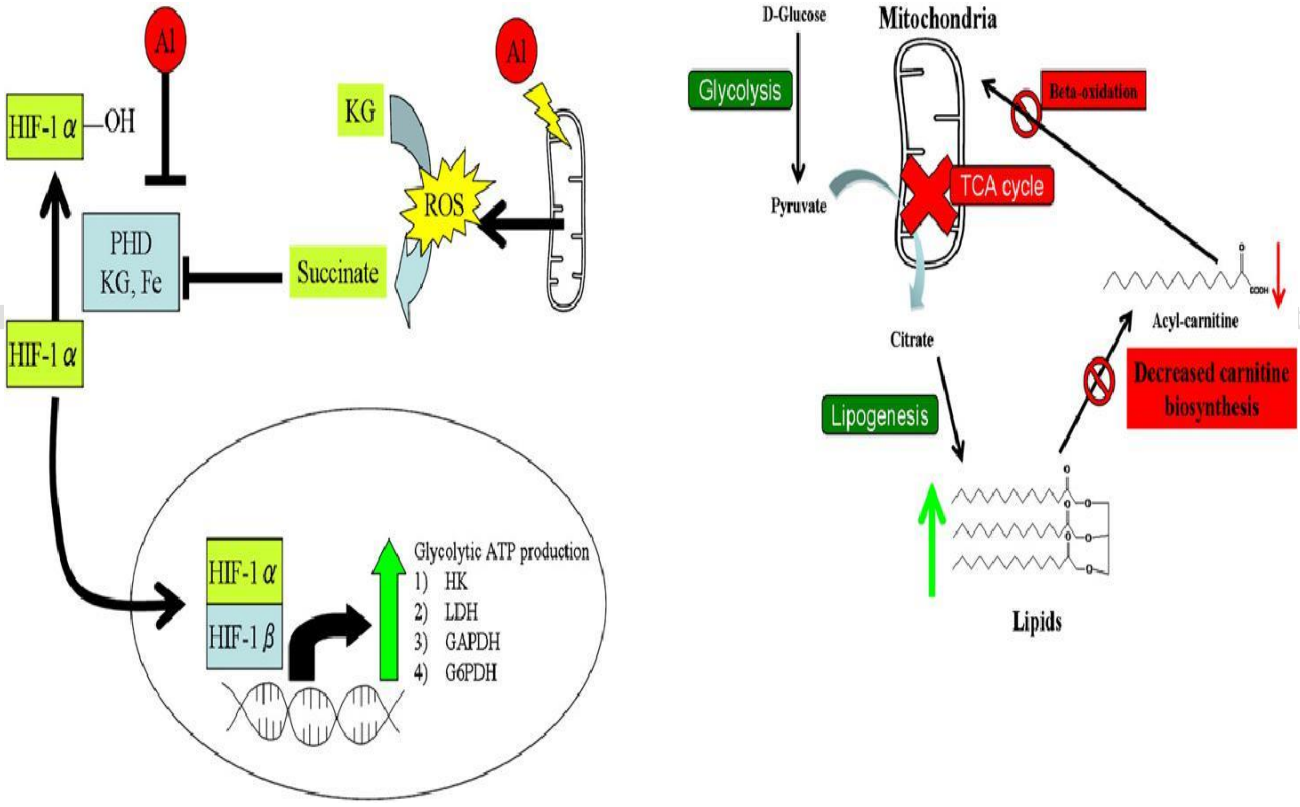

Figure 8: Aluminium Toxicity and Metabolic Pathways, Red or down arrows represent a decrease while green and up arrows represent an increase (Exley and Birchall, 1992; Serviddio *et al.*, 2011).

Aluminium interferes with several Fe-dependent enzymes within the TCA cycle and electron transport chain (ETC), resulting in the diminished production of ATP by the mitochondria (Zatta *et al.*, 2000). Aluminium toxicity is also known to alter cellular nucleotide and metabolite levels

(Murphy, 2009), ATP levels, NAD/NADH and NADP/NADPH ratios (Ying, 2008; Murphy, 2009; Mailloux *et al.*, 2011). Aluminium toxicity causes disruption of TCA cycle flux and oxidative phosphorylation which alter respiration and ATP production and accumulation of NADH. Al exposure causes a decrease of Fe-dependent enzymes such as aconitase, succinate dehydrogenase, fumarase and complex IV. Aluminium toxicity also diminishes the activity of NAD-dependent isocitrate dehydrogenase and α-ketoglutarate dehydrogenase. Inhibition of α-ketoglutarate dehydrogenase leads to the accumulation of α-ketoglutarate, which quenches ROS generating succinate as a non-enzymatic by-product as depicted in Figure 9.

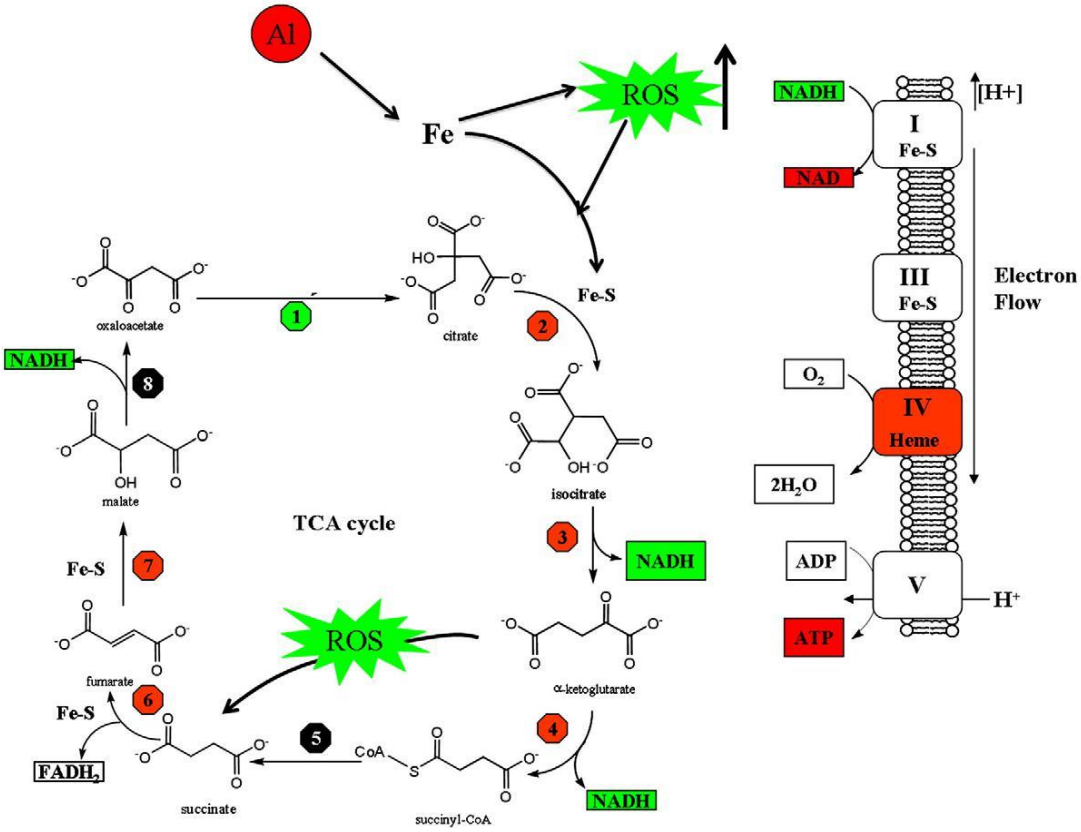

Figure 9: Metabolic Linked between Aluminium Toxicity and Fe-Dependent Enzymes within the TCA cycle and Electron Transport Chain (ETC) (*Source*: Zatta *et al.*, 2000; Ryan *et al.*, 2011). Decreases in enzyme activity or metabolite levels are indicated in red. Increases in enzyme activity or metabolite levels are indicated in green.

Calcium Ion Theory

Aluminium induces elevated and sustained levels of intracellular Ca^{2+} with significant implications not only for cellular energy metabolism but also uncontrolled phosphorylation of biomolecules (Lukiw *et al.,* 2005). The presence of biologically reactive aluminium imposes an immediate energy requirement upon a neuron, whether simply because of the need to produce more Ca^{2+}-buffering proteins or because of the requirement to clean-up the consequences of hyperphosphorylation (Lukiw *et al.,* 2005; Exley, 2012; Khan *et al.,* 2013). The toxic effects of aluminium may include interference with second-messenger signalling systems in cells, including phosphoinositol de-derived signalling and Ca^{2+}-signalling pathways, and in the formation of lipid peroxides (Rengel, 2004). It was reported that the impaired neural function caused by aluminium is related to its damage to intracellular Ca^{2+} homeostasis (Kaur and Gill, 2005).

Oxidative Stress Theory

Aluminium has been postulated to induce oxidative stress in various cell types (Oguz *et al.,* 2001; Abubakar *et al.,* 2003; Gura, 2010; Yuan *et al.,* 2012; Cheraghi *et al.,* 2017) as shown in Figure 10. Aluminium causes the production of reactive oxygen species either by a direct pathway with the formation of the ·OOH radical or indirectly by influencing the redox equilibrium in the Fenton reaction. Aluminium directly binds to negatively charged phospholipids, which contain polyunsaturated fatty acids and are easily attacked by reactive oxygen species (ROS) such as $O_2^{\cdot}$-, H_2O_2, $OH^{\cdot}$, and OH- (Verstraeten *et al.,* 1997).

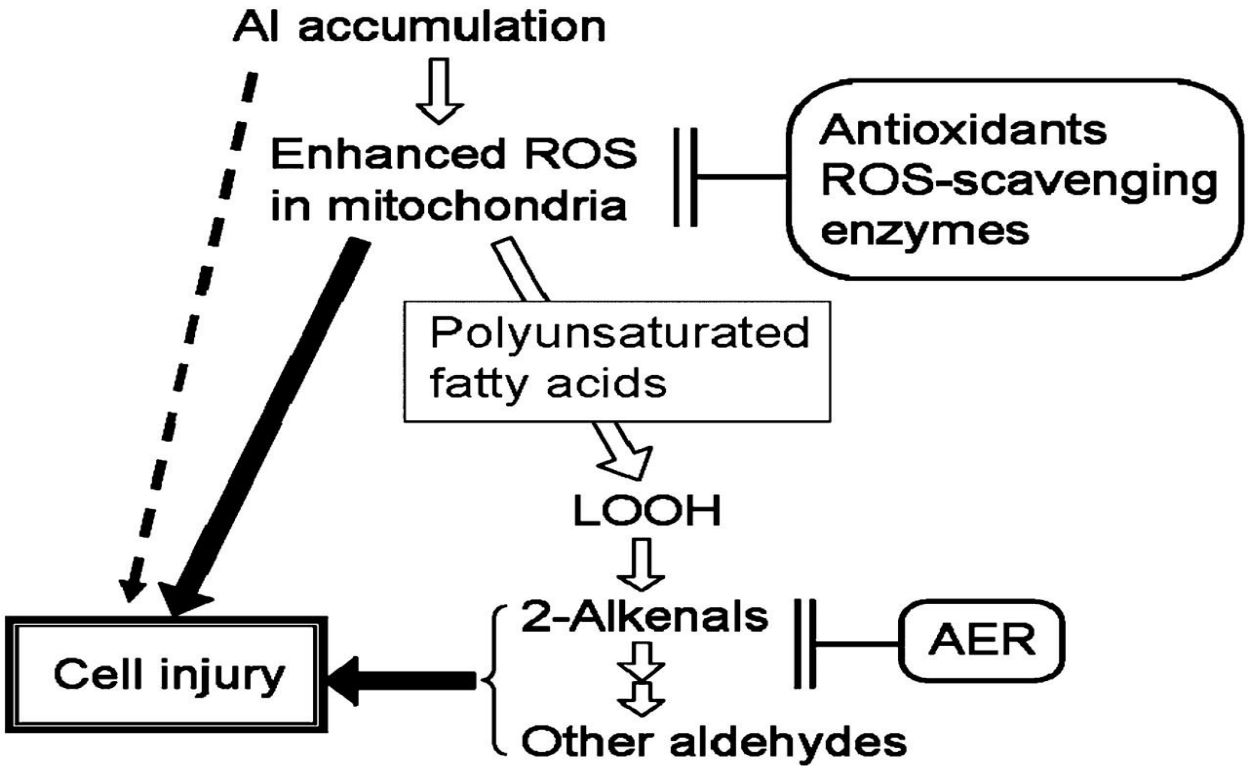

Figure 10: Aluminium Accumulation Causes Toxicity (Berthon, 2002)

Reactive oxygen species may also cause cellular damage by oxidizing amino acid residues on proteins, forming protein carbonyls (Chevion *et al.,* 2000; Kowalczyk *et al.,* 2004).

Fenton reaction

Aluminium causes the production of reactive oxygen species through the promotion of Fenton reaction. The presence of aluminium (Al^{3+}) in the aqueous environment stabilized superoxide ($O_2^{\cdot}$-) resulting in the formation of Al^{3+}-superoxide (Al-$O_2^{\cdot}$)-complex.

$Fe^{3+} + O_2^{-\cdot} \longleftrightarrow Fe^{2+} + O_2$

$\downarrow Al^{3+}$ (Abubakar *et al.,* 2002; 2003; 2004 and 2008)

Al-O_2-complex

The resultant Al^{3+}-superoxide complex reduced Fe^{3+} to Fe^{2+}, provoking the release of a neutral O_2 from the first solvation layer of aluminium.

Superoxide dismutation is catalysed by SOD to produce hydrogen peroxide (H_2O_2)

$O_2^{-\cdot} + O_2^{-\cdot} + 2H^+ \longrightarrow H_2O_2 + O_2$ (Abubakar *et al.*, 2002; 2003; 2004 and 2008)

The Fe^{2+} from the reduced Fe^{3+} reacts with H_2O_2 to produce the highly reactive hydroxyl radical ($HO\cdot$). This is known as the Fenton reaction.

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO\cdot + OH^-$ (Abubakar *et al.*, 2002; 2003; 2004 and 2008)

The reactive oxygen species generated then trigger oxidative stress, recovering the initial aluminium hydrolytic species, which is ready again to promote a Fenton reaction cycle (Figure 11).

However, the Haber – Weiss reaction can also generate $HO\cdot$ in an interaction between $O_2^{-\cdot}$ and H_2O_2 in the presence of Fe^{3+}/Fe^{2+}

$O_2^{-\cdot} + H_2O_2 \longrightarrow HO\cdot + OH^- + O_2$ (Abubakar *et al.*, 2002; 2003; 2004 and 2008)

Hence, one would expect that the destruction of the superoxide radicals or hydrogen peroxide by superoxide dismutase (SOD) or catalase (CAT) respectively would diminish Al toxicity, as would factors able to scavenge the hydroxyl radical.

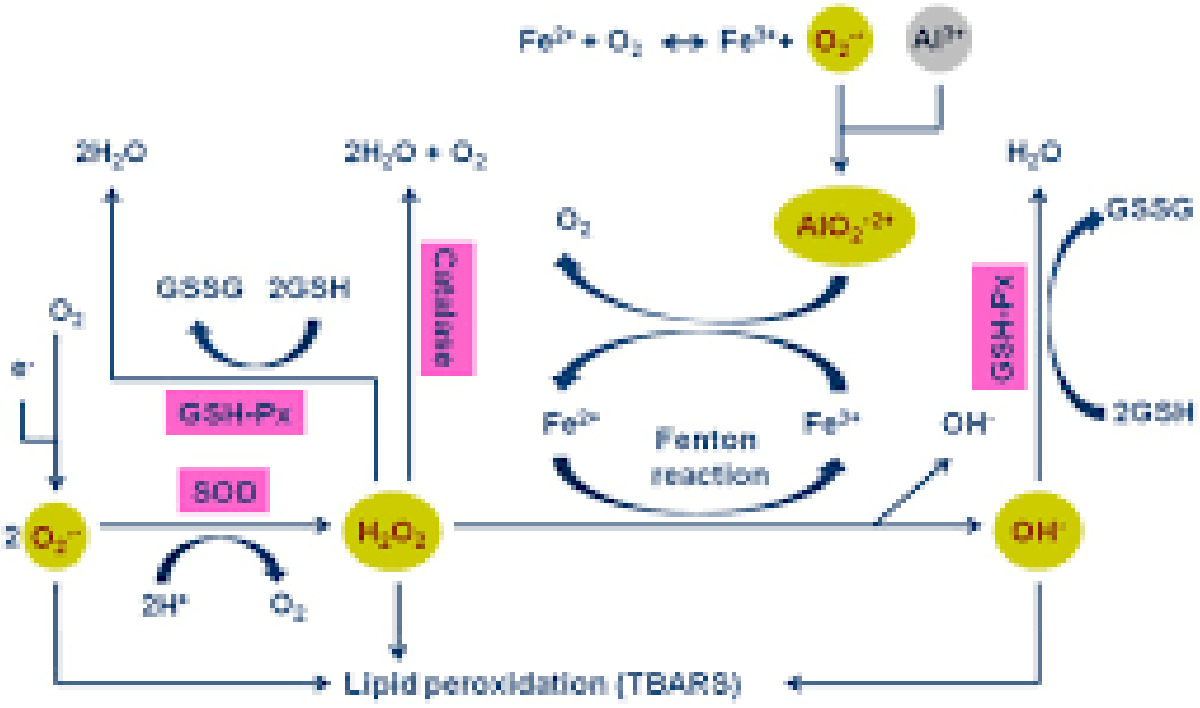

Figure 11: Diagrammatic Representation of the Relation among the Aluminium (gray), Reactive Oxygen Species (yellow), Anti-Oxidative Enzymes (pink) and Lipid Peroxidation. TBARS=thiobarbituric acid reactive substances; SOD=superoxidase dismutase; GPx=glutathione peroxidase (Exley, 2004; Halliwell and Gutteridge, 2007).

Genetic level (Gene Expression)

Aluminium can bind to histone-DNA complex and induce conformational changes of chromatin and induce topological changes of DNA (Latha *et al.*, 2002; Bharathi *et al.*, 2003). Aluminium can also alter gene expression by inducing decreased expression of neurofilaments and tubulin, altered expression of genes of neurofilaments, amyloid precursor protein (APP), and neuron-specific enolase, decreased expression of transferrin receptor, altered expression of RNA polymerase I, altered expression of oxidative stress marker genes (SOD1, glutathione reductase, etc.), and altered expression of β-APP secretase (Lukiw *et al.*, 1998; Lin *et al.*, 2008; Luo *et al.*, 2009).

Besides a direct relationship with oxidative stress accumulation, aluminium inhibits biological oxidative stress management systems by interfering with the glutathione S-transferase (GST)

detoxification system (Sumathi *et al.*, 2011; Prakash *et al.*, 2013). GSTs are multi-gene isoenzymes that are encoded by three separate families of genes, including cytosolic, microsomal, and mitochondrial transferases (Josephy, 2010; Higgins and Hayes, 2011), which are involved in the cellular detoxification of both xenobiotic and endobiotic compounds (Nebert and Vasiliou, 2004). The human GST gene superfamily comprises eight classes: alpha, kappa, mu, omega, pi, theta, sigma, and zeta (Josephy, 2010). Glutathione S-transferase pi (GSTP1), glutathione S-transferase mu (GSTM1), and glutathione S-transferase theta (GSTT1) play important roles in detoxification of xenobiotics (Rossignol *et al.*, 2014) and polymorphisms in these genes may affect biologic responses to aluminium.

GST genes encode enzymes that catalyze the conjugation of the reduced form of GSH to xenobiotics, such as heavy metals, thereby reducing the toxic effects and promoting excretion of the conjugated form of the xenobiotic (Josephy, 2010). In three studies, rodents treated with aluminium have reduced amounts of GSH (Khanna and Nehru, 2007; Sumathi *et al.*, 2011; Prakash *et al.*, 2013). The aluminium-associated GST/GSH effects observed in animal models have been reproduced in human studies. For example, a study of industrial workers noted that people with the highest levels of aluminium in urine also have low GST enzymatic activity in erythrocytes (Halatek *et al.*, 2006).

WHAT IS KNOWN SO FAR

Aluminium is known to interfere with enzymatic activities (Zatta *et al.,* 2000; Abubakar *et al*., 2003). Aluminium inhibits the activity of hexokinase, phosphofructokinase, and glucose-6-phosphate dehydrogenase (Socorro *et al.,* 2000; Kumar *et al.,* 2008; Lemire *et al.,* 2009).

Aluminium interferes with several Fe-dependent enzymes within the TCA cycle and electron transport chain (ETC). Aluminium inhibits the activity of Fe-dependent enzymes such as aconitase, succinate dehydrogenase, fumarase, and complex IV. NAD-dependent isocitrate dehydrogenase and α-ketoglutarate dehydrogenase are also inhibited by aluminium exposure (Zatta *et al.,* 2000; Ryan *et al.,* 2011).

Aluminium interferes with anti-oxidative enzymes including; superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Abubakar *et al*., 2003; Exley, 2004; Halliwell and Gutteridge, 2007).

Aluminium diminishes the production of adenine-triphosphate (ATP) (Zatta *et al.,* 2000) and alters NAD/NADH and NADP/NADPH ratios (Ying, 2008; Murphy, 2009; Mailloux *et al.,* 2011). Aluminium toxicity is also known to alter cellular nucleotide and metabolite levels (Murphy, 2009).

Aluminium interferes with biochemical processes requiring metal ions such as Fe^{3+}, Mg^{2+}, and Ca^{2+} causes changes in intercellular communication, cellular growth and secretory functions. (Krewski *et al.,* 2009).

Aluminium interferes with second-messenger signalling systems in cells, including phosphoinositide-derived signalling (Rengel, 2004) and Ca^{2+}-signalling pathways (Rengel, 2004; Kaur and Gill, 2005), and in the formation of lipid peroxides (Rengel, 2004).

Aluminium is known to binds histone-DNA complex and induces conformational changes of chromatin and topological changes of DNA (Latha *et al.,* 2002; Bharathi *et al.,* 2003).

Aluminium alters gene expression by inducing decreased expression of neurofilaments, tubulin, and transferrin receptor, and altered expression of RNA polymerase I, and β-APP secretase (Lukiw *et al.,* 1998; Lin *et al.,* 2008; Luo *et al.,* 2009).

Aluminium form low-molecular-weight complexes with organic acids, amino acids, nucleotides, phosphates and carbohydrates (EFSA, 2008; Metthew *et al*., 2019).

Aluminium toxicity is associated with various pathological conditions including anaemia (Farina *et al.,* 2002; Osinska *et al.,* 2004; Lambert *et al.,* 2010), osteomalacia (COT, 2005), obesity (Paolo *et al.,* 2002; Becaria *et al.,* 2002; Exley, 2004; Jaffe *et al.,* 2005; Mailloux *et al.,* 2007; Peto, 2010), neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis and encephalopathy (Nakamura *et al.,* 2000; Rondeau *et al.,* 2000; Mold *et al.,* 2018), amyotrophic lateral sclerosis (He *et al.,* 2000; Roos *et al.,* 2006) hepatotoxicity (Abubakar *et al*., 2001; Bogdanovic *et al.,* 2008; Türkez *et al.,* 2011; Geyikoglu *et al.,* 2013), or diverse reproductive disorders (Sharma *et al.,* 2003; Guo *et al.,* 2005; Yousef *et al.,* 2005; Yousef *et al.,* 2007; Guo *et al.,* 2009; Yousef and Salama, 2009).

In conclusion, it is not surprising to find that aluminium is a powerful inhibitor of many biochemical processes requiring metal ions, resulting in so many neurodegenerative diseases.

POSSIBLE INTERVENTION OF Al-TOXICITY

Interaction with;

- Desferrioxamine
- Magnesium
- Selenium
- Antioxidants such as Vitamin E, C, or A

(Abubakar *et al.,* 2002; 2003; 2004 and 2008)

PROBLEMS

The air we breathe, the water we drink, and the food we eat are the primary sources of aluminium (Yokel and McNamara, 2001; ATSDR, 2010).

Pharmaceutical preparations such as antacids, phosphate binders, buffered aspirins, adjuvant, and therapeutic vaccines or antiperspirants are the common sources of aluminium (Reinke *et al.,* 2003; Krewski *et al.,* 2007; ATSDR, 2008)

Aluminium is also found in some food products including food additives (processed cheese, baked goods, jellyfish, fried twisted cruller, or microalgal supplements) (Rzymski *et al.*, 2015; Zhang *et al.,* 2016; Rzymsk *et al.,* 2018) food packagings, emulsifying cheeses, and binding meats (Krewski *et al.,* 2007; ATSDR, 2008; Yokel *et al.,* 2008)

Human consumed excess (10 mg/day) aluminium from all products with a unique challenge to maintain recommended daily intake to avoid accumulation to its toxic levels (Vargel, 2004).

Exposure to aluminium in human is significantly increased by various activities which include specific industrial and agriculture occupations, first-hand and second-hand smoking, and the use

of recreational drugs; such as heroin or cocaine (Rzymski *et al.,* 2015; Zhang *et al.,* 2016; Rzymski *et al.,* 2018).

Prolong aluminium exposure induces oxidative stress and pathological alterations in diverse areas of the brain (Abubakar *et al.,* 2004; Yuan *et al.,* 2012).

Neurotoxicity potential for aluminium has been linked to neurodegenerative disorders including; Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), dialysis encephalopathy (DE) and amyotrophic lateral sclerosis (ALS) (Kawahara, 2005; WHO, 2013).

MY CONTRIBUTION

Understanding specific problems related to the mechanisms of Al-induced neurotoxicity from an oxidative stress point of view.

Focusing on the possible role of the protective agents like Mg^{2+} & Se and vitamins C & E in the modification of toxicity (Abubakar *et al.,* 2002; 2003; 2004 and 2008). It is particularly thought that these substances may have some antagonistic effect on the expression of Al-induced toxicity

METHODS AND TECHNIQUES UTILISED

- Plasma vitamin E was measured by HPLC as previously described (Ferns *et al*., 2000).
- Aluminium concentrations were determined by atomic absorption spectrometry, as previously described (Taylor & Walker, 1992).

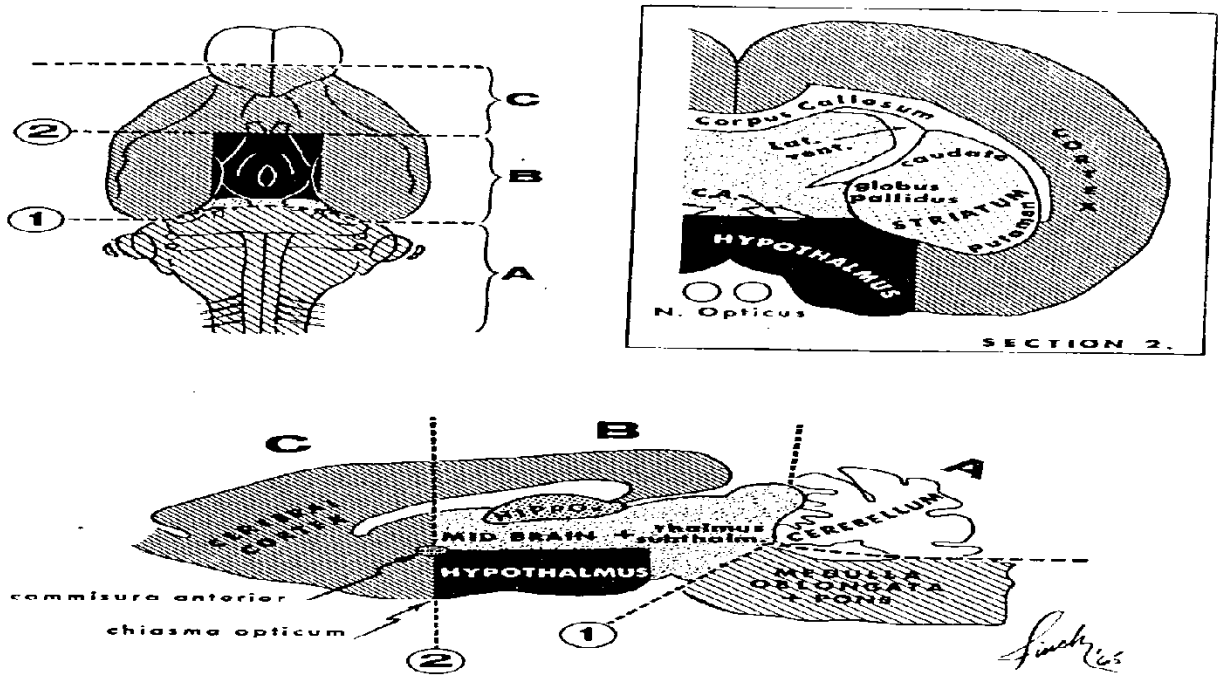

Figure 12: Diagrammatic Representation of Dissection Procedure for Rat Brain (Glowinski and Iversen (1966). Dotted lines indicate lines of dissections.

RAMANSCOPE

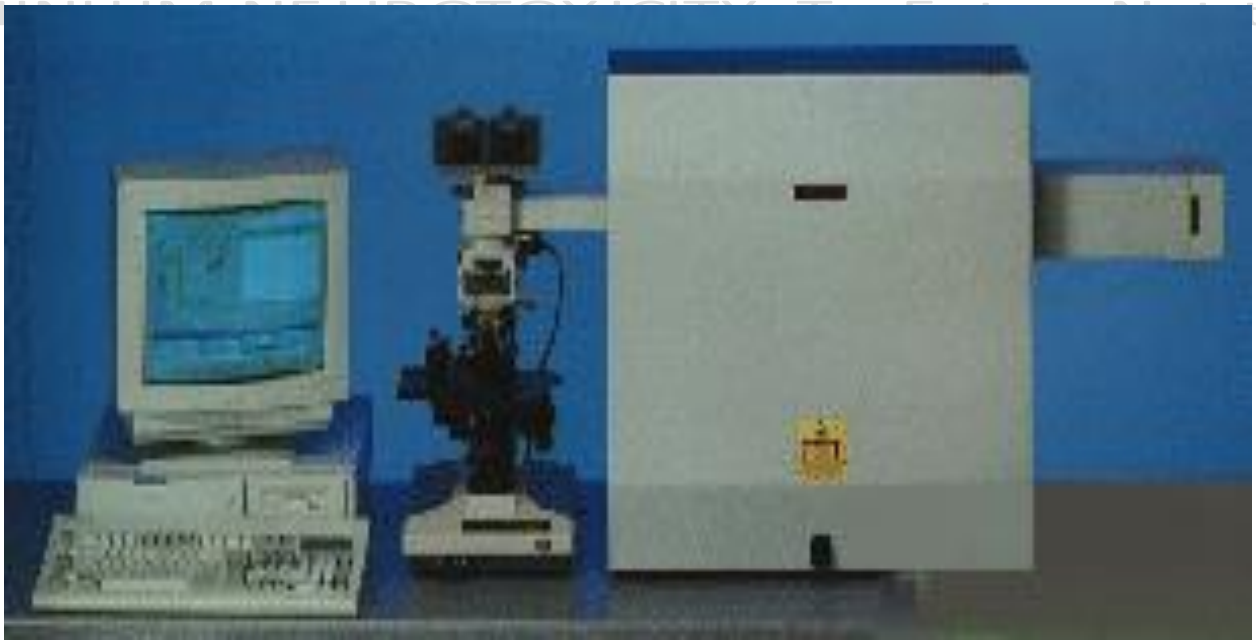

Figure 13: Ramanscopic Technique

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Full Length Research Paper

The effects of aluminium and selenium supplementation on brain and liver antioxidant status in the rat

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This *in vivo* study was designed to investigate the potential of aluminium (Al), in the absence of added iron, to participate in either antioxidant or pro-oxidant events. Some markers of oxidative stress were determined in liver and brain of rats exposed to aluminium lactate, either alone or in the presence of dietary supplements of selenium (se) as selenite. Exposure to aluminium for 21 days resulted in a statistically significant (P<0.05) decrease in brain glutathione. However, a non-significant increase in hepatic glutathione was observed in animals supplemented with either Se or Al, but Al in combination with Se prevented this elevation. In the brain a statistically non-significant increase (P>0.05) was observed in the GSH content. Contrary to what is known, Al exposure resulted in statistically significant decrease (P<0.001) in lipid peroxidation as measured by production of malondialdehyde in both liver and brain. Aluminium exposure had no significant effect on the liver and brain superoxide dismutase activity. Results of the present study suggest that in rat aluminium exposure may have both pro-oxidant and antioxidant effect. Furthermore, Se supplementation may offer some protection against aluminium toxicity but this needs to be further elucidated.

Key words: Aluminium, selenium, rat, brain, liver, antioxidant enzymes.

INTRODUCTION

Long-term haemo-dialysis using fluids containing aluminium has been associated with encephalopathy (Alfrey et al., 1976), oesteomalacia (Parkinson et al., 1979) and anaemia (Elliott et al., 1978) due to aluminium toxicity. Dialysis dementia is characterised by speech disorders, myoclonus, coma and possibly death (McMillan et al., 1993). In experimental models of aluminium toxicity, encephalopathy, nerve cell degeneration, demyelination of the brain stem cells, and impaired motor co-ordination are observed (Ebina et al., 1984). Cerebral accumulation of aluminium has also been reported in several other neuro-pathological disorders including Alzheimer's disease (Good et al., 1992; Lukiw, 1997; Perl and Brondy, 1980), Down's syndrome (Crapper et al., 1973), amylotrophic lateral sclerosis (Gadjusek and Salazer, 1982; Perl et al., 1982)

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Aluminium administration is associated with enhanced hepatic oxidant stress that may be offset by dietary vitamin E in the rat

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Summary. It has been proposed that aluminium toxicity may be mediated, at least in part, by free radical generation. We have investigated the effects of aluminium lactate administration on indices of hepatic oxidant stress, and the consequences of concomitant dietary vitamin E, in male albino Wistar rats. Aluminium lactate was administered for 4 weeks, by ip injection at 10 mg aluminium/kg body weight. Groups of animals received a chow diet containing 0, 5, 15, or 20 mg vitamin E/g of food. A control group of rats received a normal chow diet, without being injected with aluminium. The rats were killed after 4 weeks, and blood and liver tissue removed for the measurement of aluminium and markers of oxidative stress. Plasma and liver aluminium levels were increased in all groups of animals receiving aluminium lactate ($P < 0.01$), although these levels were significantly reduced in rats receiving concomitant vitamin E ($P < 0.05$). Aluminium treatment was associated with significantly increased levels of hepatic reactive oxygen species (ROS) ($P < 0.01$) that were attenuated by concomitant vitamin E ($P < 0.05$). Hepatic catalase and reduced glutathione levels were both reduced in animals treated with aluminium ($P < 0.05$).

Keywords: aluminium, catalase, glutathione, liver, rat, reactive oxygen species, vitamin E

Introduction

There has been considerable debate as to whether chronic exposure to aluminium may be involved in neuro-degenerative disorders, such as Alzheimer's disease (Perl & Brody 1980; Good *et al.* 1992; Bjertness *et al.* 1996; Lukiw 1997; Flaten 2001), dialysis and Parkinson's dementias (Hirsch *et al.* 1991; Erasmus *et al.* 1995), and hepatotoxicity (Yumoto *et al.* 1993; Chinoy & Patel 1999). The toxic effects of aluminium appear to be mediated, at least in part, by free-radical generation (Mourman *et al.* 2001); Anane & Creppy 2001). However, this premise has been challenged

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The Internet Journal of Toxicology
Volume 4 Number 2

Effect of Aluminium Toxicity on Primary Cortical Astrocytes

M Abubaker, A Taylor, G Ferns

Citation

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Abstract

The in vitro potential of aluminium to induce pro-oxidant or antioxidant effects, were studied in rat primary cortical astrocytes. These cells were exposed to aluminium (as aluminium sulphate) at different concentration. The results revealed that aluminium has a differential effect on the rat primary cortical astrocytes. The toxic effects was assessed using mitochondrial dehydrogenase activity, measured by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium (MTT); cell viability as revealed by Fluorescein diacetate-Propidium iodide (FDA-PI) staining; glutathione content; lipid peroxidation as determined by malondialdehyde production and reactive oxygen production (ROS). The data suggests that aluminium has both pro-oxidant and antioxidant effects.

INTRODUCTION

Many in vitro and in vivo model systems have been employed to study aluminium toxicity ([1,2,3,4,5,6,7]). But despite this extensive effort the molecular/cellular mechanisms of Al toxicity are still yet to be clarified. Using isolated cell lines of primary culture and cells of neuronal origin, several workers have tried to justify their cell type in terms of responsiveness to acute /chronic exposure to chemical toxicity, particularly Al in these respects. However the most interesting features to note are where the compound is localised and what features are associated with it.

To date there is no ideal model for the study of aluminium neurotoxicity in vitro, probably due to its ubiquitous nature and difficulties in maintaining adult neurones in culture. In the present study primary cortical astrocytes from the brain of new-born rat was chosen as model systems for the in vitro testing of the effect of Al. These represent a classical monotypic culture of astrocytes. The choice of monotypic cultures of astrocytes from the brain of new-born rats was based on the fact that, in the mammalian brain cortex, cells with particular astrocytic morphology account for at least 30% in terms of volume although this varies with both region and species ([8]). Correspondingly astrocytes in rats are still dividing at the time of birth, unlike most neurones which are already postmotic. Furthermore astrocytes are more robust and continue to divide until they populate the entire dish, whereas in a suspension of brain cells, the neurones are more vulnerable and have lost ability to divide. These attributes have often made astrocyte to be regarded as cells expressing glial fibrillary acidic protein (GFAP) ([9, 10]). a similar protein found in brain cortex in vivo. Transport within GFAP has also been reported to be adversely affected following Al accumulation in aluminium toxicity.

Biochemical studies revealed that astrocytes are involved in production and metabolism of the amino acid transmiters glutamine and l-amino-butyric acid (GABA), as well as in K^+ homeostasis at the cellular level, in addition to being metabolically active ([11]). Glial cells play a critical role in the development as well as physiological maintenance of the neurones ([12]) and may be the target and mediator of many insults to the CNS ([13]). Further studies have demonstrated that astrocytes are more resistant to ROS-mediated damage than the other neural cells. This may be related to the high GSH content (≈20 nmol/mg protein) ([14, 15]). though as high as 8 mM has been reported ([16]). Astrocytes survive in culture for as long as there is a source of glucose in the medium and die only when glucose is completely depleted followed by ATP depletion ([17]).

As mentioned earlier many in vivo studies ([18-20, 21]) are available that clearly report on the toxic effect of aluminium.

The above mentioned properties in addition to direct involvement of this cell type to chemical insult stimulated the interest of these cellular models to explore the likely

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TOXICOLOGY

Regional accumulation of aluminium in the rat brain is affected by dietary vitamin E

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Abstract

The regional accumulation of aluminium in the brain of male albino Wistar rats was investigated following 4 weeks of administration by intraperitoneal injection of aluminium lactate (10 mg aluminium/kg body weight). The consequences of concomitant dietary vitamin E (5, 15, or 20 mg vitamin E/g of food) were also studied. Rat brains were dissected into functional regions, for the measurement of aluminium and markers of oxidative stress. Plasma aluminium levels were increased in all groups of animals receiving aluminium lactate ($p < 0.01$), and these levels were significantly reduced in rats receiving concomitant vitamin E ($p < 0.05$). In the group of rats receiving aluminium alone, levels of brain tissue aluminium were increased in all regions of brain examined ($p < 0.01$). Brain tissue aluminium levels were reduced by concomitant dietary vitamin E. Catalase and reduced glutathione levels were both reduced in several regions of brain in animals treated with aluminium ($p < 0.05$). Aluminium treatment was not associated with a significant increase in reactive oxygen species (ROS) generation ($p > 0.05$), although ROS production was attenuated by dietary vitamin E ($p < 0.05$) in some regions.

Keywords: Rat brain; Vitamin E; Aluminium

Introduction

There has been considerable debate as to whether chronic exposure to aluminium may be involved in neurodegenerative disorders, such as Alzheimer's disease [1–4], and dialysis and Parkinson's dementias [5,6]. It has been proposed that the toxic effects of aluminium are mediated, at least in part, by free-radical generation [7,8]. However, this premise is inconsistent with the fact that aluminium ions are not able to promote membrane lipid peroxidation independently, although they may enhance Fe^{2+}-dependent membrane lipid peroxidation [9–11]. The mechanism by which this can occur is unclear, although it has been suggested that interactions with aluminium induce subtle structural changes to cellular membranes with consequent functional disturbances including increased vulnerability to damage from free radicals and effects on lysosomal and mitochondrial function [11–14]. The brain is particularly vulnerable to oxidative damage, due to its high oxygen consumption, and high contents of easily oxidisable lipids and transition metal ions, capable of catalysing the formation of reactive oxygen species (ROS) [15]. Brain tissues from patients with Alzheimer's disease

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Differences in Raman Spectra of Aluminium Treated Brain Tissue Sample

M Abubaker, A Taylor, G Ferns, H Herman

Citation

M Abubaker, A Taylor, G Ferns, H Herman. *Differences in Raman Spectra of Aluminium Treated Brain Tissue Sample*. The Internet Journal of Toxicology. 2007 Volume 4 Number 2.

Abstract

Raman microscopy was used to measure the effect of aluminium exposure on paraffin-embedded brain tissue sections. Despite the complexity of the system, we are able to show a differential Raman spectral characteristic between the Al-treated and untreated brain tissue samples. These are attributed to changes in the packing and conformation of protein material. Much work remains to be done to quantify the effect and to optimise experimental conditions, nevertheless, the results reported here demonstrate the benefits of these Raman microspectroscopic studies in such complex biosamples.

INTRODUCTION

Raman spectroscopy is a laser technique that provides vibrational spectra from different molecular species due to their different molecular bonds. But the technique only become viable as a medical tool in the mid 1980's with introduction of the Fourier Transform Raman instrument ([1]). The inherent weakness of the Raman effects is the intense Rayleigh scatter coupled with sample auto-fluorescence. Hence visible-light Raman spectrometers are poor spectroscopic tools for biological samples. However, the longer wavelength used in Fourier Transform Raman systems reduced the effects of tissue fluorescence ([2]). Besides reduced fluorescence intensity, less photolytic degradation occurs due to the longer wavelength laser, allowing higher laser powers to be used. The high throughput and multiplexing capability of the instruments also partially compensates for the low scattering efficiency and poor detector sensitivity in the near infrared. Raman spectra of tissue have been used to differentiate between normal and diseased tissues as well as different chemical state of organs and cells. The chemical structural change of cells and tissues is a good indicator of disease and is often apparent in Raman spectroscopy before it can be detected by the usual conventional methods. Raman spectrum can permits the studies of protein dynamics, drug interactions and single cells, bacteria, and viruses. Raman effect has been shown to adequately quantify species in vivo, such as arterial plaque and silicone molecules from ruptured breast implant. Dapple et al. ([3]) have isolated globules of fat surrounded by connective tissue, adding an element of spatial selectivity to the analysis. Brain tissue can also be studied, although analysis of cerebral tissue is difficult because the biochemistry and pharmacology of brain tissue is complex and heterogeneous ([4]). But using Raman spectroscopy, white and grey matter can easily be differentiated with micrometer resolution ([5]). Several methods have been developed to investigate the biochemistry associated with brain injury and activity ([6, 7]). Some of the techniques are slower with broader species sensitivity while others are fast and have species limited sensitivity. An ultraviolet resonance Raman system, using UV resonance Raman spectra of some small-molecules, peptides and lipids (free fatty acids) was used to measure the effect of aluminium exposure on paraffin-embedded brain tissue.

So far we have not came across any data showing the effect of aluminium exposure on brain tissue sample using Raman spectroscopy, but there are information on the use of Raman spectroscopy and other similar techniques to detect other chemical compounds in the brain tissue ([8]).

MATERIAL AND METHODS

Male Wistar rats weighing 170-180g (age three weeks) were divided into four groups with n=5 in each group; (a) aluminium treated group, (b) aluminium treated and a dietary supplement of 20 mg/g of vitamin E, (c) 20 mg/g vitamin E supplemented diet alone and (d) control group received only normal chow. Aluminium was administered i.p. as aluminium lactate (10 mg Al/Kg body weight) 5 times a week for 4 weeks, and the animals were not injected on

ANTIOXIDANT ROLE OF VITAMIN C IN ALUMINUM INDUCED OXIDATIVE STRESS IN RAT BRAIN

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Aluminium is naturally occurring metal that has been utilized by human for a very long time. In recent years, aluminium salts have been suspected of playing role in neuro-degenerative disorders, such as Alzheimer's and parkinson's disease and prompted concerns about aluminium contamination from aluminium cooking utensils and use of alum to treat drinking water supply that could lead to toxicity. The present study investigates the antioxidant role of vitamin C in aluminium induced oxidative stress in rat brain. Experimental rats were randomly divided into six groups (n=5/group). Groups of rats were exposure aluminium chloride 10 mg per kg body weight with or without vitamin C supplementation. for 21 days. The results obtained showed a statistically significant ($P<0.05$) increase in Aluminium blood levels and decrease in glutathione level in the brain and blood in rat treated with aluminum alone. . But the groups supplemented with various concentration of vitamin C showed significant ($P<0.05$) decrease in aluminium concentration compared to the aluminium alone treated group, and a significant increase ($P<0.05$) in brain and plasma glutathione content. The supplementation also resulted in significant increase ($P<0.05$) in plasma protein in vitamin C treated groups compared to aluminium alone treated group. A significant decrease was also observed ($P<0.05$) on malondialdehyde level in both liver and brain of the rat. Supplemented with vitamin C compared to control and aluminium alone treated groups. Therefore, from this study, it was demonstrated that vitamin C may confer protection against aluminium induced oxidative stress.

Keywords: Alumium, Vitamin C, Glutathione, Malondialdehyde

ALUM ot to Eat

15 Dietary Vitamin E Reduces Plasma and Liver Markers of Oxidant Stress in the Aluminium Treated Rat.

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Aluminium (Al) toxicity may be mediated in part via reactive oxygen species (ROS). We have investigated the effects of the antioxidant vitamin E on Al-induced effects on the liver using male Wistar albino rats. A1 was administered i.p. as aluminium lactate (10 mg/Kg body weight) 5 times a week for 4 weeks. Groups (n=5 each) were either treated with aluminium alone, or with a dietary supplement of 5, 15, and 20 mg/g, of vitamin E. Further groups received **20** mg/g vitamin E supplemented diet or normal chow without Al. Following treatment, the animals were killed and, the liver and blood removed for measurement of aluminium and markers of oxidative stress.

Al treatment caused a significant increase in aluminium content of plasma **(P<** 0.001) and liver **(P<** 0.001) in all groups. Liver ROS were significantly higher (P<O.ol) in the Al-treated groups and this was significantly attenuated (P<0.05) in the vitamin E treated groups. The aluminium-induced increase in ROS was associated with a significant reduction (P<0.05) in liver reduced glutathione levels and also a reduction of hepatic catalase activity. Hence aluminium hepatotoxicity may involve oxidative stress; reduced glu- tathione may serve as a defence mechanism in aluminium exposure and dietary vitamin E supplementation may offer further protection. Keywords: aluminium, vitamin E, rat, liver, reactive oxygen species.

PUBLICATIONS

M. G. ABUBAKAR, ANDREW TAYLOR, AND GORDON A. FERNS, (2004). Regional accumulation of Aluminium in the Rat Brain is affected by dietary Vitamin E. *J. Trac. Elem. Biol.* 18: 53-59.

M. G. ABUBAKAR, A. TAYLOR AND G. A. FERNS (2008). Differences in Raman Spectra of Aluminium Treated Brain Tissue Sample. *The Internet Journal of Toxicology* Vol. 4 No. 2

M. G. ABUBAKAR, A. TAYLOR AND G. A. FERNS (2008). Effect of Aluminium Toxicity on Primary Cortical Astrocytes. *The Internet Journal of Toxicology* Vol. 4 No. 2

M. G. ABUBAKAR, A. TAYLOR, AND G. A. A. FERNS, (2003). Aluminium administration is associated with enhanced hepatic oxidant stress that may be offset by dietary vitamin E in the rat. *Int. J. Expt. Path*. 84: 49 – 54.

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SUMMARY

Al^{+3} interfere/complex or bind/inhibit with several endogenous physiological substances. Many basic theoretical and experimental pieces of evidence have shown the involvement of Aluminium in many diseases. The biochemical processes and molecular mechanism (s) via which Al^{+3} exert its toxicity in the biological system, particularly its potency often-selective neurotoxicity, are yet to be fully understood.

POTENTIAL BENEFITS OF THE RESEARCH

Aluminium neurodegenerative disorders have for a very long time affected several individuals, particularly the elderly and patient with chronic renal failure.

This research contributes enormously towards alleviating the personal suffering, medical, financial and social burdens encountered by individuals or likely to be encountered in the near future.

CONCLUSION

'ALUMINIUM TO EAT OR NOT TO EAT' is entirely an individual decision. However, as an expert, my advice is to utilise any aluminium and aluminium containing substances in moderate amount. Because "ALL SUBSTANCES ARE POISONOUS, THERE IS NONE THAT IS NOT A POISON. THE ONLY THING THAT DIFFERENTIATES A POISON FROM NON-POISON IS THE AMOUNT" SO THEREFORE BE SAFE AND EAT WISELY

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