Interdiscip Toxicol. 2019; **Vol. 12**(2): 45–70.
doi: 10.2478/intox-2019-0007

sciendo

interdisciplinary toxicology

REVIEW ARTICLE

Aluminium toxicosis: a review of toxic actions and effects

Ikechukwu Onyebuchi IGBOKWE [1], Ephraim IGWENAGU [1], Nanacha Afifi IGBOKWE [2]

[1] Department of Veterinary Pathology, Faculty of Veterinary Medicine, University of Maiduguri, Maiduguri, Nigeria
[2] Department Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, University of Maiduguri, Maiduguri, Nigeria

ITX120219A01 • Received: 22 November 2018 • Accepted: 29 August 2019

ABSTRACT

Aluminium (Al) is frequently accessible to animal and human populations to the extent that intoxications may occur. Intake of Al is by inhalation of aerosols or particles, ingestion of food, water and medicaments, skin contact, vaccination, dialysis and infusions. Toxic actions of Al induce oxidative stress, immunologic alterations, genotoxicity, pro-inflammatory effect, peptide denaturation or transformation, enzymatic dysfunction, metabolic derangement, amyloidogenesis, membrane perturbation, iron dyshomeostasis, apoptosis, necrosis and dysplasia. The pathological conditions associated with Al toxicosis are desquamative interstitial pneumonia, pulmonary alveolar proteinosis, granulomas, granulomatosis and fibrosis, toxic myocarditis, thrombosis and ischemic stroke, granulomatous enteritis, Crohn's disease, inflammatory bowel diseases, anemia, Alzheimer's disease, dementia, sclerosis, autism, macrophagic myofasciitis, osteomalacia, oligospermia and infertility, hepatorenal disease, breast cancer and cyst, pancreatitis, pancreatic necrosis and diabetes mellitus. The review provides a broad overview of Al toxicosis as a background for sustained investigations of the toxicology of Al compounds of public health importance.

KEY WORDS: aluminium; intoxication; pathology; toxicity; toxicosis

Introduction

Aluminium (Al) is the most widely distributed metal in the environment (Delhaize and Ryan, 1995; Ranjbar *et al.*, 2008; Exley and House, 2011) occurring naturally in the trivalent state (Al^{+3}) as silicates, oxides and hydroxides, but may combine with other elements such as chlorine, sulphur, fluorine, as well as form complexes with organic matter (Jones and Bennet, 1986; Ganrot, 1986; Martin, 1992). Environmental media may be contaminated by Al from anthropogenic sources and through the weathering of rocks and minerals. Weathering processes on rocks release more Al to the environment than human-related activities (Lantzy and MacKenzie, 1979). Exposures to Al occur in occupations associated with mining and processing of ore, scrap metal recycling, deployment and use of Al-containing compounds and products, and during engagement in Al metal cutting, sawing, filing and welding. Animals and humans living in environments contaminated by industrial wastes may also be exposed to high levels of Al (Sorgdrager *et al.*, 1998; Vandenplas *et al.*, 1998; Boran *et al.*, 2013).

Several chemical compounds with Al are in extensive use in various products and processes associated with human activities. These compounds are Al chloride, Al hydroxide (alumina trihyrate), Al nitrate, Al phosphate, Al sulfate (alum), Al potassium (potash alum), Al ammonium sulfate (ammonium alum) and Al silicate (Anon, 1982; Lewis, 2001). The compounds are used in crude oil refining and cracking of petroleum; manufacturing of cooking utensils and foils, parchment paper, printing ink, glass, ceramics, pottery, incandescent filaments, fireworks, explosives, photographic flashlight, electric insulators, cement, paints and varnishes, fumigants and pesticides, lubricants, detergents, cosmetics, pharmaceuticals (drugs), vaccines, as well as in water treatment and purification, treating sewage and fur, tanning leather, waterproofing clothes and concretes, industrial filtration, hemodialysis, measuring radiation exposure, in products as flame retardant and fireproofing, anticorrosion agent, food additives to prevent caking as well as components of baking powders and colorants (Anon, 1982, 2008a; Malakoff, 2000; Lewis, 2001; Soni *et al.*, 2001; Saiyed and Yokel, 2005).

The Al ion has no physiological role in metabolic processes (Exley and House, 2011) but it can be a metallic

Correspondence address:
Ikechukwu Onyebuchi Igbokwe, DVM, MVSc, PhD, FCVSN
Faculty of Veterinary Medicine, University of Maiduguri,
Strategic Animal Research Group
P O Box 8000, Maiduguri, Nigeria
E-MAIL: ikeigbokwe@gmail.com; ikeigbokwe@unimaid.edu.ng

toxicant to humans and animals (Becaria *et al.*, 2002) when there is high body burden of the metal after natural or unnatural exposure (Exley, 2013). Al was considered unsafe to humans after the discovery of increased levels of Al in brain tissues of patients with encephalopathy, having been exposed to Al accumulation through dialysis (Alfrey and Solomons, 1976). Toxicosis due to Al accumulation in mammalian tissues was associated with various pathologic effects (Wills and Savory, 1983; Kaiser *et al.*, 1984; Boyce *et al.*, 1986; Drüeke *et al.*, 1986; Hewitt *et al.*, 1990; Bushinsky *et al.*, 1995; Reinke *et al.*, 2003; Abubakar *et al.*, 2004; Bogdanović *et al.*, 2008; Yousef and Salama, 2009; Khattab *et al.*, 2010; Blaylock, 2012; Buraimoh and Ojo, 2013; Sumathi *et al.*, 2013). Recent reviews on toxic effects of Al covered reproductive toxicity (Mouro *et al.*, 2017), pulmonary lesions (Kongerud and Søyseth, 2014; Taiwo, 2014), impact on the breast (Darbre, 2016), bone abnormalities (Chappard *et al.*, 2016; Klein, 2019), immunotoxity (Zhu *et al.*, 2014a) and neurologic disorders (Colomina and Peris-Sampedro, 2017; Morris *et al.*, 2017). This review is an abridged and global overview of toxic effects of Al and its compounds, covering some relevant aspects of exposure and updated systemic toxicosis in humans and animals, relevant as background for prospective toxicopathologic studies.

Literature search justification and methods

The initial goal in our study group was to explore the role of the ubiquitous Al ion in erythrocyte membrane dysfunction (Igbokwe, 2016) and metabolic dysregulation (Igwenagu, 2017). With the preliminary literature search starting in 2013 and looking backwards in time, research publications revealed a myriad of toxic actions of Al causing pathological conditions. Several narrative literature reviews, referred to in the introductory section, were discovered to have focused on Al toxicity of one system of the body in each review, covering the scope of nervous, reproductive, respiratory, mammary, skeletal and immune tissue toxicities. One review addressed the toxicities in bone, hematopoietic tissue and kidney (Jeffrey *et al.*, 1996) and another summarized the physiological alterations in the musculoskeletal, respiratory, cardiovascular, hepatobiliary, endocrine, urinary and reproductive systems(Nayak, 2000). Thus the question raised was whether Al toxicosis, as a disease entity, existed in the literature with current research information. The literature search for Al toxicosis as a narrative review (Green *et al.*, 2006) with a broad thematic approach was unproductive and this observation justified the need for the current review.

Toxicosis associated with Al exposure is the pathological condition or disease caused by the toxic actions of Al and its compounds. The literature search was intended to collate, synthesize and integrate the published reports on the subject matter without meta-analysis and critical evaluation of published data. For this review, the major themes for the literature search under the title included exposure modalities, toxic actions and effects in cells, tissues and systems of the body (Figure 1). These themes provided the key words and phrases for the internet search. The initial search platform was usually GOOGLE.COM with the linked GOOGLE SCHOLAR helping to search related articles. Subsequently, the search was extended to MEDLINE, PUBMED, PMC Europe, RESEARCHGATE, SCOPUS, SCIENCEDIRECT, SAGE, TANDFONLINE and SPRINGERLINK. On each platform, an article that was found could also have links to related articles and these links were followed to enrich the search outcomes. Every article was read as an abstract or full article after downloading to the literature bank. At this stage, "backward search" based on references of read articles could be done and "forward search" was required when new themes emerged that needed further exploration. The

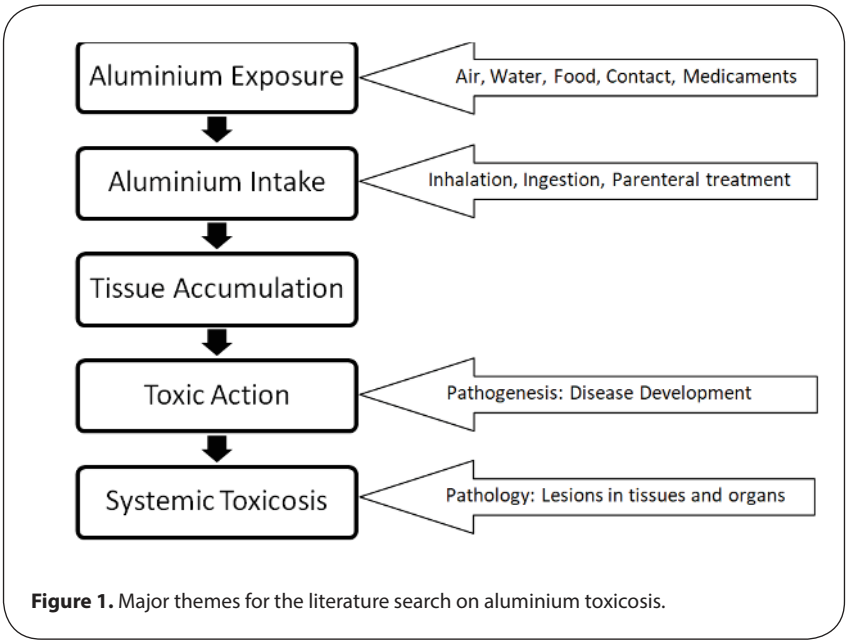

Figure 1. Major themes for the literature search on aluminium toxicosis.

integration of the literature search processes are illustrated in Figure 2. Occasionally, article request options were used to obtain restricted publications and the articles were received from authors. The literature collated from the search was read for content comprehension. The body of knowledge was summarized and narrated after cognitive reflection and integration to represent the current knowledge of the literature on Al toxicosis. The articles with thematic contents were included for the review when they were published in journals with reputable standing. The contents of the excluded articles were peripheral to the themes under review.

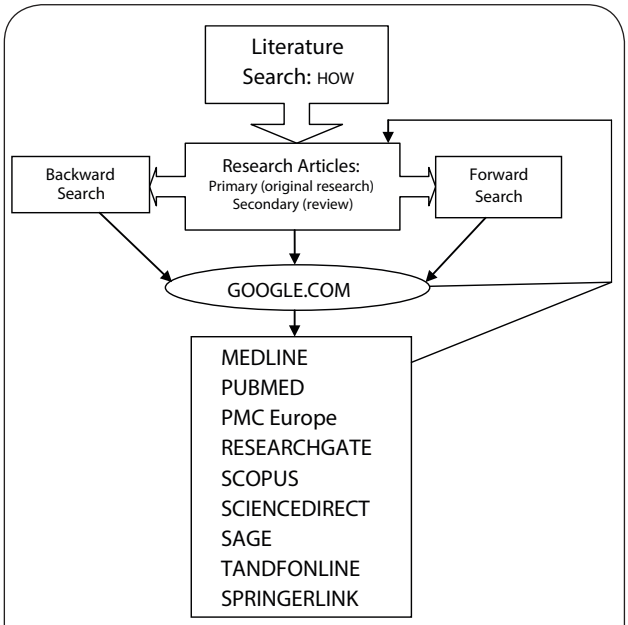

Figure 2. Integrated literature search process.

Exposure to aluminium

Aluminium intake

Aluminium in the air

The largest source of airborne Al-containing particles is the dust from soil and rocks (Lee and Von Lehmden, 1973; Sorenson *et al.*, 1974). Human activities, such as mining and agriculture, contribute to the dust in winds (Eisenreich, 1980; Filipek *et al.*, 1987). About 13% of atmospheric Al is attributed to anthropogenic emissions (Lantzy and MacKenzie, 1979). The major anthropogenic sources of Al-containing particulate matter include coal combustion, Al production, iron and steel foundries, brass and bronze refineries, motor vehicle emissions and other industrial activities such as smelting, filing, sawing, welding of Al metals (Lee and Von Lehmden, 1973; Ondov *et al.*, 1982; Que Hee *et al.*, 1982). Cigarette smoke may contribute to the concentration of Al in the air (Exley *et al.*, 2006; Kazi *et al.*, 2009; Pappas, 2011; Afridi *et al.*, 2015). The air containing Al particles or droplets becomes the source of Al in inhaled aerosols.

Aluminium in drinking water

Al occurs ubiquitously in natural waters due to weathering of Al-containing rocks and minerals and mobilization from terrestrial to aquatic environment (Campbell *et al.*, 1992). This mobilization of Al is often seasonal in nature and is associated with pH depressions (acidification) occurring during the spring snow melt or associated with erosion from specific storm events (Rosseland *et al.*, 1990; Nelson and Campbell, 1991; Campbell *et al.*, 1992). Al concentrations in surface waters can be increased directly or indirectly by human activities through industrial and municipal discharges, surface run-off, tributary inflow, groundwater seepage, and wet and dry atmospheric deposition (Eisenreich, 1980). Industrial release of Al in waste materials into surface waters from processing and manufacturing facilities could be toxic to aquatic life (Filipek *et al.*, 1987; Trieff *et al.*, 1995; His *et al.*, 1996; Gensemer and Playle, 1999). Acidic drainage from mines or acid rain may cause an increase in the dissolved Al content of the surrounding water bodies (Cronan and Schofield, 1979; Filipek *et al.*, 1987). The use of Al compounds as coagulating agents in the treatment of water for drinking could increase its Al content (Qureshi and Malmberg, 1985; Henshaw *et al.*, 1993; Cech and Montera, 2000). In pure water, Al has a minimum solubility in the pH range of 5.5–6.0 and concentrations of dissolved Al increase at higher or lower pH values (Browne *et al.*, 1990). The source of water for human and animal consumption and the purification process involved may influence the Al content of drinking water as source of exposure.

Aluminium in food

Al is present in foods naturally or from the use of Al-containing food additives (Sepe *et al.*, 2001; Flaten, 2002; Hayacibara *et al.*, 2004; Yokel *et al.*, 2008). The concentrations in foods and beverages vary widely, depending upon the food product, the type of processing used, and the geographical areas in which the food crops are grown (Sorenson *et al.*, 1974; Pennington and Schoen, 1995). The foods highest in Al are those that contain Al additives (Pennington, 1988; Greger, 1992; Saiyed and Yokel, 2005; Yokel and Florence, 2006; Yokel, 2012). The use of Al cookware, utensils and wrappings can increase the amount of Al in food (Liukkonen-Lilja and Piepponen 1992; Pennington and Schoen, 1995). The migration of Al from cookware into food increases with the acidity of the food and the duration of exposure (Valkonen and Aitio, 1997; Lin *et al.* 1997). Al was also reported to migrate into fish grilled on Al foil and the migration of Al into foods appeared to be dependent on factors such as temperature, duration of cooking, the composition and pH of the food, and the presence of other substances like organic acids and salts (Ranau *et al.*, 2001). Foods found to be naturally high in Al include potatoes, spinach and tea (Pennington and Schoen, 1995; Stahl *et al.*, 2011). Processed dairy products and flour may be high in Al if they contain Al-based food additives (Pennington and Schoen, 1995).

Daily intakes of Al in humans from food range from 3.4 to 9 mg/day (Pennington and Schoen, 1995; Biego *et al.*, 1998; Yang *et al.*, 2014). It is unlikely that Al-containing food additives are intentionally added to the diets of livestock and pets yet, Al contamination of some additives used in livestock and pet food is possible (Burgoin, 1992). Thus Al contents of harvested food products, processed foods, and cooked, baked or grilled foods may be sources of Al exposure.

Aluminium in pharmaceuticals and agrochemicals

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; Krewski *et al.*, 2007). Various intravenously administered pharmaceutical products were reported to contain 684–5977 μg/g of Al (Sedman *et al.*, 1985). Many antacids contain 104–208 mg of Al per tablet, capsule or 5 ml of suspension (Zhou and Yokel, 2005). The use of other consumer items such as dentifrices, disinfectants, fumigants, pesticides, anti-perspirants and some cosmetics are sources of Al exposure (Lewis, 2001; Pineau *et al.*, 2014). Al hydroxide, Al phosphate, Al potassium sulfate (alum), and Al silicate (zeolite) are used in the preparation of a number of vaccines to adsorb antigenic components and to serve as adjuvant that enhance immune response (Lione, 1985; Tomljenovic and Shaw, 2011; Issa *et al.*, 2014). Adjuvant as a source of Al during vaccinations has been receiving attention in research (Malakoff, 2000; Keith *et al.*, 2002; Mitkus *et al.*, 2011; Glanz *et al.*, 2015) and it is presumed that there could be mistakes in adjusting Al content of vaccines to body weights of neonates who stand the risk of Al toxicity from vaccines (Lyons-Weiler and Ricketson, 2018). More Al was absorbed into blood by rabbits after intramuscular injection with adjuvant containing Al phosphate compared to Al hydroxide (Hem, 2002). It is unlikely that parenteral Al administrations are a major source of Al exposure to livestock or pets (Issa *et al.*, 2014).

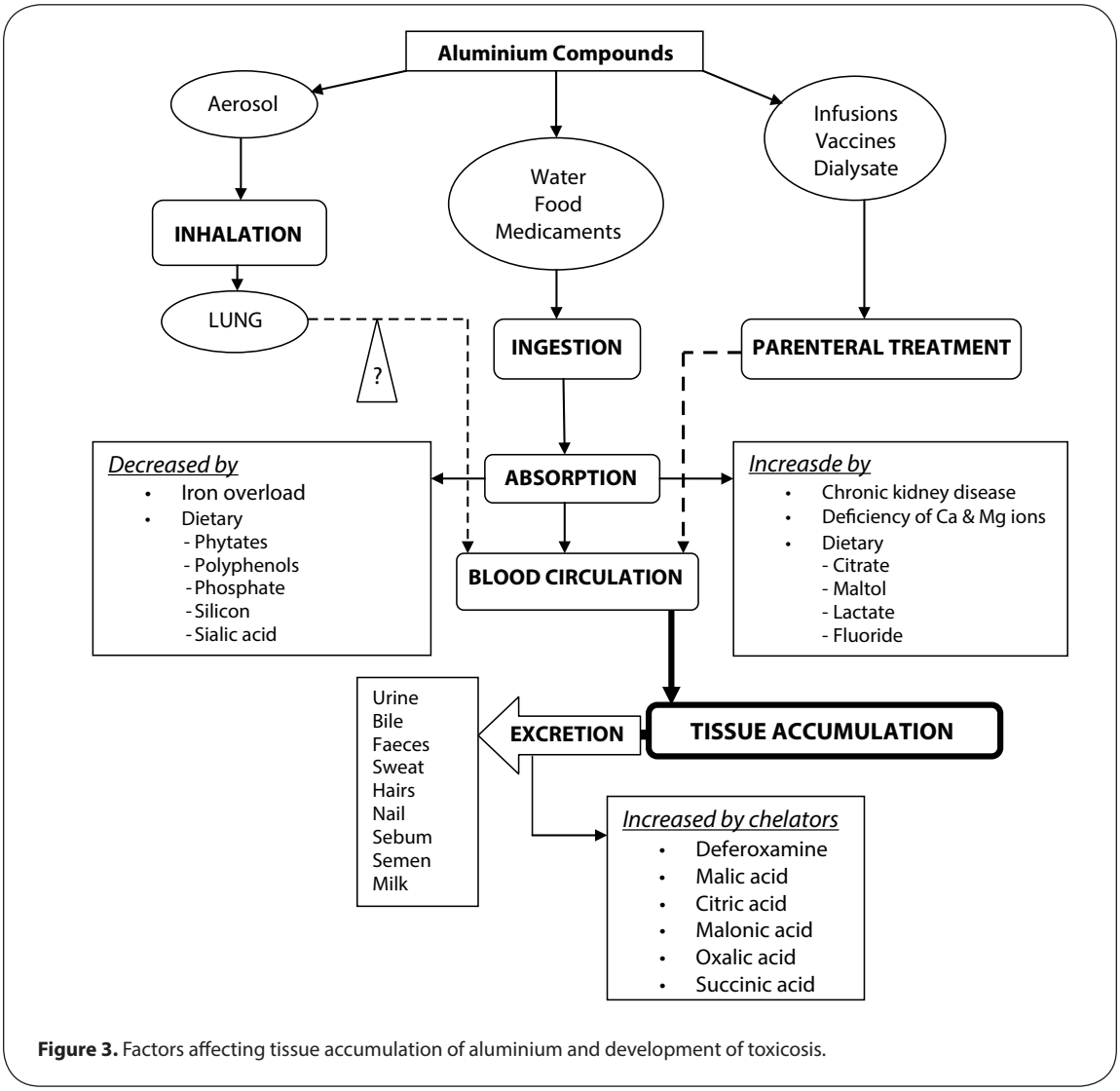

Figure 3. Factors affecting tissue accumulation of aluminium and development of toxicosis.

Food or water for livestock could be contaminated with Al when Al sulfate and zeolite are applied to litter and waste lagoons to reduce phosphorus loss from lands fertilized with the wastes and to reduce ammonia fumes in facilities (Moore *et al.*, 1999; Moore *et al.*, 2000; Codling *et al.*, 2002). Alum has also been added to dairy slurry to reduce ammonia emissions (Lefcourt and Mesinger, 2001). Thus, this section indicates that Al exposure can arise when certain pharmaceutical products are administered orally or parenterally to individuals or when agrochemicals contaminate food/feed and water taken by individuals or those in close proximity inhale aerosols from agrochemical fumigants and sprays.

Absorption, distribution and elimination of aluminium

The dynamic chain of Al intake, absorption and elimination determines the level of tissue accumulation and development of toxicosis (Figure 3). Inhalation and ingestion (via food and water) are the two main routes through which Al gets into the body (Alfrey, 1980; Teraoka, 1981; Jouhanneau *et al.*, 1997). Following inhalation, Al compounds are deposited in the lungs (Christie *et al.*, 1963; Stone *et al.*, 1979; Thomson *et al.*, 1986). The lungs continually receive Al mostly as particles of Al silicates and other poorly soluble compounds (Thomson *et al.*, 1986). The concentration of Al in the lungs tends to increase with age and may result in respiratory anomalies where the Al is localized (Alfrey, 1980; Teraoka, 1981; Taiwo, 2014). There is no available evidence in literature that particulate or soluble Al gets into the blood circulation from the lungs to be subsequently distributed to other organs of the body.

Gastrointestinal absorption, after ingestion, is the main route through which Al is systemically accumulated in animals and humans, and absorption occurs largely in the duodenum (Feinroth *et al.*, 1984; Steinhausen *et al.*, 2004). The absorption of Al is usually low and varied when compared with the amount ingested (Kawahara *et al.*, 2007). The uptake of Al through gastrointestinal pathway is complex and is influenced by various factors including individual differences, age, pH, stomach contents and type of Al compound (Priest *et al.*, 1996). Al absorption from water intake (about 0.3%) is greater than from food (about 0.1%) (Martyn *et al.*, 1989; Steinhausen *et al.*, 2004; Anon, 2008b; Zhou *et al.*, 2008).This was attributed to organic ligands in foods such as phytates and polyphenols that were suggested to form complexes with Al ion and inhibit its absorption (Reto *et al.*, 2007). Absorption of Al via the gastrointestinal tract can be enhanced in the presence of citrate, maltol, lactate and fluoride in water or food, and during chronic renal diseases, while the absorption is reduced in individuals with iron overload, or when ingested with phosphate, silicon, polyphenols and sialic acid (Brown *et al.*, 1987; Edwardson *et al.*, 1993; Anon, 2008c; Zhou *et al.*, 2008). However, there is complete Al uptake from parenteral fluids and vaccines with subsequent distribution to various parts of the body (Tomljenovic and Shaw, 2011).

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 (Day *et al.*, 1991; Harris and Messori, 2002; Hemadi *et al.*, 2003; Chen *et al.*, 2010). Cellular uptake of Al in tissues is relatively slow and is presumed to be mediated by endocytosis and intracellular transfer of the Al bound to transferrin (Hemadi *et al.*, 2003). However, Al-transferrin complex may not bind to the transferrin-receptor (Hemadi *et al.*, 2003; Sakajiri *et al.*, 2010), indicating the existence of an alternative mechanism of cellular uptake of Al (DeVoto and Yokel, 1994; Anon, 2011). The total body burden of Al in healthy humans has been reported to be approximately 30–50 mg/kg body weight and normal levels of Al in serum are approximately 1–3μg/L (Krewski *et al.*, 2007). The mean serum Al level in 44 non-exposed persons who did not use antacids was reported to be 1.6 μg/L (Valkonen and Aitio, 1997) and Chen *et al.* (2010) reported that values in hemodialysis patients were ten-fold higher than the values in unexposed individuals. About one-half of the total body Al is in the skeleton, and the levels in human bone tissue range from 5 to 10 mg/kg (Anon, 2008c). Al has also been found in human skin, lower gastrointestinal tract, lymph nodes, adrenals, parathyroid glands, and in most soft tissue organs (Anon, 2008b). In rats, accumulation of Al after oral exposure was higher in the spleen, liver, bone, and kidneys than in the brain, muscle, heart, or lungs (Anon, 2008b). It has also been reported that Al can reach the placenta and fetus and to some extent distribute to the milk of lactating mothers (Anon, 2008b). Al levels increase with age in tissues and organs (bone, muscle, lung, liver, and kidney) of experimental animals (Krewski *et al.*, 2007). Moreover, Al has been shown to rapidly enter the brain, extracellular fluid and the cerebrospinal fluid, with smaller concentrations in these organs than in the blood (Martin, 1992; Krewski *et al.*, 2007). The iron status is negatively correlated with Al accumulation in tissues and animal experiments have shown that calcium and magnesium deficiency may contribute to accumulation of Al in the brain and bone (Anon, 2011).

The Al ion in blood circulation is eliminated primarily by the kidneys (about 95%) in the urine, presumably as Al citrate (Shirley and Lote, 2005; Krewski *et al.*, 2007; Anon, 2008c). Tissue accumulation of Al is reduced by citrates and fluorides through renal excretion when the transferrin-Al binding capacity of the blood is exceeded (Anon, 2008b). Al is also excreted in the milk, bile, feces, sweat, hairs, nails, sebum and semen (Gorsky *et al.*, 1979; Greger and Sutherland, 1997; Exley, 2013). Urinary excretion of Al is enhanced by chemical chelators such as deferoxamine and malic, malonic, citric, oxalic and succinic acids, as reviewed in the later section on treatment of Al in this document. On the whole, it is noted that Al accumulation, which is responsible for Al toxicosis, is enhanced by exposure to Al and its continuous intake, as well as increased intestinal absorption and decreased excretion of the metal (Figure 3).

Toxic actions of aluminium

The toxic actions of Al responsible for the toxic effects of the toxicities are diverse and capable of causing a multifaceted systemic toxicosis. These toxic actions are summarized in Table 1. The molecular targets of action generate outcomes in the cell and disrupt cellular homeostasis with consequences that lead to lesions in the cell (Figure 4), which are responsible for systemic toxicosis associated with structural and functional abnormalities of organs.

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 (Exley, 2013). Protein polypeptides are transformed to secondary structures when Al ions interact with them through oxygen-containing amino acids, side chains and protein backbone leading to ultimate denaturation (Mujika *et al.*, 2018) or conformational or structural alteration (Exley *et al.*, 1993; Zatta *et al.*, 2005; Exley, 2006) as in β-amyloid. The aggregation and precipitation of β-amyloid is triggered and potentiated by Al exposure which is associated with Alzheimer's disease (Bondy and Truong, 1999; Zatta *et al.*, 2005; Exley, 2006) and this phenomenon may be responsible for neuritic plaque deposition, neuronal death and dysneurogenesis. Fibrillation and aggregation of human islet amyloid polypeptide hormone (amylin) was stimulated by Al exposure leading to formation of β-pleated sheet structure (Mirhashemi and Aarabi, 2011; Mirhashemi and Shahabaddin, 2011; Xu *et al.*, 2016), which may predispose pancreatic β-cell to damage. The proteolytic degradation of the amyloid peptides is also prevented by Al, thereby enhancing the accumulation of the amyloid (Sakamoto *et al.*, 2006). Extracellular surfaces and intracellular ligands may likely associate with Al to induce inhibitory or stimulatory effects (Exley and Birchall, 1992). Interaction of Al with metabolic and other enzymes causes inhibition or activation of the enzymes (Hofstetter *et al.*, 1987; Xu *et al.*, 1990; Exley *et al.*, 1994; Zatta *et al.*, 1999, 2000; Yang *et al.*, 2003; Mailloux *et al.*,

Table 1. Toxic actions associated with aluminium exposure.

Toxic action or effect	Selected references
Oxidative stress, lipid peroxidation	Kattab *et al.*, 2010; Exley, 2013; Abd-Elhady *et al.*, 2013; Zhang *et al.*, 2016; Yang *et al.*, 2018; Yu *et al.*, 2019
Pro-inflammatory: organ inflammation in lung, intestine, heart, and testis	Fogarty *et al.*, 1998; Verma *et al.*, 2007; Lerner, 2007; Exley, 2013; Taiwo, 2014; de Chambrun *et al.*, 2014; Gherardi *et al.*, 2016; Martinez *et al.*, 2017; Hangouche *et al.*, 2017
Immunosupression: induces lymphocyte apoptosis and dysfunction, inhibits lymphocyte proliferation, causes macrophage dysfunction	Nordal and Dahl, 1988; Kammalov *et al.*, 2011; She *et al.*, 2012; Zhu *et al.*, 2014; Zhuang *et al.*, 2016; Xu *et al.*, 2018; Yu *et al.*, 2019
Protein denaturation and transformation	Exley *et al.*, 2006; Mujika *et al.*, 2018
Enzymatic stimulation or inhibition	Ohsaka and Nomura, 2016
Metabolic impairment: impairs glycolysis and Kreb's cycle; promotes lipid and protein oxidation	Xu et al 1990; Mailloux *et al.*, 2006
Genotoxicity: reduced cell proliferation and differentiation, dysneurogenesis	Nam *et al.*, 2014
Amyloidogenic and anti-amyloidolytic	Sakamoto *et al.*, 2006; Xu *et al.*, 2016
Acts as metalloestrogen, promotes proliferation and migration of breast cancer cells	Bakir and Darbre, 2015; Darbre, 2016
Induces teratogenesis causing foetal and neonatal defects	Malekshah *et al.*, 2005; Wang *et al.*, 2012; El Mazoudy and Bekhet, 2016
Disrupts mineral metabolism of Fe, P, Ca, Zn, Cu by altering intestinal absorption and cellular uptake	Jeffery *et al.*, 1996; Contini, 2007; Kell, 2009; Fu *et al.*, 2014; Zhu *et al.*, 2014
Induces apoptosis, eryptosis, tissue necrosis	Niemoeller *et al.*, 2006; Xu *et al.*, 2018; Yang *et al.*, 2018; Yu *et al.*, 2019
Disrupts cell membrane permeability and receptor function, increases osmotic fragility, inhibits membrane ATPases	Fu *et al.*, 2014; Zhang *et al.*, 2016; Sun *et al.*, 2018; Gomes *et al.*, 2019
Endocrine disruption: parathyroid hormone, testosterone, luteinizing hormone, follicle stimulating hormone, estradiol, norepinephrine, cortisol, thyroid hormone, insulin	Díaz-Corte *et al.*, 2001; Chinoy and Patel, 2001; Gonzelez-Suerez *et al.*, 2005; Shahraki *et al.*, 2008; Orihuela, 2011; Sun *et al.*, 2011; Muselin *et al.*, 2016; Zhuang *et al.*, 2016; Mouro *et al.*, 2018; Wei *et al.*, 2018 Gomes *et al.*, 2019
Inhibits cartilage formation	Zhang *et al.*, 2017
Inhibits bone formation and mineralization by increasing osteoclastic activity and reducing osteoblastic activity	Cox and Dunn, 2001; Li *et al.*, 2012; Cao *et al.*, 2016; Song *et al.*, 2016; Sun *et al.*, 2016; Yang *et al.*, 2016; Huang *et al.*, 2017; Yang *et al.*, 2018; Xu *et al.*, 2018
Induces hypertension (systolic and arterial)	Zhang *et al.*, 2016
Causes ischaemic stroke and thrombosis	Abedini *et al.*, 2014
Induces contact allergy	Netterlid *et al.*, 2013
Inhibits the biological function of vitamin D in the intestine linked to calcium absorption	Dunn *et al.*, 1995

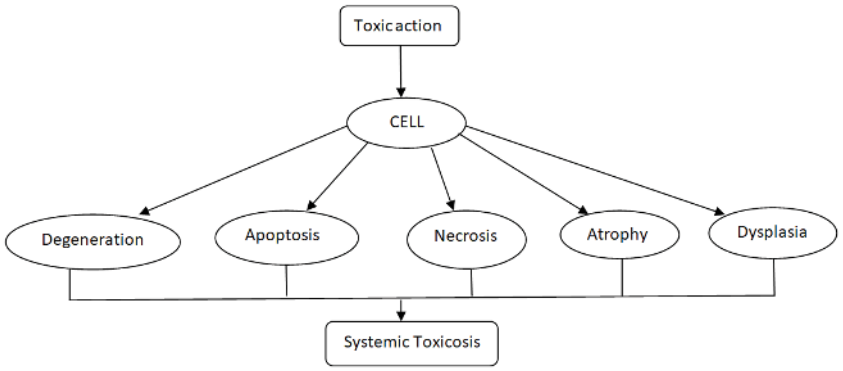

Figure 4. Cellular pathology in the systemic toxicosis of aluminium.

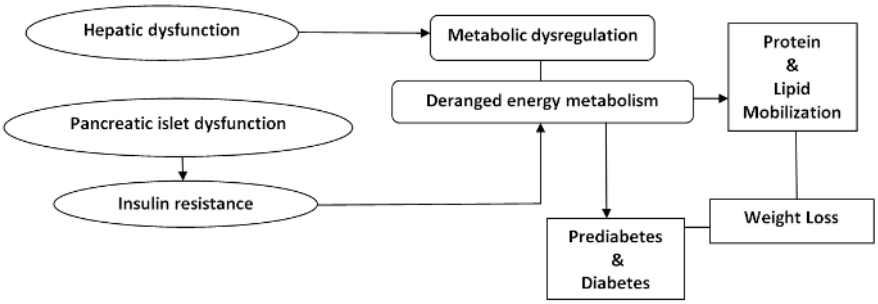

Figure 5. Metabolic abnormalities in aluminium toxicosis.

2006; Sushma *et al.*, 2007; Ohsaka and Nomura, 2016). Al binds to the phosphate groups of nucleotide such as adenosine triphosphate (ATP) and affects energy metabolism (Kawahara *et al.*, 2007). Exposure of hepatocytes to Al impedes ATP production, inhibits glycolysis, impairs the function of tricarboxylic acid (Kreb's) cycle and promotes lipid and protein oxidation (Xu *et al.*, 1990; Mailloux *et al.*, 2006) with a metabolic shift to lipogenesis in tissues (Han *et al.*, 2013). These metabolic perturbations (Figure 5) may be responsible for the reports of body weight loss and decreased production performance (like egg production) in animals exposed to Al (Wisser *et al.*, 1990; Capdevielle and Scanes, 1995; Li *et al.*, 2015).

Al exposure can cause the disruption of iron homeostasis leading to iron overload (Ward *et al.*, 2001; Contini *et al.*, 2007). Oxidative stress and injury, mediated by iron, seems to be facilitated by Al (Xiea *et al.*, 1996). Elevated concentrations of cellular iron can enhance oxidative damage to the cell and are linked to the pathogenesis of neurodegenerative disorders (Jang and Surh, 2002; Toyokuni, 2002; Adzersen *et al.*, 2003; Deugnier, 2003; Ng, 2004). Iron overload due to Al exposure has been shown to result in increased lipid peroxidation, DNA lesions, and apoptosis induced by reactive oxygen species (Bacon *et al.*, 1983; Oteiza, 1994; Kell, 2009). Apoptosis of erythrocytes (eryptosis), lymphocytes and osteoblasts is also stimulated by Al ions (Niemoeller *et al.*, 2006; Li *et al.*, 2012; Xu *et al.*, 2018; Yang *et al.*, 2018; Yu *et al.*, 2019). The oxidative injury was reported to activate the JNK apoptotic pathway in ostoblasts (Yang *et al.*, 2018). In culture, Al induced apoptosis of osteoblasts by inhibiting apoptotic Bcl-2 protein expression and increasing the expression of pro-apoptotic Bax, Bak and Bim proteins (Xu *et al.*, 2018). Al may decrease ferritin synthesis and increase the expression of transferrin receptors, thereby disrupting the normal synthesis of transferrin receptors with ferritin creating increased free iron levels in the cell, resulting in an increase of oxidative damage via the fenton reaction (Yamanaka *et al.*, 1999). The activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione (GSH) are affected by Al exposure because of oxidative stress (Oteiza *et al.*, 1993a; Julka and Gill, 1996; Campbell *et al.*, 1999). Abnormal increases in levels of malondealdehyde (MDA) and thiobarbituric acid reactive substances (TBARS) were reported along with decreased levels of antioxidants such as GSH, GPx, SOD, and CAT in tissue homogenates of rats exposed to Al (Anane and Creppy, 2001; Gonzalez *et al.*, 2007; Newairy *et al.*, 2009; Khattab *et al.*, 2010; Bai *et al.*, 2012; Exley, 2013; Abd-Elhady *et al.*, 2013; Zhang *et al.*, 2016; Yu *et al.*, 2019).

Mutagenesis and alteration of gene function may arise from the toxic action of Al with changes in transcriptional expressions (Exley, 2013). Somatic and germinal

genetoxicity in mice exposed to Al was associated with chromosomal aberrations and depression of mitosis (D'Souza *et al.*, 2014). Neuronal gene expression is influenced by the binding of Al to DNA (Lukiw *et al.*, 1998) predisposing cells to or causing genotoxicity (Pogue and Lukiw, 2016) and thus Al exposure may lead to reduction of cell proliferation and differentiation (Nam *et al.*, 2014, 2016; Sun *et al.*, 2015; Cao *et al.*, 2016; Li *et al.*, 2016; Yang *et al.*, 2016; Sun *et al.*, 2016, 2017; Huang *et al.*, 2017). Neurogenesis was impaired by Al toxicity (Nam *et al.*, 2014, 2016). Osteoblastic proliferation and differentiation were inhibited by Al when there was downregulation and inhibition of Wnt/β-catenin signaling pathway (Sun *et al.*, 2015; Cao *et al.*, 2016; Huang *et al.*, 2017; Sun *et al.*, 2017). Osteoblast differentiation was also inhibited by Al through the inhibition of BMP-2 signaling pathway (Yang *et al.*, 2016). In addition, osteoblast mineralization in vitro was inhibited by Al-induced decline in transforming growth factor (TGF)-β1 expression and action, and upregulation of Smad7 expression (Sun *et al.*, 2016) along with decreased protein expressions of osteopontin, osteocalcin and osteosialoprotein (Song *et al.*, 2017). The mineralization of bone is impaired by decreased calcium absorption (Orihuela, 2007), because Al inhibits the synthesis of calbindin, a calcium-binding protein involved in transcellular transport of calcium in enterocytes and inhibits the stimulation of synthesis of osteocalcin (the bone matrix protein) in osteoblasts by vitamin D via cellular unresponsiveness (Fanti *et al.*, 1992; Jeffery *et al.*, 1996; Cox and Dunn, 2001). The expression of cartilage stimulating growth factors, TGF-β1 and BMP-2, were inhibited by Al, thereby suppressing cartilage growth and disrupting cartilage structure (Zhang *et al.*, 2017). The effects of Al on growth manifested in developmental abnormalities of fetuses due to teratogenesis in pregnant individuals (Malekshah *et al.*, 2005; Wang *et al.*, 2012; El Mazoudy and Bekhet, 2016; Yassa *et al.*, 2017).

The proliferative and migratory characteristics of the human breast cancer cell may be affected by Al when it acts as a metalloestrogen or increases the intracellular secretion of matrix metalloproteinase (MMP9) and levels of activated MMP14 that are involved in migratory and invasive properties of cancerous cells, thereby influencing the metastatic process (Darbre *et al.*, 2013a, b; Bakir and Darbre, 2015; Darbre, 2016). It is unclear whether Al has the capacity to initiate and promote any other carcinogenic process apart from the indirect evidence provided above with regard to breast cancer.

Pro-inflammatory actions of Al have been reported in various tissues (Fogarty *et al.*, 1998; Verma *et al.*, 2007; Lerner, 2007; Exley, 2013; Taiwo, 2014; de Chambrun *et al.*, 2014; Gherardi *et al.*, 2016; Martinez *et al.*, 2017; Hangouche *et al.*, 2017). It is triggered by Al-induced oxidative stress and free radical production (Milnerowicz *et al.*, 2015). Exposure to Al increased pro-inflammatory cytokine (interleukin-1β and tumor necrosis factor alpha) levels (Jangra *et al.*, 2015) and elevated gene expression of tumor necrosis factor alpha (TNFalpha) and macrophage inflammatory protein-1alpha (MIP-1alpha) in concentration-dependent manner (Johnson and Sharma, 2003). Genes that encode pro-inflammatory signaling elements were significantly up-regulated by Al (Lukiw *et al.*, 2005). These cytokines that are released due to Al exposure can recruit leukocytes, which secrete more pro-inflammatory cytokines and other chemokines, to exacerbate the inflammation (Milnerowicz *et al.*, 2015). The inflammation can be a chronic granulomatous type (Chen *et al.*, 1978; de Vuyst *et al.*, 1987; Forgarty *et al.*, 1998; Gherardi and Authier, 2012) and Al has been reported to cause granuloma formation in vitro (de Chambrun *et al.*, 2014). Chronic exposure of mice (5 months) to Al sulfate in drinking water elicited time-dependent systemic inflammation characterized by increased serum interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), C-reactive protein (CRP) and a triad of pro-inflammatory microRNAs (miRNA-9, miRNA-125b and miRNA-146a) and the biomarkers of inflammation indicated progressive chronic inflammation in the exposed animals (Pogue *et al.*, 2017). The inflammatory conditions associated with Al exposure are summarized in Figure 6.

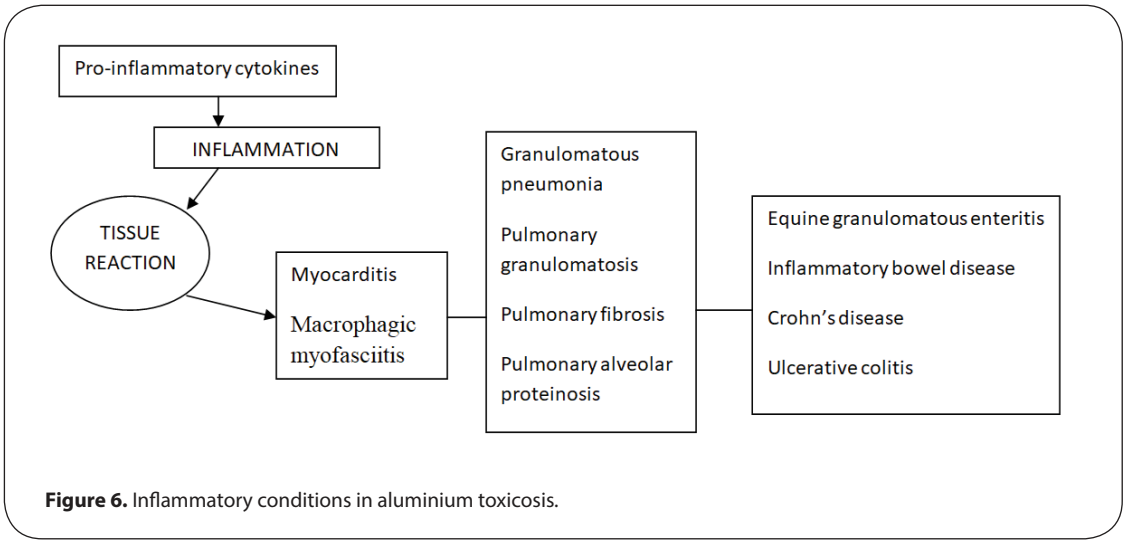

Figure 6. Inflammatory conditions in aluminium toxicosis.

Table 2. Effects of aluminium exposure on endocrine secretions in animals.

Hormone	Animal/human	Increase	Decrease	Normal	Reference
Plasma growth hormone	Duckling			+	Capdevielle *et al.*, 1995
Plasma insulin-like growth factor 1	Duckling			+	Capdevielle *et al.*, 1995
Plasma cortisol	Rat	+			Vasanthan and Joshi, 2018
Blood norepinephrine	Rat	+			Zhuang *et al.*, 2016
Serum estradiol	Mice		+		Chinoy and Patel, 2001
Serum testosterone	Gerbil (*Meriones unguiculatus*)	+			Reza and Palan, 2006; Gomes *et al.*, 2019
	Rat		+		Shahraki *et al.*, 2008; Sun *et al.*, 2011; Muselin *et al.*, 2016; Mouro *et al.*, 2018
Serum luteinizing hormone	Rat		+		Shahraki *et al.*, 2008; Sun *et al.*, 2011; Muselin *et al.*, 2016
	Rat	+			Reza and Palan, 2006
Serum follicule stimulating hormone	Rat			+	Reza and Palan, 2006; Sun *et al.*, 2011
	Rat		+		Shahraki *et al.*, 2008
Serum/plasma parathyroid hormone	Rat		+		Cannata *et al.*, 1983; Díaz-Corte *et al.*, 2001; Gonzelez-Suerez *et al.*, 2005
	Human patient with chronic renal failure, on haemodialysis	+			Sherrard *et al.*, 1985; Cournot-Witmer and Plachott, 1990
Serum thyroid hormone, T4	Rat		+		Orihuela, 2011
Serum thyroid hormone, T3	Rat		+		Orihuela, 2011
Serum thyroid hormone, free T4	Rat			+	Orihuela, 2011
Serum thyrotropin (TSH)	Rat			+	Orihuela, 2011
Insulin	Rat	+ (Acute)	+ (Chronic)		Wei *et al.*, 2018

As an adjuvant, Al in vaccines induces local inflammation that involves the NLRP3 inflammasome and NLRP3-independent pathways where macrophages, B- and T-lymphocytes play important roles in enhancing antigen-specific immune responses and increasing inflammatory cytokine production (Exley *et al.*, 2010; Hogenesch, 2013; Zlatkovic *et al.*, 2013; He *et al.*, 2015). Toxic exposure to Al causes immunotoxicity leading to inhibition of lymphocyte and macrophage functions (Nordal *et al.*, 1988; Zhu *et al.*, 2014a). Immunosuppression arises from oxidative stress which is associated with apoptosis of lymphocytes (Yu *et al.*, 2019) and damage to thymocytes and lymphocytes (Kamalov *et al.*, 2011). Immune functions of splenic B- and T-lymphocytes were inhibited in vitro by reduction of lymphocyte proliferation, cytokine secretion and proportions of CD-3(+) and CD-4(+) lymphocytes (She *et al.*, 2012). LPS-induced NLRP3 inflammasome activation, IL-1β, IL-6 and TNF-α expression and release in peritoneal macrophages were also suppressed by Al exposure (Xu *et al.*, 2018). Norepinerphrine release and activation of β-adenoceotors/cAMP pathway were promoted by Al in vivo, and this endocrine factor suppressed macrophage expressions of MIF and TNF-α (Zhuang *et al.*, 2016). Contact allergy to Al has been reported as an aberrant immune response in those having atopic dermatitis (Netterlid *et al.*, 2013).

The endocrine disruptions or hormonal changes associated with Al exposure are summarized in Table 2. Al accumulates in endocrine glands and causes damage to the glands through oxidative stress, thereby decreasing the level of the hormones secreted (Morrissey *et al.*, 1983) into the bloodstream for action at the target organs, causing organ hypofunction. For instance, there are reports of testicular and ovarian failures (Mohammed *et al.*, 2008; Fu *et al.*, 2014; Miska-Scramm *et al.*, 2017) from inadequate androgenic hormone levels (Chinoy and Patel, 2001; Shahraki *et al.*, 2008; Sun *et al.*, 2011; Muselin *et al.*, 2016; Mouro *et al.*, 2018) and decreased androgen receptor functions (Fu *et al.*, 2014; Sun *et al.*, 2018; Gomes *et al.*, 2019), bone pathology due to dysfunction of parathyroid gland (Cannata *et al.*, 1983; Sherrard *et al.*, 1985; Cournot-Witmer and Plachott, 1990; Díaz-Corte *et al.*, 2001; Gonzelez-Suerez *et al.*, 2005), prediabetes and diabetes due to pancreatic islet damage (Wei *et al.*, 2018). Parathyroid function can be impaired by the Al ion acting on calcium-sensing receptors when calcium level is low, with a higher efficiency than calcium and decreasing the expression of the receptors in the gland (Gonzelez-Suerez *et al.*, 2005). The metabolic effect of some levels of thyroxine (T3 and T4) decline without change in free T4 level is yet to be ascertained (Orihuela, 2011). The secretion of the hormone, sometimes increases when Al ion is stimulatory to the gland or because the target organs are refractory or unresponsive to the hormone when there is receptor depletion or decreased expression of the receptor on the cell membrane. The Al ions act as chemical stressor by promoting the release of norepinerphrine (Zhuang *et al.*, 2016) and cortisol (Vasanthan and Joshi,

2018); and the elevated levels of these hormones can cause increase in blood pressure (Zhang *et al.*, 2016). Elevated blood insulin level is associated with insulin resistance due to depletion of glucose transporter-4 protein expression in skeletal muscles during Al exposure (Wei *et al.*, 2018). Pseudohyperparathyroidism is associated with osteitis fibrosa in human patients with renal failure and hypercalcemia when exposed to Al intoxication (Sherrard *et al.*, 1985).

The cellular membrane is vital for the viability of the cell and Al exposure disrupts membrane activity via oxidative stress in various ways. In Alzheimer's disease associated with Al exposure, membrane fluidity increased in platelets and decreased in erythrocytes; and this observation was corroborated by a study where in vitro exposure of membrane suspensions to Al increased fluidity of platelet membranes and decreased the fluidity of erythrocyte membranes (van Rensburg *et al.*, 1992) with consequent effect on the viability of platelets (Neiva *et al.*, 1997) and erythrocytes (Vittori *et al.*, 2002). Erythrocyte membrane permeability and osmotic fragility are affected by *in vivo* and *in vitro* Al exposures (Igbokwe, 2018). Erythrocyte osmotic fragility decreased (Bazzoni *et al.*, 2005) or increased (Zatta *et al.*, 1989; Hernández *et al.*, 2008; Al-Qayim *et al.*, 2014; Oztürk and Ozdemir, 2015, Zhang *et al.*, 2016; Cheng *et al.*, 2018) depending on the Al speciation and type of erythrocyte injury. Eryptotic (apoptotic) injury reduces the erythrocyte aggregate size (Bazzoni *et al.*, 2005) because of the shrinking effect, thereby increasing osmotic resistance (Igbokwe, 2016). On the other hand, eryptotic injury which progresses to oncotic injury may cause swelling of the erythrocyte and increase osmotic fragility. It is therefore presumed that Al may cause either shrinking or swelling effect when the erythrocyte membrane is destabilized by Al exposure because of altered membrane permeability to intracellular and extracellular ions (Igbokwe, 2016). Cell membrane functions which regulate transmembrane transport of ions are expected to be disrupted when ATPase in cell membrane loses some level of activity during Al exposure. There are reports showing that Al inhibited activities of Na^+K^+-ATPase, Mg^{2+}-ATPase and Ca^{2+}-ATPase in erythrocytes (Zhang *et al.*, 2016), vascular endothelial cells (Vorbrodt *et al.*, 1994), testes (Sun *et al.*, 2018) and ovaries (Fu *et al.*, 2014) of rats. The Al-induced change in erythrocyte size may also be accompanied by change in erythrocyte shape resulting in the formation of echinocytes (Suwalsky *et al.*, 2004), acanthocytes and stomatocytes (Vittori *et al.*, 2002) in vitro, due to altered membrane morphology (Lukyanenko *et al.*, 2013). After long-term oral intake of Al, schistocytes and target cells were observed in stained peripheral blood of rats (Vittori *et al.*, 1999). The lipid bilayer of the plasma and mitochondrial membranes was morphologically altered in lymphocytes (Skarabahatava *et al.*, 2015). The protein components of membranes are degraded or inadequately expressed during Al exposure, as observed in the loss of band 3 protein of erythrocyte membrane (Vittori *et al.*, 2002; Vota *et al.*, 2012; Cheng *et al.*, 2018), inaction of membrane-bound enzymes, inhibition of calbindin protein level in enterocytic membrane (Cox and Dunn, 2001) and downregulation of GLUT4 protein expression in the membrane of skeletal muscle (Wei *et al.*, 2018). The surface of cell membranes could be affected by Al exposure through externalization of phosphatidylserine after apoptosis (Vota *et al.*, 2012), inhibition of membrane receptor protein expression in gonads (Fu *et al.*, 2014; Sun *et al.*, 2018; Gomes *et al.*, 2019), dysregulation of erythropoietin receptor functions on erythroid progenitors (Vittori *et al.*, 2005) and loss of membrane surface sialic acid residues on vascular endothelial tissue with impaired intercellular junctions (Vorbrodt *et al.*, 1994).

Systemic toxicosis

Pulmonary effect

Pulmonary lesions in humans linked to Al exposure during production of Al products include granulomatous pneumonia, pulmonary granulomatosis, pulmonary fibrosis, pulmonary alveolar proteinosis and desquamative interstitial pneumonia (Chen *et al.*, 1978; Herbert *et al.*, 1982; Miller *et al.*, 1984; De Vuyst *et al.*, 1987; Jederlinic *et al.*, 1990; Taiwo, 2014; Iijima *et al.*, 2017). Asthma may be caused by Al exposure (Burge *et al.*, 2000), though the asthma among Al workers may be due to other chemical factors like gases and smoke (Taiwo *et al.*, 2006). Reactive airways dysfunction syndrome was rarely reported among Al smelter workers (Wesdock and Arnold, 2014). Acute-duration oral exposure to Al phosphide has been reported to cause pulmonary edema in persons following accidental or volitional ingestion (Chopra *et al.*, 1986; Khosla *et al.*, 1988). The toxicity was probably due to the formation of highly toxic phosphine gas rather than to Al exposure (Alter *et al.*, 2001; Kamanyire and Murray, 2003; Moghadamnia, 2012). Intermediate- and chronic-duration studies found no organ weight or histological changes in the lungs of rats exposed to 70 mg Al/kg/day as Al chloride in drinking water for 30, 60 or 90 days (Dixon *et al.*, 1979), rats exposed to 133 mg Al/kg/day as Al nitrate in drinking water for 30 days (Gomez *et al.*, 1986), rats and mice exposed to 0.6 or 1.2 mg Al/kg/day as Al potassium sulfate in drinking water for 24 months (Schroeder and Mitchener, 1975a, b), or mice exposed to 979 mg Al/kg/day as Al potassium sulfate in food for 20 months (Oneda *et al.*, 1994). However, Hasseeb *et al.* (2011) reported neutrophilic and mononuclear cell infiltrations of lung alveoli of rats administered 37 mg/kg/day of Al chloride in drinking water for 8 weeks. Congested blood vessels in inter-alveolar spaces were reported after administration of different concentrations of Al chloride via gavage for 8 weeks (Buraimoh and Ojo, 2013). Pulmonary lesions are rare and inconsistent in experimental animals where Al exposure is not through aerosol vehicles. Under natural conditions, the vehicular substances and the Al speciation may influence the stimulation of chronic pathologic reactions in the lung.

Cardiovascular effects

Toxic myocarditis, myocardial hypokinesia, left ventricular thrombosis and myocardial dysfunction were reported in a case of Al phosphide intoxication (Hangouche *et al.*, 2017). Ischemic stroke due to thrombosis in the right middle cerebral artery was reported as the delayed complication of Al phosphide poisoning (Abedini *et al.*, 2014). However, other Al compounds may not cause cardiovascular lesion. Cardiac teratogenessis was reported in embryonic chick heart where defects in ventricular septation and ventricular myocardium were reported (El Mazoudy and Bekhet, 2016). There was significant association between increased maternal hair Al contents and risk of total congenital heart defects in offspring, especially in subtypes such as septal defects, conotruncal defects and right ventricular outflow obstruction in female rats (Wang *et al.*, 2012). No histological changes were observed in the hearts of rats given 70 mg Al/kg/day as Al chloride in drinking water for 30, 60, or 90 days (Dixon *et al.*, 1979). Similarly, no effect on organ weight nor histological changes were found in the hearts of rats that ingested 133 or 284 mg Al/kg/day as Al nitrate in drinking water or base diet for 30 days (Gomez *et al.*, 1986) or 100 days, respectively (Domingo *et al.*, 1987). Organ weight and histological changes were not observed in the hearts of dogs that consumed 75 mg Al/kg/day (Katz *et al.*, 1984) or 88 mg Al/kg/day (Pettersen *et al.*, 1990) as sodium Al phosphate in the diet for 6 months. In summary, cardiovascular effects due to toxicosis are congenital heart defects, inflammation and dysfunction of the myocardium and cardiovascular thrombosis.

Gastrointestinal effects

In horses, Al was found in tissues, blood vessel walls and granulomatous lesions of the intestines associated with equine granulomatous enteritis (Fogarty *et al.*, 1998), and Al was demonstrated to have the capacity to induce granuloma formation in vitro (de Chambrun *et al.*, 2014). Oral intake of Al may affect the intestinal microbiota, permeability and immune response which influence the local inflammatory conditions (Vignal *et al.*, 2016). In individuals that are genetically susceptible to Crohn's disease, Al is linked to the induction and persistence of the chronic relapsing intestinal inflammation (Lerner, 2007). Inflammatory bowl diseases, consisting of disease entities like Crohn's disease and ulcerative colitis, are characterized by excessive intestinal inflammation and experimental evidence in mice indicates that Al promotes intestinal inflammation, thereby implicating Al in the pathogenesis of inflammatory bowl diseases (de Chambrun *et al.*, 2014). Chemically-induced acute colitis and chronic colitis in transgenic mice lacking interleukin 10 were aggravated by oral exposure to Al, because Al increased the intensity and duration of intestinal inflammation and decreased regeneration or renewal of the intestinal epithelial mucosal cells (de Chambrun *et al.*, 2014). Furthermore, intestinal barrier function was impaired by Al exposure under basal conditions; and there was a synergistic stimulation of pro-inflammatory cytokine expression by Al and lipopolysaccharides (de Chambrun *et al.*, 2014). Oral Al chloride exposure caused epithelial degeneration, goblet cell proliferation and lymphocyte infiltration in the mucosa of the small intestine of Wistar rats (Buraimoh and Ojo, 2012). Few experimental studies (Gomez *et al.*, 1986; Oneda *et al.*, 1994) did not report intestinal lesions after oral exposure to Al at 133 mg Al/kg/day as Al nitrate in drinking water to rats for 30 days and 979 mg Al/kg/day as Al potassium sulfate in the food of mice for 20 months. The acute and chronic inflammations in the intestine may induce poor intestinal digestion and absorption.

Hematologic effects

Al exposure has been associated with significant inhibition of colony forming units-erythroid (CFU-E) development in the bone marrow of mice exposed to 13 mg Al/kg as Al citrate or chloride administered via gavage for 5 days/week for 22 weeks (Garbossa *et al.*, 1996), rats exposed to 27 mg Al/kg as Al citrate administered via gavage 5 days/week for 15 weeks (Garbossa *et al.*, 1998), and rats exposed to 230 mg Al/kg/day as Al citrate in drinking water for 8 months (Vittori *et al.*, 1999). The effect of Al on erythroid progenitor cells and erythrocytes was associated with slow growth and increased degradation of membrane band 3 proteins, respectively (Vittori *et al.*, 2002). The genotoxicity from Al exposure in mice resulted in mitodepressive effect in the bone marrow (D'Souza *et al.*, 2014). Anemia caused by Al toxicity is not associated with adequate regenerative activity of the bone marrow and reticulocytosis (Chmielnicka *et al.*, 1994; Osman *et al.*, 2012). The additional causes of anemia appear to be multi-factorial and include defective hemoglobin production due to inhibition of the enzymes of heme synthesis, altered erythrocyte membrane structure and fragility, shortening of red blood cell life span due to eryptotic and oncotic injuries, and inadequate iron utilization (Zatta *et al.*, 1989; Perez *et al.*, 2001; Bazzoni *et al.*, 2005; Vittori *et al.*, 2002; Niemoeller *et al.*, 2006; Hernández *et al.*, 2008; Sadhana, 2011; Vota *et al.*, 2012; Lukyanenko *et al.*, 2013; Al-Qayim *et al.*, 2014; Oztürk and Ozdemir, 2015; Zhang *et al.*, 2016; Cheng *et al.*, 2018). Significant decreases in hemoglobin, hematocrit (packed cell volume) and erythrocyte osmotic fragility were reported after Al exposure (Garbossa *et al.*, 1996; Garbossa *et al.*, 1998; Vittori *et al.*, 1999; Farina *et al.*, 2005). The anemia is characterized by decreases in mean corpuscular volume (microcytosis) and mean corpuscular hemoglobin (hypochromia), but in chronic exposures, the erythrocyte parameters recover with persistence of microcytosis and hypochromia (Mahieu *et al.*, 2000). In rats loaded with Al, heme dyshomeostasis was reported with evidence of decreased activity of aminolevulinic acid dehydratase and increased activity of heme oxygenase in the rat liver associated with activation of JNK pathway, indicating an increase in heme degradation (Lin *et al.*, 2013). No alterations in hemoglobin, hematocrit and erythrocyte osmotic fragility were reported in a number of experimental Al exposures (Katz *et al.*, 1984; Gomez *et al.*, 1986; Domingo *et al.*, 1987; Pettersen *et al.*, 1990;

Table 3. Summary of haematologic effects of aluminium toxicosis.

Toxic effects	Toxic actions
Depressed erythropoiesis	Inhibition of CFU-E
	Slow growth of erythroid cells
	Inhibition of heme synthesis
	Increased heme degradation
	Dysregulated erythropoietin receptor function
Anaemia	Reduced erythrocyte life span
	Erythrocyte apoptosis (eryptosis)
	Altered erythrocyte fragility
	Decreased erythrocyte membrane fluidity
	Inhibition of erythrocyte membrane ATPase
	Altered erythrocyte shape: echinocytes, acanthocytes, stomatocytes, target cells

Oteiza *et al.*, 1993b; Garbossa *et al.*, 1996**).** Vittori *et al.* (1999) did not find significant alterations in plasma iron levels or total iron binding capacity in rats exposed to 230 mg Al/kg/day as Al citrate in drinking water for 8 months; however, they reported impaired iron uptake and decreased iron incorporation into heme in the bone marrow. Farina *et al.* (2005) found significant decreases in blood iron concentrations and no change in total iron binding capacity in rats exposed to 54.7 mg Al/kg/day as Al sulfate in a sodium citrate solution in drinking water for 18 months. Florence *et al.* (1994) reported decreases in serum iron levels, total iron binding capacity, and transferrin saturation in rats exposed to 75 mg Al/kg/day as Al citrate in the diet for 6 months. Chronic Al exposure in rats disrupted iron homeostasis (Zhang *et al.*, 2010). In summary, the hematologic effect of toxicosis consists of anemia due to erythrocyte and erythroid pathology with suppression of erythropoiesis (Table 3)

Neurologic effects

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 (King *et al.*, 1981; Savory *et al.*, 1996; Kawahara and Kato-Negishi, 2011; Arain *et al.*, 2015; Jones *et al.*, 2017; Mirza *et al.*, 2017; Mold *et al.*, 2018). The Al in brains of 5 out of 12 donors with familial Alzheimer's disease was > 10 μg/g dry weight (Mirza *et al.*, 2017). In autism, Al in parts of the brain was up to 19 μg/g dry weight (Mold *et al.*, 2018). There is a role for Al in multiple sclerosis because patients excrete high amounts of Al in urine, facilitated by drinking silicon-rich mineral water (Jones *et al.*, 2017). Subchronic exposure to Al was associated with reduced population of neural stem cells and hampered cell proliferation and neuroblast differentiation in the brain of mice (Nam *et al.*, 2014, 2016). Injection of Al, especially intra-cisternally, induced neurological changes in animal models (Wisniewski *et al.*, 1980; Anon, 2008c). Rats orally administered Al (100 mg/kg/day) for 90 days accumulated more Al in their brains, had increased brain acetyl cholinesterase activity and had decreased brain choline acetyltransferase activity (Bilkei-Gorzó, 1993). Mice fed high Al levels (1,000 mg/kg diet of Al as Al lactate) were less active, had decreased grip strength, and increased startle responses after 90 days when compared with control (Golub *et al.*, 1992). Oteiza *et al.* (1993b) reported that mice fed diets containing 1,000 mg/kg diet of Al (as Al chloride) with sodium citrate accumulated more Al in the brain nuclear fraction and spinal cord, had lower grip strength, and greater startle responsiveness after 5 and 7 weeks. Old (18 months of age) rats exposed to Al (100 mg/kg/day) in drinking water with citrate (356 mg/kg/day of citrate) had decreased numbers of synapses and a greater percentage of perforated synapses than controls, but no changes in behavior (Colomina *et al.*, 2002). Garruto *et al.* (1989) reported that cynomolgus monkeys fed a low calcium diet (3,200 mg/kg diet) with Al (125 mg/day) for 41 to 46 months had more degenerative changes that were consistent with early Alzheimer's disease or Parkinson's dementia in the central nervous system than control monkeys. Golub and Germann (2001) observed growth depression and poorer performance on standardized motor tests in mice offspring when dams were exposed to Al (1,000 mg/kg diet as Al lactate) with marginal levels of calcium and magnesium during pregnancy and lactation. Mice fed lower rather than recommended levels of calcium (2,500 versus 5,000 mg/kg diet of calcium) with Al (15,600 mg/kg diet as Al hydroxide) for 11 to 25 months accumulated more hyperphosphorylated tau protein in the cortical neurons and had more atrophic neurons in the central nervous system (Kihira et al,. 2002). Transgenic mice with over-expressed human amyloid precursor protein had increased brain isoprostane levels and more amyloid-β peptide formation and deposition when Al was added to their diets, but the effects of Al were reversed by additional dietary vitamin E (Pratico *et al.*, 2002), suggesting that Al could contribute to neurodegeneration by enhancing amyloid deposition and aggravating lesions by oxidative events (Campbell and Bondy, 2000; Yuan *et al.*, 2012; Chen and Zhong, 2014; Liaquat *et al.*, 2019). In a nutshell, Al exposure promotes oxidative stress and amyloid deposition in the nervous tissue which results in neurodegeneration, neuronal necrosis and dysneurogenesis, which constitute the basis for the neurological diseases associated with Al intoxication.

Musculoskeletal effects

The major myopathy induced by Al exposure is macrophagic myofasciitis (aluminic granuloma) associated with chronic arthromyalgia or myalgia and chronic fatigue syndrome (Exley *et al.*, 2009; Gherardi and Authier, 2012; Rigolet *et al.*, 2014; Gherardi *et al.*, 2016; Miller, 2016). Skeletal muscle necrosis occurred in the diaphragm and abdominal muscles of rats adjacent to the peritoneum after intraperitoneal injection of Al lactate (Levine *et al.*, 1992). Muscle fiber atrophy, with retardation of growth, was reported in growing pigs which was associated with hypophosphatemia induced by dietary Al

hydroxide supplementation (Haglin *et al.*, 1994). Smooth muscle contraction induced by K+ ion was inhibited by Al exposure (Nasu *et al.*, 1998). Myocardial function may be altered in diabetic individuals by Al exposure, in as much as Al toxicity potentiates the decline in calcium uptake into the sarcoplasmic reticulum of the myocardial fibers of such individuals (Levine *et al.*, 1990). In individuals where neurodegerative conditions affect the nerve supply to muscles, the muscles may undergo denervation atrophy and become dysfunctional as in multiple sclerosis or amyotropic lateral sclerosis. Taken together, Al toxicosis may cause muscle damage, inflammation and dysfunction

The bone diseases associated with Al exposure are osteoporosis, osteomalcia, rickets, exostosis, osteodystrophy and osteitis fibrosa (Sherrard *et al.*, 1985; Chappard *et al.*, 2016; Rodríguez and Mandalunis, 2018; Klein, 2019). There is increased risk of osteoporosis and low bone mineral density during Al exposure (Cao *et al.*, 2016; Sun *et al.*, 2016) because of disruption of bone formation, and inhibition of osteoblast proliferation, differentiation and mineralization (Li *et al.*, 2012, 2016; Cao *et al.*, 2016; Sun *et al.*, 2016; Yang *et al.*, 2016; Zhu *et al.*, 2016b; Song *et al.*, 2017; Sun *et al.*, 2017; Huang *et al.*, 2017). In individuals with Al overload, undecalcified bone matrix contains Al and bone conditions like exostosis and osteomalacia may occur in circumstances that increase Al uptake and colocalization as observed in celiac disease, hemochromatosis and sickle cell anemia (Chappard *et al.*, 2016). Osteoclastogenesis is promoted by low-dose exposure while osteoclast apoptosis is caused by high-dose exposure (Yang *et al.*, 2018). There are case reports of osteomalacia and rickets in infants and adults using Al-containing antacids for the treatment of gastrointestinal illnesses (Chines and Pacifici, 1990; Pivnick *et al.*, 1995; Woodson, 1998). The Al in antacids binds with dietary phosphorus and prevents its absorption resulting in hypophosphatemia and phosphate depletion (Woodson, 1998). Osteomalacia, characterized by bone softening, increased spontaneous fractures and pain, has been reported in dialyzed uremic adults and children exposed to Al-contaminated dialysate or orally administered Al-containing phosphate-binding agents (Mayor *et al.*, 1985; Wills and Savory, 1989; Andreoli, 1990). Low osseous remodeling rate and peripheral resistance to parathyroid hormone are associated with Al intoxication (Pun *et al.*, 1990). Decreased Al urinary excretion caused by impaired renal function with, possibly, an increase in gastrointestinal absorption of Al results in increased Al load leading to markedly increased bone Al levels and the presence of Al between the junction of calcified and non-calcified bones (Alfrey, 1993). Long-term oral exposure to Al results in an increase in Al levels in the bone (Ahn *et al.*, 1995; Konishi *et al.*, 1996) that is responsible for the bone disease.

In brief, the review has identified the following events to occur during Al exposure to disrupt bone morphology: (a) interference with the availability of calcium for bone formation at the level of intestinal absorption and hormonal control through parathyroid hormone; (b) inhibition of osteoid formation and mineralization through osteoblast dysregulation; and (c) destabilization of osteoclast functions with alteration in osteoclastogenesis and osteoclast apoptosis (Figure 7).

Reproductive and developmental effects

Human reproduction may be affected negatively by Al exposure (Klein *et al.*, 2014; Mouro *et al.*, 2017). Human semen and spermatozoa contain Al and patients with oligospermia had higher Al concentration than healthy individuals (Klein *et al.*, 2014). At human dietary level of Al and continuous exposure for 60 days, the rat testes accumulated low Al levels of 3.35 µg/g and it was associated with increased oxidative stress and inflammation, decreased daily sperm production, reduced sperm count and motility and increase in abnormal spermatozoa (Martinez *et al.*, 2017). In male rats, subchronic exposure to Al chloride did not result in elevated Al accumulation in the testes, but toxic effects reported in the testes included impairment of spermatogenesis and increase in sperm malformation rate (Zhu *et al.*, 2014b). Imbalance in trace mineral metabolism occurred in the testis with

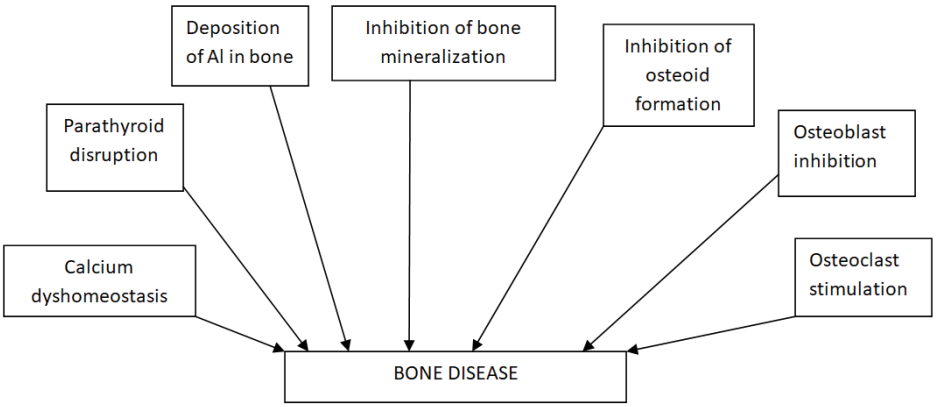

Figure 7. Pathogenesis of bone disease in aluminium toxicosis.

testicular levels of iron and zinc increasing and that of copper decreasing during exposure (Zhu *et al.*, 2014b). Furthermore, metabolic inhibition in the testis was reported with regard to the functions of acid phosphatase, succinate dehydrogenase, and lactate dehydrogenase and its isoenzymes (Zhu *et al.*, 2014b), alongside with testicular membrane dysfunction due to inhibition of membrane ATPase activities in Al-exposed rats (Sun *et al.*, 2018). The weights of the testes and epididymides were decreased by Al exposure in rats as serum testosterone levels dropped (Mouro *et al.*, 2018). In male rats, testicular development was impaired by Al exposure, associated with reduction in serum levels of testosterone and luteinizing hormone (LH) levels and decrease in androgen receptor protein expression without effect on serum follicle stimulating hormone (FSH) (Sun *et al.*, 2011, 2018). The offspring of exposed rats (F0) in a three-generation study belonging to F1 and F2 had decreased testosterone and LH levels, decreased testicular weight, and increase in the production of abnormal immobile spermatozoa, whereas the parental F0 group did not present with such reproductive abnormalities (Muselin *et al.*, 2016). In rats that were injected with Al chloride (4.125 pmole) in artificial cerebrospinal fluid via the lateral ventricle, there were significant decreases in serum FSH, LH and testosterone levels, and reduction in sperm count from the vas deferens and epididymides (Shahraki *et al.*, 2008). Bank voles (*Myodes glareolus*) exposed to Al produced lower quality and quantity of sperm than normal, but reproductive capacity was not significantly affected in females (Miska-Schramm *et al.*, 2017). After intraperitoneal treatment at 50 mg/kg for 20 days, blood testosterone and LH levels were increased in male rats, but FSH level was not affected (Resa and Palan, 2006). Khattab *et al.* (2010) reported that administration of Al chloride (20 mg/kg) to male rats via gavage for 70 days caused fertility disturbances and testicular dysfunction. Other reports showed that Al induced decrease in sperm counts, motility and viability, with increase in dead and abnormal sperm counts (Bataineh *et al.*, 1998; Guo *et al.*, 2005; Yousef *et al.*, 2007; Yousef and Salama, 2009; D'Souza *et al.*, 2014). Testicular and epididymal weights and serum testosterone and luteinizing hormone levels were reduced by Al exposure (Reza and Palan, 2006; Mouro *et al.*, 2017). In male and female gerbils (*Meriones unguiculatus*), Al exposure disrupted prostate development in neonates, with the consequence of adult offspring having elevated serum testosterone levels with low androgen receptor frequency associated with increased proliferation of cells of the prostate (Gomes *et al.*, 2019).

Chinoy and Patel (2001) exposed female mice to Al chloride at 200 mg/kg for 30 days and observed decreased steroidogenesis in the ovaries associated with decreased serum estradiol levels. Exposure to Al sulphate during gestation caused reduction in maternal body weight, reduction in fetal weight and crown rump length, and impairment of fetal bone development and preossification (Yassa *et al.*, 2017). In adult mice exposed to Al at 1000–1400 ppm in drinking water or 19–39 mg/kg intraperitoneally, pregnancy rate decreased with increased frequency of atretic follicles; after pregnancy, failure of pregnancy increased with increased rate of uterine resorption and decrease in the number of viable fetuses and implantation sites (Mohammed *et al.*, 2008). Fu *et al.* (2014) reported that Al exposure damaged ovarian structure, disrupted metabolism of iron, zinc and copper in the ovary and decreased the activities of ovarian ATPases and expressions of androgenic receptors for FSH and LH; and could consequently lead to infertility due to inhibition of ovulation and development of corpus luteum. Exposure to Al during mouse pregnancy resulted in reduced fetal weight and increased frequency of external anomalies in fetuses (Malekshah *et al.*, 2005) and fetal micronucleated erythrocytes (D'Souza *et al.*, 2014). Khalaf *et al.* (2007) reported perinatal and postnatal adverse effects of Al exposure on fetuses and neonates during gestation and lactation of female rats. The hepatic toxicity of Al chloride was also reported in pregnant rats and their offspring with observation of decreased fetal weight and size (Mestaghanmi *et al.*, 2003). Exposed embryonic chicks and rat fetuses developed congenital myocardial defects (Wang *et al.*, 2012; El Mazoudy and Bekhet, 2016).

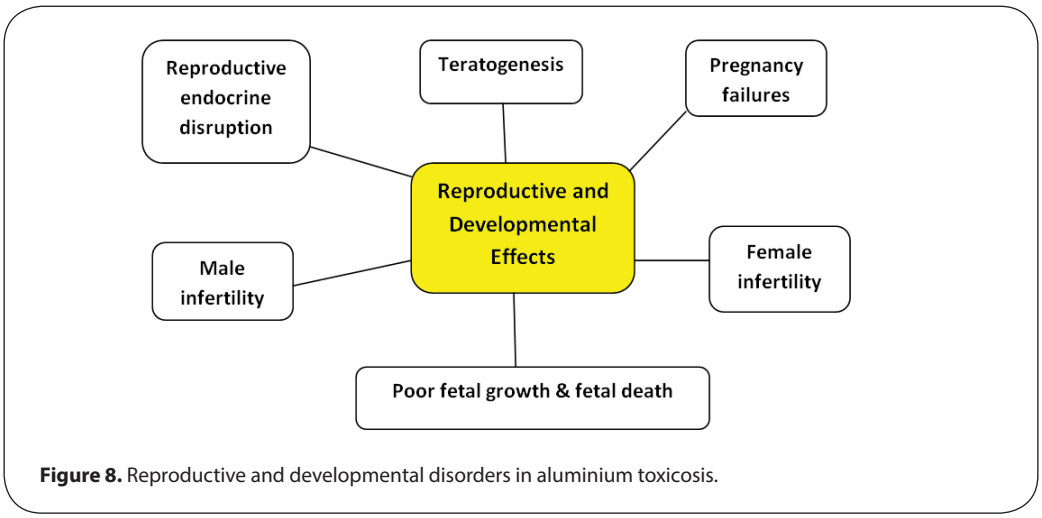

Figure 8. Reproductive and developmental disorders in aluminium toxicosis.

On the whole, Al toxicosis caused lesions in the testes and ovaries resulting in impairment of spermatogenesis and ovarian function related to ovulation, with the consequence of reproductive inefficiency associated with pregnancy failures and poor fetal development (Figure 8).

Hepato-renal and pancreatic effects

Al causes oxidative injuries to the kidney and liver leading to tissue degeneration and necrosis, and associated serum biochemical derangements (Nikolov *et al.*, 2010; Mailloux *et al.*, 2011; Bai *et al.*, 2012; Li *et al.*, 2015; Xu *et al.*, 2017). Abdel-Wahab (2012) reported a significant increase in the activities of alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST) and total bilirubin, as well as increased serum urea and creatinine levels after oral administration of 20 mg/kg of Al chloride for 30 days in experimental rats. Ingestion of aluminium phosphide pellets was reported to induce acute pancreatitis in one patient (Verma *et al.*, 2007). Rats had moderate pancreatic islet necrosis after intermediate oral exposure (50 mg/kg for 28 days) to Al chloride (Figure 9) which was associated with impaired fasting blood glucose and impaired oral glucose tolerance (Igwenagu, 2017; Igwenagu *et al.*, 2019). Rats treated intra-peritoneally with Al chloride at 10 mg/kg for 30 days had significantly increased fasting blood glucose, serum insulin level and insulin resistance index on days 10 and 20 of treatment, but as treatment progressed to day 30, serum insulin level had decreased, indicating that pancreatic β-cell function decreased as pancreatic damage occurred with progression of treatment (Wei *et al.*, 2018). The hepatic and pancreatic lesions cause changes in metabolism (Figure 5) which result in hyperglycaemia, hypoproteinaemia, hyperlipidaemia, hypercholesterolaemia and hypertriglyceridaemia (Omar *et al.*, 2003; Kowalczyk *et al.*, 2004; Türkez *et al.*, 2011; Abdel-Wahab, 2012; Belaïd-Nouira *et al.*, 2013).

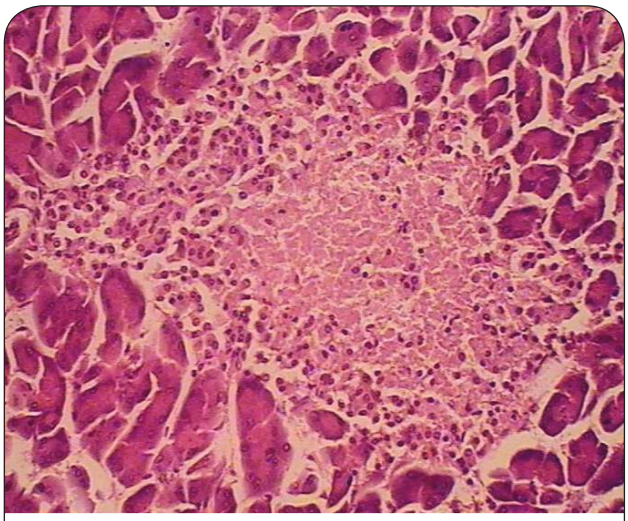

Figure 9. Photomicrograph of pancreas of aluminium chloride-treated rat showing coagulative necrosis of the pancreatic islet tissue with disorganization of its architecture (H & E, x 400) From Igwenagu *et al.* (2019).

Mammary gland or breast effects

Breast cancers and cysts are mammary gland conditions where emerging evidence are suggesting that Al may be involved in their causation (Darbre, 2016). Al chlorohydrate in antiperspirant cosmetics and other underarm cosmetic products may be an important source of Al exposure (Pineau *et al.*, 2014; Linhart *et al.*, 2017). In a case control study (Linhart *et al.*, 2017), the use of underarm cosmetic products containing Al was significantly associated with breast cancer incidence and the Al levels in breast tissues were significantly higher in breast cancer cases than controls (5.8 versus 3.8 nmol/g). Breast cancer patients had higher levels of Al in breast tissues than in blood serum (Darbre *et al.*, 2013b). There were higher levels of Al in nipple aspirates of cancer patients than healthy controls and higher Al levels in breast cyst fluid than serum or milk (Darbre *et al.*, 2011). The Al contents of nipple aspirates of breast cancer patients correlated with biomarkers of oxidative stress and inflammation in the breast microenvironment (Mannello *et al.*, 2013). The Al accumulating in the breast tissue may influence the biological characteristics of breast epithelial cells and carcinogenesis is considered a probable outcome (Pineau *et al.*, 2014). The content of Al in breast tissues from mastectomies are being efficiently and accurately estimated in order to properly assess the involvement of Al in the aetiology of breast cancer (House *et al.*, 2013). Current evidence suggests that Al can induce DNA damage in human breast epithelial cells and subsequently induce proliferation of the cells (Darbre *et al.*, 2013a, b). Thus, Al may increase the risk of breast cancer by acting as a metalloestogen (Darbre, 2016). The migratory and invasive properties of oestogen-responsive MCF-7 human breast cancer cells were increased in the presence of Al (Darbre *et al.*, 2013a). Long-term Al exposure also increased the migration of oestrogen-unresponsive MDA-MB-231 human breast cancer cells in culture where their expression of matrix metalloproteinases (MMP9/14) was increased (Bakir and Darbre, 2015).

Diagnosis and treatment of aluminium intoxication

Al can be measured in the blood, bone, urine, and feces to confirm Al load and association with toxicosis. A variety of analytical methods have been used to measure Al levels in biological materials and they include accelerator mass spectroscopy, graphite furnace atomic absorption spectrometry, flame atomic absorption spectrometry, electro-thermal atomic absorption spectrometry, neutron activation analysis, inductively coupled plasma atomic emission spectrometry, inductively coupled plasma mass spectrometry, and laser microprobe mass spectrometry (Maitani *et al.*, 1994; Owen *et al.*, 1994; Van Landeghem *et al.*, 1994; Razniewska and Trzcinka-Ochocka, 2003). Contamination is a major problem encountered in the

analysis of Al by all methods except that using radioactive ^{26}Al. When using the other methods, all items used during collection, preparation, and assay should be checked for Al contribution to the procedure.

Treatment of Al intoxication is done with the chelating agent, deferoxamine, which is a colourless crystalline base, produced by the bacterium, *Streptomyces pilosus*. Structurally, it is composed of one molecule of acetic acid, two molecules of succinic acid and three molecules of 1-amino-5 hydroxylamine pentane (Keberle, 1964). Deferoxamine is mainly used as an iron-chelating agent to treat iron overload. But due to the chemical similarity between Al and iron, it can also successfully mop-up excess Al from the body (Day, 1986; Martin *et al.*, 1987). Deferoxamine administered intravenously has been shown to reduce the body Al load and to ameliorate injury to the bone and brain in patients receiving hemodialysis and peritoneal dialysis (Malluche *et al.*, 1984). It has also been used successfully to treat Al toxicity in children (Warady *et al.*, 1986; Ogborn *et al.*, 1991). Deferoxamine therapy seems beneficial for those with established Al toxicity; however, this therapy is not without hazards. It may cause allergic reactions such as pruritus, wheals and anaphylaxis. Other adverse effects include dysuria, abdominal discomfort, diarrhea, fever, leg cramps, cataract, and tachycardia (Klaassen, 1990).

Malic acid is also a potent chelator of Al used in treatment of Al intoxication (Domingo *et al.*, 1988). Treatment with malic acid has been reported to greatly increase the fecal and urinary excretion of Al and reduce the concentration of Al present in various organs and tissues (Rim, 2007; Crisponi *et al.*, 2012; Al-Qayim *et al.*, 2014). Other chelating agents such as citric, malonic, oxalic, and succinic acids have been used experimentally to reduce aluminum load in rats and mice (Domingo *et al.*, 1988).

Antioxidants and free radical scavengers such as selenium, melatonin, boric acid and vitamin C have been employed experimentally to ameliorate the deleterious effects of free radicals produced as a result of Al intoxication (Omar *et al.*, 2003; Abubakar *et al.*, 2004; Fyiad, 2007; Turkez *et al.*, 2011). Other researchers have used plant extracts of fenugreek seed, grape seed, ginger, wheat grass powder, black tea, *Allium cepa, Caesalpinia crista, Arthrophytum* (*Hammada scoparia*), *Moringa oleifera* and *Celastrus paniculatus* to ameliorate the toxicosis caused by Al exposure (Khattab *et al.*, 2010; Hasseeb *et al.*, 2011; Osman *et al.*, 2012; Belaïd-Nouira *et al.*, 2013; Sumathi *et al.*, 2013; Bitra *et al.*, 2014; Osama *et al.*, 2014; Mathiyazahan *et al.*, 2015; Singh and Goel, 2015; Taïr *et al.*, 2016; Ravi *et al.*, 2018). The neuronal death in the hippocampus of the brain associated with neurodegeneration in rats caused by Al exposure was attenuated by quercetin (Sharma *et al.*, 2016). Ginsenoside Rb1 was reported to prevent Al-induced oxidative stress and reverse the osteoblast viability and growth after impairment by Al (Zhu *et al.*, 2016a). Chlorogenic acid was effective as a chelating agent and antioxidant in protection against the toxicity of Al (Wang *et al.*, 2018; Cheng *et al.*, 2017, 2019). Chenodeoxycholic acid ameliorated the neurotoxic effect of Al by improving insulin sensitivity (Bazzari *et al.*, 2019). Türkez *et al.* (2010) reported that propolis prevented the genetic and hepatic damages induced by Al intoxication.

On the whole, the approach to the treatment of Al toxicosis after diagnosis involves strategies that include the following: prevention of Al intake, reduction of Al absorption, increasing Al excretion, maintaining functional kidneys, reducing Al load by chelation with chelating agents and amelioration of toxic effects with antioxidants and other agents that reduce toxicity (Figure 10)

General perspective and conclusion

This review has provided an overview of the pathologic basis of Al toxicosis. The association of Al intoxications with various pathologic syndromes and pathogenic mechanisms linked to toxic actions may provide avenues for strategic interventions. The study of these pathologies

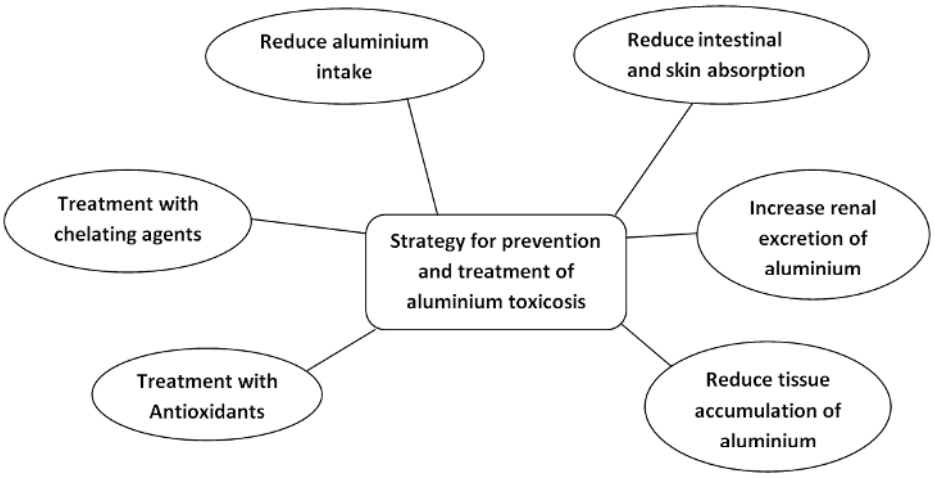

Figure 10. Prevention and treatment of aluminium toxicosis.

have received recent attention in epidemiological surveys in regard to some human diseases such as Alzheimer's disease, autism, osteoporosis, diabetes mellitus, inflammatory bowel disease and others mentioned in the review. We have reviewed the process of Al intoxication, toxic actions and systemic effects with an exploratory approach to provide the subsequent highlights of the review in this section.

After the intake of Al and its deposition in tissues, the cell is the primary target of the toxic action of Al, where the ion interacts with the plasma membrane moieties, cytoplasmic biomolecules, mitochondria and nuclear structures. The major toxic action of Al is to generate oxidative stress by producing reactive free radicals which can overwhelm the antioxidant defenses of the cell to perpetrate cellular injuries. The oxidative injuries emanate from the oxidation of proteins, lipids and nucleotides, which result in generation of altered functional biomolecules with defective operational capabilities towards cellular homeostasis. The disruption of homeostatic environments of the cell has the capacity to change the semi-permeability and receptor functions of the plasma membrane, alter the reactivity of metabolic intermediary molecules and the functions of enzymes and cofactors, and breach the energetic profile and synthetic infrastructure at transcriptional and post-transcriptional stages. In Al toxicosis, we identified the inhibition of cellular viability and function of neurons, osteoblasts, endocrine cells, lymphocytes, macrophages, erythrocytes, erythroid cells, enterocytes, myocytes, germinal cells, and pulmonary alveolar, hepatic, renal and pancreatic islet cells. Progenitor or blast cells were not able to proliferate, differentiate and function in accordance with their genetic resources. The secretory functions of specialized cells were impaired and several signaling pathways were recruited in abnormal chemico-biological settings. Cytokine expression was accelerated by oxidative cellular injuries to initiate inflammatory processes and alter immune responses that support inflammation and immunosuppression, respectively. There were Al-induced endocrine disruptions and altered sensitivities to hormones such as insulin, parathyroid hormone and hormonal vitamin D.

In Al toxicosis, the cellular structures were damaged by molecular mechanisms which cause degenerative changes (from lipid and amyloid depositions), cell death by apoptosis or necrosis, and dysplasia from genetically driven cell growth abnormalities. Cellular degeneration occurred in nervous tissue, liver and kidney. Apoptosis was associated with damage to immune cells, erythroid cells, erythrocytes, osteoblasts and germinal cells. Necrosis was encountered in pancreatic islet, liver, kidney, neurons and muscles. Dysplasia from chromosomal aberrations was associated with developmental defects, teratogenesis and growth abnormalities in fetuses and mammary epithelial cells. Mutagenesis, cell proliferation and impaired mitosis in Al toxicosis are gray areas requiring clarification because of the observed antithesis.

The systemic effects caused by Al toxicosis are diverse and multifaceted, but co-morbidities from multisystemic toxicosis are rarely reported in epidemiological cohorts. The convergence of toxic actions to engage multiple organ systems in an individual is often an observation in experimental animal models and lacks validity in observational studies in human or animal populations. The possible action of Al in the pathogenesis of diabetes mellitus and the concurrence of neurological disorders associated with Alzheimer's disease and other dementias (Arnold *et al.*, 2018) point to the common cellular basis of the pathogenesis of both metabolic and cognitive disorders, which can arise from toxic actions of Al. Longitudinal studies in the future may reveal co-morbidities and multisystemic toxicosis in Al-loaded individuals in locations where there is high risk of Al exposure.

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. Chenodeoxycholic acid improved insulin sensitivity to ameliorate the neurotoxic effect of Al (Bazzari *et al.*, 2019). As new researches on the cellular mechanisms in the toxicosis continue to be further elucidated through in vitro and in vivo studies of the metallic toxicant, new therapies against the toxicosis should also focus on alleviating the known aberrations in signaling pathways, synthetic and secretory functions, cellular energetics and membrane integrity.

REFERENCES

Abd-Elhady RM, Elsheikh AM, Khalifa AE. (2013). Anti-amnestic properties of *Ginkgo biloba* extract on impaired memory function induced by aluminum in rats. *Int J Dev Neurosci* **31**(7): 398–607.

Abdel-Wahab WM. (2012). $AlCl_3$-induced toxicity and oxidative stress in liver of male rats: protection by melatonin. *Life Sci J* **9**: 1173–1182.

Abder-Rahman H. (1999). Effect of aluminum phosphide on blood glucose level. *Vet Hum Toxicol* **41**: 31–32.

Abedini M, Fatehi F, Tabrizi N. (2014). Ischemic stroke as a rare manifestation of aluminium phosphide poisoning: a case report. *Acta Med Iran* **52**(12): 947–949.

Abraham TM, Fox CS. (2013). Implications of rising prediabetes prevalence. *Diabetes Care* **36**(**8**): 2139–2141.

Abubakar MG, Taylor A, Ferns GA. (2004). The effects of aluminium and selenium supplementation on brain and liver antioxidant status in the rat. Afr J Biotechnol **3**: 88–93.

Adzersen KH, Becker N, Steindorf K,Frentzel-Beyme R. (2003). Cancer mortality in a cohort of male German iron foundry workers. *Am J Ind Med* **43**: 295–305.

Afridi HI, Kazi TG, Kazi N, Baig JA, Jamali MK, Arain MB, Sarfraz RA, Sheikh HU, Kandhro GA, Shah AQ. (2009). Status of essential trace metals in biological samples of diabetic mother and their neonates. *Arch Gynecol Obstet* **280**: 415–423.

Afridi HI, Talpur FN, Kazi TG, Brabazon D. (2015). Effect of trace and toxic elements of different brands of cigarettes on the essential elemental status of Irish referent and diabetic mellitus consumers. *Trace Elem Res* **167**(2): 209–224.

Aguilar MV, Saavedra P, Arrieta FJ, Mateos CJ, Gonzalez MJ, Meseguer I, Martinez-Para MC. (2007). Plasma mineral content in type-2 diabetic patients and their association with the metabolic syndrome. *Ann Nutr Metab* **51**: 402–406.

Ahmad W. (2013). Overlapped metabolic and therapeutic links between Alzheimer's disease and diabetes. *Mol Neurobiol* **47**(1): 399–424.

Ahn HW, Fulton B, Moxon D, Jeffery EH. (1995). Interactive effects of fluoride and aluminum uptake and accumulation in bones of rabbits administered both agents in their drinking water. *J Toxicol Environ Health* **44**: 337–350.

Akhlaghi F, Bagheri SM, Rajabi O. (2012). A comparative study of relationship between micronutrients and gestational diabetes. *ISRN Obstet Gynecol* **2012**, Article ID 470419, 4 pages, http: //dx.doi.org/10.5402/2012/470419.

Akinola OB, Biliaminu SA, Adedeji OG, Oluwaseun BS, Olawoyin OM, Adelabu TA. (2016). Combined effects of chronic hyperglycaemia and oral aluminium intoxication on testicular tissue and some male reproductive paameters in Wistar rats. *Andrologia* **48**(7): 779–786.

Al-Qayim MAJ, Ghali LS, Al-Azwai TS. (2014). Comparative effects of propolis and malic acid on hematological parameters of aluminum exposed male rats. *Global J Bio-Sci Biotechnol* **3**: 6–11.

Alfrey AC. (1980). Aluminum metabolism in uremia. *Neurotoxicology* **1**: 43–53.

Alfrey AC. (1993). Aluminum toxicity in patients with chronic renal failure. *Ther Drug Monit* **15**(6): 593–597.

Alfrey AC, Solomons C. (1976). Bone pyrophosphate in uremia and its association with extraosseous calcification. *J Clin Invest* **57**: 700–705.

Alter P, Grimm W, Maisch B. (2001). Lethal heart failure caused by aluminium phosphide poisoning. *Intensive Care Med* **27**: 327–331.

Anane R, Creppy EE. (2001). Lipid peroxidation as pathway of aluminium cytotoxicity in human skin fibroblast cultures: prevention by superoxide dismutase+catalase and vitamins E and C. *Hum Exp Toxicol* **20**: 477–481.

Andreoli SP. (1990). Aluminum levels in children with chronic renal failure who consume low phosphorus infant formula. *J Pediatr* **116**: 282–285.

Anon (1982). *Drinking Water and Health*. National Research Council, National Academy Press, Washington, DC **4**: 155–201.

Anon (2008a). *Aluminum and compounds.* Hazardous Substances Data Bank. Bethesda, MD: National Library of Medicine. http: //toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB Accessed 9 January 2016.

Anon (2008b). Safety of aluminium from dietary intake. *EFSA J* **754**: 1–34.

Anon (2008c). *Toxicological profile for aluminum.* Atlanta, GA, United States Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. http: //www.atsdr.cdc.gov/toxprofiles/tp22.pdf Accessed 27 January 2016.

Anon (2011). On the evaluation of a new study to the bioavailability of aluminium in food. *EFSA J* **9**: 1–16.

Arain MS, Afridi HI, Kazi TG, Talpur FN, Arain MB, Kazi A, Arain SA, Ali J. (2015). Correlation of aluminum and manganese concentrations in scalp hair samples of patients having neurological disorders. *Environ Monit Assess* **187**(2): 10.

Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang H, Ahima RS, Craft S, Gandy S, Buettner C, Stoeckel LE, Holtzman DM, Nathan DM. (2018). Brain insulin resistance in type 2 diabetes and Alzheimer's disease: concept and conumdrums. *Nature Rev Neurol* **14**(3): 168–181.

Bacon R, Tavill A, Brittenham G, Park C, Recknagel R. (1983). Hepatic lipid peroxidation in vivo in rats with chronic iron overload. *J Clin Invest* **71**: 429–439.

Bai C, Wang F, Zhao H, Li Y. (2012). Effects of subchronic aluminum exposure on liver function in rats. *J Northeast Agric Univ* **19**(2): 62–65.

Bakir A, Darbre PD. (2015). Effect of aluminium on migration of oestrogen unresponsive MDA-MB-231 human breast cancer cells in culture. *J Inorg Biochem* **152**: 180–185.

Bank WA, Kastin AJ, Maness LM, Huang W, Jaspan JB. (1995). Permeability of the blood-brain barrier by amylin. *Life Sci* **57**(22): 1993–2001.

Bataineh H, Al-Hamood MH, Elbetieha AM. (1998). Assessment of aggressive, sexual behavior and fertility in adult rat following long term ingestion of four industrial metals salts. *Hum Exp Toxicol* **17**: 570–579.

Bazzari F, Abdallah DM, El-Abhar HS. (2019). Chenodeoxycholic acid ameliorates $AlCl_3$-induced Alzheimer's disease neurotoxicity and cognitive deterioration via enhanced insulin signaling in rats. *Molecules* **24**(10): 1992.

Bazzoni GB, Bollini AN, Hernández GN, Contini MC, Rasia ML (2005). *In vivo* effect of aluminium upon the physical properties of the erythrocyte membrane. *J Inorg Biochem* **99**(3): 822–827.

Becaria A, Campbell A, Bondy SC. (2002). Aluminum as a toxicant. *Toxicol Ind Health* **10**(7): 309–320.

Belaïd-Nouira Y, Bakhta H, Haouas Z, Flehi-Slim I, Cheikh HB. (2013). Fenugreek seeds reduce aluminum toxicity associated with renal failure in rats. *Nutr Res Pract* **7**: 466–474.

Biego GH, Joyeux M, Hartemann P, Debry G. (1998). Daily intake of essential minerals and metallic micropollutants from foods in France. *Sci Total Environ* **217**: 27–36.

Bilkei-Gorzó A. (1993). Neurotoxic effect of enteral aluminum. *Food Chem Toxicol* **31**: 357–361.

Bitra VR, Rapaka D, Mathala N, Akula A. (2014). Effect of wheat grass powder on aluminum induced Alzheimer's disease in Wister rats. *Asian Pac J Trop Med* **7**(S1): S278–S281.

Blaylock RL. (2012). Aluminium induced immunoexcitotoxicity in neurodevelopmental and neurodegenerative disorders. *Current Inorg Chem* **2**: 1–8.

Bogdanović M, Janeva AB, Bulat P. (2008). Histopathological changes in rat liver after a single high dose of aluminium. *Arch Ind Hyg Toxicol* **59**: 97–101.

Bondy SC. (2016). Low levels of aluminum can lead to behavioral and morphological changes associated with Alzheimer's disease and age-related neurodegeneration. N*eurotoxicology* **52**: 222–229.

Bondy SC, Truong A. (1999). Potentiation of beta-folding of β-amyloid peptide 25-35 by aluminum salts. *Neurosci Lett* **267**(1): 25–28.

Boran AM, Al-Khatib AJ, Alanazi BS, Massadeh AM (2013). Investigation of aluminum toxicity among workers in aluminum industry sector. *Eur Scient J* **9**: 440–451.

Boyce BF, Mocan MZ, Junor BJR. (1986). Toxic effect of aluminium and other substances on bone turnover. *Nefrologia* **6**: 103–108.

Brown S, Savory J, Wills MR. (1987). Absorption of aluminum from citrate or chloride in everted rat gut sac. *Clin Chem* **33**: 933–934.

Browne BA, McColl JG, Driscoll CT. (1990). Aluminum speciation using morin: I. morin and its complexes with aluminum. *J Environ Qual* **19**: 65–82.

Buraimoh AA, Ojo SA. (2012). Effects of aluminium chloride exposure on the histology of the small intestine of wistar rats. *Int J Appl Sci Technol* **2**(10): 123–132.

Buraimoh AA, Ojo SA. (2013). Effects of aluminium chloride exposure on the histology of lungs of wistar rats. *J Appl Pharm Sci* **3**: 108–112.

Burge PS, Scott JA, McCoach J. (2000). Occupational asthma caused by aluminum. *Allergy* **55**(8): 77–780.

Burgoin BP. (1992). Alumino-silicate content in calcium supplements derived from various carbonate deposits. *Bull Environ Contam Toxicol* **48**: 803–808.

Bushinsky DA, Sprague SM, Hallegot P, Girod C, Chabala JM, Levi-Setti R. (1995). Effect of aluminum on bone surface ion composition. *J Bone Miner Res* **10**: 1988–1997.

Cao Z, Fu Y, Sun X, Zhang Q, Xu F, Li Y. (2016). Aluminum inhibits osteoblastic differentiation through inactivation of Wnt/β-catenin signaling pathway in rat osteoblasts. *Environ Toxicol Pharmacol* **42**: 198–204.

Campbell A, Bondy SC. (2000). Aluminum induced oxidative events and its relation to inflammation: a role for the metal in Alzheimer's disease. *Cell Mol Biol* **46**(4): 721–730.

Campbell A, Prasad KN, Bondy SC. (1999). Aluminum-induced oxidative events in cell lines: glioma are more responsive than neuroblastoma. *Free Rad Biol Med* **26**: 1166–1671.

Campbell PGC, Hansen HJ, Dubreuil B, Nelson WO. (1992). Geochemistry of Quebec north shore salmon rivers during snowmelt: Organic acid pulse and aluminum mobilization. *Can J Fish Aquat Sci* **49**: 1938–1952.

Cannata JB, Briggs JD, Junor BJ, Fell GS, Beastall G. (1983). Effect of acute aluminium overload on calcium and parathyroid-hormone metabolism. *Lancet* **1**(8323): 501–503.

Capdevielle MC, Scanes CG. (1995). Effect of dietary acid or aluminum on growth and growth-related hormones in mallard ducklings (Anas platyrhynchos). *Arch Environ Contam Toxicol* **29**(4): 462–468.

Cech I, Montera J. (2000). Spatial variations in total aluminum concentrations in drinking water supplies studied by geographic information system (GIS) methods. *Water Res* **34**: 2703–2712.

Chafe R, Aslanov R, Sarkar A, Gregory P, Comeau A, Newhook LA. (2018). Association of type 1 diabetes and concentrations of drinking water components in Newfoundland and Labrador, Canada. *BMJ Open Diabetes Res Care* 6(1): e000466.

Chappard D, Bizot P, Mabilleau G, Hubert L. (2016). Aluminum and bone: review of new clinical circumstances associated with Al(3+) deposition in the calcified matrix of bone. *Morphologie* **100**(329): 95–105.

Chen BB, Zeng Y, Hu B. (2010). Study on speciation of aluminum in human serum using zwitterionic bile acid derivative dynamically coated C18 column HPLC separation with UV and on-line ICP-MS detection. *Talanta* **81**: 180–186.

Chen WJ, Monnat RJ Jr, Chen M, Mottet NK. (1978). Aluminum induced pulmonary granulomatosis. *Hum Pathol* **9**(6): 705–711.

Chen YW, Yang CY, Huang CF, Hung DZ, Leung YM, Liu SH. (2009). Heavy metals, islet function and diabetes development. *Islets* **1**: 169–176.

Chen Z, Zhong C. (2014). Oxidative stress in Alzheimer's disease. *Neurosci Bull* **30**(2): 271–281.

Cheng D, Tang J, Wang X, Zhang X, Wang S. (2018). Effect of aluminum (Al) speciation on erythrocytic antioxidant defense process: Correlations between lipid membrane peroxidation and morphological characteristics. *Ecotoxicol Environ Saf* **157**: 201–206.

Cheng D, Zhang X, Tang J, Kong Y, Wang X, Wang S. (2019). Chlorogenic acid protects against aluminum toxicity via MAPK/Akt signaling pathway in murine RAW264.7 macrophages. *J Inorg Biochem* **190**: 113–120.

Cheng D, Zhang X, Xu L, Li X, Hou L, Wang C. (2017). Protective and prophylactic effects of chlorogenic acid on aluminum-induced acute hepatotoxicity in mice. *Chem Biol Interact* **273**: 125–132.

Chines A, Pacifici R. (1990). Antacid and sucralfate-induced hypophosphatemic osteomalacia: A case report and review of the literature. *Calcif Tissue Int* **47**: 291–295.

Chinoy NJ, Patel TN. (2001). Effect of sodium fluoride and aluminium chloride on ovary and uterus of mice and their reversal by some antidotes. *Fluoride* **34**(1): 9–20.

Chmielnicka J, Nasiadek M, Pinkowski R, Paradowski M. (1994). Disturbances of morphological parameters in blood of rats orally exposed to aluminum chloride. *Biol Trace Elem Res* **42**: 191–199.

Chopra JS, Kalra OP, Malik VS, Sharma R, Chandna A. (1986). Aluminum phosphide poisoning: A prospective study of 16 cases in one year. *Postgrad Med J* **62**: 1113–1115.

Christie H, MacKay RJ, Fisher AM. (1963). Pulmonary effects of inhalation of aluminum by rats and hamsters. *AIHA J (Fairfax, Va)* **24**: 47–56.

Codling EE, Chaney RL,Mulchi CL. (2002). Biomass yield and phosphorus availability to wheat grown on high phosphorus soils amended with phosphate inactivating residues. I. Drinking water treatment residue. *Commun Soil Sci Plant Anal* **33**: 1039–1061.

Colomina MT, Peris-Sampedro F. (2017). Aluminum and Alzheimer's disease. *Adv Neurobiol* **18**: 183–197.

Colomina MT, Roig JL, Sanchez DJ, Domingo JL. (2002). Influence of age on aluminum-induced neurobehavioral effects and morphological changes in rat brain. *Neurotoxicology* **23**: 775–781.

Contini MC, Ferri A, Bernal CA, Carnovale CE. (2007). Study of iron homeostasis following partial hepatectomy in rats with chronic aluminum intoxication. *Biol Trace Elem Res* **115**: 31–45.

Cournot-Witmer G, Plachot JJ. (1990). Parathyroid glands in chronic aluminum intoxication. *Ultrastruct Pathol* **14**(3): 211–219.

Cox KA, Dunn MA. (2001). Aluminum toxicity alters the regulation of calbindin-D28k protein and mRNA expression in chick intestine. *J Nutr* **131**(7): 2007–2013.

Crisponi G, Nurchi VM, Bertolasi V, Remelli M, Faa G. (2012). Chelating agents for human diseases related to aluminium overload. *Coord Chem Rev* **256**: 89–104.

Cronan CS, Schofield CL. (1979). Aluminum leeching response to acid precipitation: Effect on high-elevation watersheds in the northeast. *Science* **204**: 304–306.

Darbre PD. (2016). Aluminium and the human breast. *Morphologie* **100**(329): 65–74.

Darbre PD, Bakir A, Iskakova E. (2013a). Effect of aluminium on migratory and invasive properties of MCF-7 human breast cancer cells in culture. *J Inorg Biochem* **128**: 245–249.

Darbre PD, Mannello F, Exley C. (2013b). Aluminium and breast cancer: sources of exposure, tissue measurmenets and mechanisms of toxicological actions of breast of breast biology. *J Inorg Biochem* **128**: 257–261.

Darbre PD, Pugazhendhi D, Mannello F. (2011). Aluminium and Human breast diseases. *J Inorg Biochem* **105**(11): 1484–1488.

Dasappa H, Fathima FN, Prabhkar R, Sarin S. (2015). Prevalence of diabetes and prediabetes and assessment of risk factors in urban slums of Bangalore. *J Family Med Prim Care* **4**(3): 399–404.

Day JP. (1986). Chemical aspects of aluminum chelation by desferrioxamine, in *Aluminum and other trace elements in renal disease* (Taylor A ed) pp. 184–192, Baillere-Tindall, London.

Day JP, Barker J, Evans LJA, Perks J, Seabright PJ, Ackrill P, Lilley JS, Drumm PV, Newton GWA. (1991). Aluminum absorption studied by ^{26}Al tracer. *Lancet* **337**: 1345.

de Chambrun GP, Body-Malapel M, Frey-Wagner I, Djouina M, Deknuydt F, Atrott K, Esquerre N, Altare F, Neut C, Arrieta MC, Kanneganti T-D, Rogler G, Colombel JF, Cortot A, Desreumaux P, Vignal C. (2014). Aluminum enhances inflammation and decreases mucosal healing in experimental colitis in mice. *Mucosal Immunol* **7**(3): 589–601.

de la Monte SM, Wand JR. (2008). Alzheimer's disease is type 3 diabetes- Evidence reviewed. *J Diabetes Sci Technol* **2**(6): 1101–1113.

Delhaize E, Ryan RP. (1995). Aluminum toxicity and tolerance in plants. *Plant Physiol* **107**: 315–321.

Deugnier JL. (2003). Iron and liver cancer. *Alcohol* **30**: 145–150.

DeVoto E, Yokel RA. (1994). The biological speciation and toxicokinetics of aluminum. *Environ Health Perspect* **102**: 940–951.

de Vuyst P, Dumortier P, Schandené L, Estenne M, Verhest A, Yernault JC. (1987). Sarcoid-like lung granulomatosis induced by aluminum dusts. *Am Rev Respir Dis* **135**(2): 493–497.

Díaz-Corte C, Fernández-Martín JL, Barreto S, Gómez C, Fernández-Coto T, Braga S, Cannata JB. (2001). Effect of aluminium load on parathyroid hormone synthesis. *Nephrol Dial Transplant* **16**(4): 742–745.

Dixon RL, Sherins RJ, Lee IP. (1979). Assessment of environmental factors affecting male fertility. *Environ Health Perspect* **30**: 53–68.

Dokken BB, Saengsirisuwan V, Kim JS, Teachey MK, Henriksen EJ. (2008). Oxidative stress-induced insulin resistance in rat skeletal muscle: role of glycogen synthase kinase-3. American Jounal of Physiology. *Endocrinol Metab* **294**(3): E615–621.

Domingo JL. (1995). Reproductive and developmental toxicity of aluminum: a review. *Neurotoxicology* **17**(4): 515–521.

Domingo JL, Gomez M, Liobet JM, Corbella J. (1988). Comparative effects of several chelating agents on the toxicity, distribution, and excretion of aluminum. *Hum Toxicol* **7**: 259–262.

Domingo JL, Llobet JM, Gomez M, Tomas JM, Corbella J. (1987). Nutritional and toxicological effects of short-term ingestion of aluminum by the rat. *Res Commun Chem Pathol Pharmacol* **56**: 409–419.

D'Souza SP, Vijayalaxmi KK, Prashantha N. (2014). Assessment of genotoxicity of aluminium acetate in bone marrow, male germ cells and fetal cells of Swiss albino mice. *Mutat Res Genet Toxicol Environ Mutagen* **766**: 16–22.

Drüeke T, Touam M, Lacour B. (1986). Aluminum-induced microcytic anemia in experimental chronic renal failure. *Nefrologia* **6**: 67–69.

Dunn MA, Ishizakie AS, Liew MYB, Too SL, Johnson N. (1995). Dietary aluminum chloride inhibits the ability of vitamin D to regulate intestinal calbindin-D28k levels in chicks. *J Trace Elem Exp Med* **8**: 47–57.

Edwardson JA, Moore PB, Ferrier IN, Lilley JS, Newton GWA, Barker J, Templar J, Day JP. (1993). Effect of silicon on gastrointestinal absorption of aluminium. *Lancet* **342**: 211–212.

Eisenreich SJ. (1980). Atmospheric input of trace metals to Lake Michigan (USA). *Water Air Soil Pollut* **13**: 287–301.

El Mazoudy RH, Bekhet GA. (2016). In ovo toxico-teratological effects of aluminum on embryonic chick heart and vascularization. *Environ Sci Pollut Res Int* **23**(21): 21947–21956.

Exley C. (2004). The proxidant activity of aluminium. *Free Rad Biol Med* **36**(3): 380–387.

Exley C. (2006). Aluminium and iron, but neither copper nor zinc, are key to the precipitation of beta-sheets of A beta (42) in senile plaque cores in Alzheimer's disease. *J Alzheimers Dis* 10: 173–177.

Exley C. (2013). Human exposure to aluminium. *Environ Sci Process Impacts* **15**: 1807–1816.

Exley C. (2016). The toxicity of aluminium in humans. *Morphologie* **100**(329): 51–55.

Exley C, Begum A, Woolley MP, Bloor RN. (2006). Aluminum in tobacco and cannabis and smoking-related disease. *Am J Med* **119**(3): 276.e9–11.

Exley C, Birchall JD. (1992). The cellular toxicity of aliminium. *J Theor Biol* **159**(1): 83–98.

Exley C, Birchall JD, Price N. (1994). Luminum inhibition of hexokinase activity in vitro: A study in biological availability. *J Inorg Biochem* **54**(4): 297–304.

Exley C, House E. (2011). Aluminium in the human brain. *Monatshefte fur Chemie* 142: 357–363.

Exley C, Price NC, Kelly SM, Birchall JD. (1993). An interaction of β-amyloid with aluminium in vitro. *FEBS Lett* **324**(3): 293–295.

Exley C, Siesjo P, Eriksson H. (2010). The immunobiology of aluminium adjuvants: how do they really work? *Trends Immunol* **31**: 103–109.

Exley C, Swarbrick L, Gherardi RK, Authier FJ. (2009). A role for the body burden of aluminium in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome. *Med Hypotheses* **72**(2): 135–139.

Fanti P, Kindy MS, Mohapatra S, Klein J, Columbo G, Malluche HH. (1992). Dose-dependent effects of aluminum on osteocalcin synthesis in osteoblast like ROS 17/2 cells in culture. *Am J Physiol* **263**: E1113–E1118.

Farina M, Rotta LN, Soares FA, Jardim F, Jacques R, Souza DO, Rocha JB. (2005). Hematological changes in rats chronically exposed to oral aluminum. *Toxicology* **209**: 29–37.

Fernández MS. (2014). Human IAPP amyloidogenic properties and pancreatic β-cell death. *Cell Calcium* **56**(5): 416–427.

Feinroth M, Feinroth MV, Berlyne GM. (1984). Aluminum absorption in the rat everted gut sac. *Miner Electrolyte Metab* **8**: 29–35.

Feng W, Cui X, Liu B, Liu C, Xiao Y, Lu W, Guo H, He M, Zhang X, Yuan J, Chen W,Wu T. (2015). Association of urinary metal profiles with altered glucose levels and diabetes risk: a population-based study in China. *PLoS One* **10**: 1–11.

Filipek LH, Nordstrom DK, Ficklin WH. (1987). Interaction of acid mine drainage with waters and sediments of West Squaw Creek in the West Shasta mining district, California. *Environ Sci Technol* **21**: 388–396.

Flaten TP. (2001). Aluminium as a risk factor in Alzheimer's disease, with emphasis on drinking water. *Brain Res Bull* **55**(2): 187–196.

Flaten TP. (2002). Aluminium in tea-concentrations, speciation and bioavailability. *Coord Chem Rev* **228**: 385–395.

Florence AL, Gauthier A, Ponsar C, Van den Bosch de Aguilar P, Crichton RR. (1994). An experimental animal model of aluminum overload. *Neurodegeneration* **3**: 315–323.

Flores CR, Puga MP, Wrobel K, Sevilla MEG, Wrobel K. (2011). Trace elements status in diabetes mellitus type 2: Possible role of the interaction between molybdenum and copper in the progress of typical complications. *Diabetes Res Clin Pract* **91**: 333–341.

Fogarty U, Perl D, Good P, Ensley S, Seawright A, Noonan J. (1998). A cluster of equine granulomatous enteritis cases: the link with aluminium. *Vet Hum Toxicol* **40**(5): 297–305.

Fu Y, Jia FB, Wang J, Song M, Liu SM, Li YF, Liu SZ, Bu QW. (2014). Effects of sub-chronic aluminum chloride exposure on rat ovaries. *Life Sci* **100**(1): 61–66.

Fyiad AA. (2007). Aluminium toxicity and oxidative damage reduction by melatonin in rats. *J Appl Sci Res* **3**: 1210–1217.

Ganrot PO. (1986). Metabolism and possible health effects of aluminum. *Environ Health Perspect* **65**: 363–441.

Garbossa G, Galvez G, Castro ME, Nesse A. (1998). Oral aluminum administration to rats with normal renal function. 1. Impairment of erythropoiesis. *Hum Exp Toxicol* **17**: 312–317.

Garbossa G, Gutnisky A, Nesse A. (1996). Depressed erythroid progenitor cell activity in aluminum overloaded mice. *Miner Electrolyte Metab* **22**: 214–218.

Garruto RM, Shankar SK, Yanagihara R, Salazar AM, Amyx HL, Gajdusek DC. (1989). Low-calcium, high-aluminum diet-induced motor neuron pathology in cynomolgus monkeys. *Acta Neuropathol* **78**: 210–219.

Gensemer RW, Playle RC. (1999). The bioavailability and toxicity of aluminum in aquatic environments. *Crit Rev Environ Sci Technol* **29**(4): 315–450.

Gherardi RK, Aouizerate J, Cadusseau J, Yara S, Authier FJ. (2016). Aluminum adjuvants of vaccines injected in muscle: Normal fate, pathology and associated disease. *Morphologie* **100**(329): 85–94.

Gherardi RK, Authier FJ. (2012). Macrophagic myofaciitis: characterization and pathophysiology. *Lupus* **21**(2): 184–189.

Glanz JM, Newcomer SR, Daley MF, McClure DL, Baxter RP, Jackson ML, Naleway AL, Lugg MM, DeStefano F. (2015). Cummulative and episodic vaccine aluminum exposure in a population based cohort of young children. *Vaccine* **33**(48): 6736–6744.

Golub MS, Germann SI. (2001). Long-term consequences of developmental exposure to aluminum in a suboptimal diet for growth and behavior of Swiss Webster mice. *Neurotoxicol Teratol* **23**: 365–372.

Golub MS, Han B, Keen CL, Gershwin ME. (1992). Effects of dietary aluminum excess and manganese deficiency on neurobehavioral endpoints in adult mice. *Toxicol Appl Pharmacol* **112**: 154–160.

Gomes LS, Costa JR, Campos MS, Marques MR, Biancardi MF, Taboga SR, Ghedini PC, Santos FCA. (2019). Aluminum disrupts the prenatal development of male and female gerbil prostrate (Meriones unguiculatus). *Exp Mol Pathol* **107**: 32–42.

Gomez M, Domingo JL, Llobet JM, Tomas JM, Carbella J. (1986). Short-term oral toxicity study of aluminum in rats. *Arch Pharmacol Toxicol* **12**: 145–151.

Gonzalez MA, Alvarez ML, Pisani GB. (2007). Involvement of oxidative stress in the impairment in biliary secretory function induced by intraperitoneal administration of aluminum to rats. *Biol Trace Elem Res* **116**: 329–348.

Gonzelez-Suerez I, ÁLvarez-Hernendez D, Carrillo-Lepez N, Naves-Deaz M, Fernendez-Marten JL, Cannata-Andea JB. (2005). Aluminum posttranscriptional regulation of parathyroid hormone synthesis: A role for the calcium-sensing receptor. *Kidney Int* **68**(6): 2484–2496.

Gorsky JE, Dietz AA, Spencer H. (1979). Metabolic balance of aluminum in persons receiving aluminum antacids. *Clin Chem* **25**: 244–248.

Green BN, Johnson CD, Adams A. (2006). Writing narrative literature reviews for peer-reviewed journals: secrets of the trade. *J Chiropr Med* **5(3)**: 101–117.

Greger JL. (1992). Dietary and other sources of aluminum intake. In: Aluminum in Biology and Medicine. *Ciba Found Symp* **169**: 26–49.

Greger JL, Sutherland J. (1997). Aluminum exposure and metabolism. Critical Review. *Clin Lab Sci* 34: 439–474.

Guo C, Lu Y, Hsu GSW. (2005). The influence of aluminum exposure on male reproduction and offspring in mice. *Environ Toxicol Pharmacol* **20**: 135–141.

Haglin L, Essén-Gustavsson B, Lindholm A. (1994). Hypophosphatemia induced by dietary aluminium hydroxide in growing pigs: effects on erythrocytes, myocardium, skeletal muscle and liver. *Acta Vet Scand* **35(3)**: 263–271.

Han S, Lemire J, Appanna VP, Auger C, Castonguay Z, Appanna VD. (2013). How aluminium, an intracellular ROS generator, promotes hepatic and neurological diseases: the metabolic tale. *Cell Biol Toxicol* **29(2)**: 75–84.

Hangouche AJE, Fennich H, Alaika O, Dakka T, Raisouni Z, Oukerraj L, Doghmi N, Cherti M. (2017). Reversible myocadial injury and intraventricular thrombus associated with aluminium phosphide poisoning. *Case Rep Cardiol* **2017**, Article ID 6287015, 6 pages, https: //doi.org/10.1155/2017/6287015.

Hansen AB, Ravnskjær L, Loft S, Andersen KK, Bräuner EV, Baastrup R, Yao C, Ketzel M, Becker T, Brandt J, Hertel O, Andersen ZJ. (2016). Long-term exposure to fine particulate matter and incidence of diabetes in the Danish Nurse Cohort. *Environ Int* **91**: 243–250.

Harris WR, Messori L. (2002). A comparative study of aluminum (III), gallium (III), indium (III), and thallium (III) binding to human serum transferrin. *Coord Chem Rev* **228**: 237–262.

Hasan NA. (2009). Effects of trace elements on albumin and lipoprotein glycation in diabetic retinopathy. *Saudi Med J* **30**: 1263–1271.

Hasseeb MM, Al-Hizab AF, Hussein AY. (2011). A histopathologic study of the protective effect of grape seed extract against experimental aluminum toxicosis in male rat. *Scient J King Faisal Univ (Basic Appl Sci)* **12**: 283–297.

Hayacibara MF, Queiroz CS, Tabchoury CPM,Cury JA. (2004). Fluoride and aluminum in teas and tea-based beverages. *Rev Saude Publica* **38**: 100–105.

He P, Zou Y, Hu Z. (2015). Advances in aluminum hydroxide-based adjuvant research and its mechanism. *Hum Vaccin Immunother* **11(2)**: 477–488.

Hem SL. (2002). Elimination of aluminum adjuvants. *Vaccine* **20**: S40–43.

Hemadi M, Miquel G, Kahn PH, Chahine JME. (2003). Aluminum exchange between citrate and human serum transferrin and interaction with transferrin receptor 1. *Biochemistry* **42**: 3120–3130.

Henriksen EJ. (2010). Dysregulation of glycogen synthase kinase-3 in skeletal muscle and the etiology of insulin resistance and type 2 diabetes. *Curr Diabetes Rev* **6(5)**: 285–293.

Henshaw PF, Bewtra JK, Biswas N. (1993). Occurrence of aluminum, lead, and trihalomethanes in drinking water from the Great Lakes. *J Great Lakes Res* **19**: 521–532.

Herbert A, Sterling G, Abraham J, Corrin B. (1982). Desquamative interstitial pneumonia in an aluminum welder. *Hum Pathol* **13(8)**: 694–699.

Hernández G, Bollini A, Huarte M, Bazzoni G, Piehl L, Chiarotto M, Rubin de Celis E, Rasia M. (2008). *In vitro* effect of aluminium upon erythrocyte membrane properties. *Clin Hemorheol Microcirc* **40(3)**: 191–205.

Hewitt CD, Savory J, Wills MR. (1990). Aspects of aluminium toxicity. *Clin Lab Med* **10**: 403–422.

His E, Beiras R, Seaman MN, Pagano G, Trieff NM. (1996). Sublethal and lethal toxicity of aluminum industry effluents to early developmental stages of the Crassostrea gigas oyster. *Arch Environ Contam Toxicol* **30**: 335–339.

Hofstetter JR, Vincent I, Bugiani O, Richter JA. (1987). Aluminum-induced decreases in choline acetyltransferase, tyrosine hydroxylase and glutamate decarboxylase in selected regions of rabbit brain. *Neurochem Pathol* **6**(3): 177–193.

Hogenesch H. (2013). Mechanism of immunopotentiation and safety of aluminum adjuvants. *Frontiers Immunol* **10**: 406.

House E, Polwart A, Darbre P, Barr L, Metaxas G, Exley C. (2013). The aluminium content of breast tissue taken from women with breast cancer. *Med Biol* **27(4)**: 257–266.

Huang W, Wang P, Shen T, Hu C, Han Y, Song M, Bian Y, Li Y, Zhu Y. (2017). Aluminum trichloride inhibited osteoblastic proliferation and downregulated the Wnt/β-catenin pathway. *Biol Trace Elem Res* **177(2)**: 323–330.

Igbokwe NA. (2016). Characterization of the osmotic stability of Sahel goat erythrocytes in ionic and non-ionic hypotonic media. PhD thesis, Department of Physiology, Pharmacology and Biochemistry, Faculty of Veterinary Medicine, University of Maiduguri, Maiduguri, Nigeria.

Igbokwe NA. (2018). A review of the factors that influence erythrocyte osmotic fragility. *Sokoto J Vet Sci* **16(4)**: 1–23.

Igwenagu E. (2017). Pathologic effects of oral aluminium administration in non-diabetic and diabetic rats. MVSc dissertation, Department of Veterinary Pathology, University of Maiduguri, Maiduguri, Nigeria.

Igwenagu E, Igbokwe IO, Egbe-Nwiyi TN. (2019). Fasting hyperglycaemia, glucose intolerance and pancreatic islet necrosis in albino rats associated with subchronic oral aluminium chloride exposure. *Comp Clin Pathol* http://dx.doi.org/10.1007/s00580-019-03028-4.

Iijima Y, Bando M, Yamasawa H, Moriyama H, Takemura T, Niki T, Sugiyama Y. (2017). A case of mixed dust pneumoconiosis with desquamative interstitial-like reaction in an aluminum welder. *Respir Med Case Rep* **20**: 150–153.

Issa AM, Salim MS, Zidan H, Mohamed AF, Farrag AH. (2014). Evaluation of the effects of aluminum phosphate and calcium phosphate nanoparticles as adjuvants in vaccinated mice. *Int J Chem Eng Appl* **5**: 367–373.

Jang JH, Surh YJ. (2002). β-Amyloid induces oxidative DNA damage and cell death through activation of c-Jun N terminal kinase. *Ann N Y Acad Sci* **973**: 228–236.

Jangra A, Kasbe P, Pandey SN, Dwivedi S, Gurjar SS, Kwatra M, Mishra M, Venu AK, Sulakhiya K, Gogoi R, Sarma N, Bezbaruah BK, Lahkar M. (2015). Hesperidin and silibinin ameliorate aluminum-induced neurotoxicity: modulation of antioxidants and inflammatory cytokines level in mice hippocampus. *Biol Trace Elem Res* **168**: 462–471.

Järup L. (2003). Hazards of heavy metal contamination. *British Med Bull* **68**: 167–82.

Jederlinic PJ, Abraham JL, Churg A, Himmelstein JS, Epler GR, Gaensler EA. (1990). Pulmonary fibrosis in aluminum oxide workers. Investigation of nine workers with pathologic examination and microanalysis in three of them. *Am Rev Respir Dis* **142(5)**: 1179–1184.

Jeffery EH, Abreo K, Burgess E, Cannata J, Greger JL. (1996). Systemic aluminum toxicity: effect on bone haematopoietic tissue and kidney. *J Toxicol Environ Health* **46(6)**: 649–665.

Jones KC, Bennet BG. (1986). Exposure of man to environmental aluminium-an exposure commitment assessment. *Sci Total Environ* **52**: 65–82.

Jones K, Linhart C, Haekin C, Exley C. (2017). Urinary excretion of aluminium and silicon in secondary progressive multiple sclerosis. *EBioMedicine* **26**: 60–67.

Johnson VJ, Sharma RP. (2003). Aluminum disrupts the pro-inflammatory cytokine/neurotrophin balance in primary brain rotation-mediated aggregate cultures: possible role in neurodegeneration. *Neurotoxicology* **24(2)**: 261–268.

Jouhanneau P, Raisbeck GM, Yiou F, Lacour B, Banide H, Drueke TB. (1997). Gastrointestinal absorption, tissue retention, and urinary excretion of dietary aluminum determined by using ^{26}Al. *Clin Chem* **43**: 1023–1028.

Julka D, Gill KD. (1996). Altered calcium homeostasis: a possible mechanism of aluminium-induced neurotoxicity. *Biochem Biophys Acta* **1315**: 47–54.

Kaiser L,Schwartz KA, Burnatowska-Hledin MA. (1984). Microcytic anemia secondary to intraperitoneal aluminum in normal and uremic rats. *Kidney Int* **26**: 269–274.

Kamalov J, Carpenter DO, Birman I. (2011). Cytotoxicity of environmentally relevant concentrations of aluminum in murine thymocytes and lymphocytes. *J Toxicol* **2011**: 796719.

Kamanyire R, Murray V. (2003). Occupational exposures to fumigants. *J Toxicol Clin Toxicol* **41**: 489–490.

Kandimalla R, Thirumala V, Reddy PH. (2017). Is Alzheimer's disease a type 3 diabetes? A critical appraisal. *Biochim Biophys- Mol Basis Dis* **1863**(5): 1078–1089.

Kandimalla R, Vallamkondu J, Corgiat EB, Gill KD. (2016). Understanding aspects of aluminum exposure in Alzheimer's disease development. *Brain Pathol* **26**(2): 139–154.

Katz AC, Frank DW, Sauerhoff MW, Zwicker GM, Freudenthal RI. (1984). A 6-month dietary toxicity study of acidic sodium aluminum phosphate in beagle dogs. *Food Chem Toxicol* **22**: 7–9.

Kawahara M, Kato-Negishi M. (2011). Link between aluminum and the pathogenesis of Alzheimer's disease: The integration of the aluminum and amyloid cascade hypothesis. *Int J Alzheimer's Dis* **2011**: 276393.

Kawahara M, Konoha K, Nagata T, Sadakane Y. (2007). Aluminum and human health: its intake, bioavailability and neurotoxicity. *Biomed Res Trace Elem* **18**: 211–220.

Kazi TG, Afridi HI, Kazi N, Jamali MK, Arain MB, Jalbani N, Kandhro GA. (2008). Copper, chromium, manganese, iron, nickel and zinc levels in biological samples of diabetes mellitus patients. *Biol Trace Elem Res* **122**: 1–18.

Kazi TG, Jalbani N, Arain MB, Jamali MK, Afridi HI, Shah AQ. (2009). Determination of toxic elements in different brands of cigarette by atomic absorption spectrometry using ultrasonic assisted acid digestion. *Environ Monit Assess* **154**(1–4): 155–167.

Keberle H. (1964). The biochemistry of DFO and its relation to iron metabolism. *Ann N Y Acad Sci* 1**19**: 758–776.

Keith LS, Jones DE, Chou CH. (2002). Aluminum toxicokinetics regarding infant diet and vaccinations. *Vaccine* **20**: 13–17.

Kell BD. (2009). Iron behaving badly: inappropriate iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases. *BMC Med Genomics* **2**: 1–79.

Khalaf AA, Morgan AM, Mekawy MM, Ali MF. (2007). Developmental toxicity evaluation of oral aluminum in rats. *J Egypt Soc Toxicol* **37**: 11–26.

Khattab HAH, Abdallah IZA, Kamel GM. (2010). Grape seed extract alleviate reproductive toxicity caused by aluminium chloride in male rats. *J American Sci* **6**: 1200–1209.

Khosla SN, Nand N, Khosla P. (1988). Aluminum phosphide poisoning. *J Trop Med Hyg* **91**: 196–198.

Kihira T, Yoshida S, Yase Y, Ono S, Kondo T. (2002). Chronic low- Ca/Mg high–Al diet induces neuronal loss. *Neuropathology* **22**: 171–179.

King SW, Savory J, Wills MR, Gitelman HJ. (1981). The clinical biochemistry of aluminum. *Crit Rev Clin Lab Sci* **14**: 1–20.

Klaassen CD. (1990). Heavy metals and heavy-metal antagonists, in *Goodman and Gilman's: The Pharmacological Basis of Therapeutics* (Gilma AG, Rall TW, Nies AS, Taylor P eds), pp 1592–1614, Pergamon Press, New York.

Klein GL. (2019). Aluminum toxicity to bone: A multisystem effect. *Osteoporos Sarcopenia* **5**(1): 2–5.

Klein JP, Mold M, Mery L, Cottier M, Exley C. (2014). Aluminum content of human semen: implications for semen quality. *Reprod Toxicol* **50**: 43–48.

Koltz K, Weistenhöfer W, Neff F, Hartwig A, van Thriel C, Drexler H. (2017). The health effects of aluminum exposure. *Dtsch Arztebl Int* **114**(39): 653–659.

Konda VR, Eerike M, Chary RP, Arunachalam R, Yeddula VR, Meti V, Devi TS. (2017). Effect of aluminum chloride on blood glucose level and lipid profile in normal, diabetic and treated diabetic rats. *Indian J Pharmacol* **49**: 357–365.

Kongerud J, Søyseth V. (2014). Respiratory disorders in aluminum smelter workers. *J Occup Environ Med* **56**(5 suppl): S60–70.

Konishi Y, Yagyu K, Kinebuchi H, Salto N, Yamaguchi T, Ohtsuki Y. (1996). Chronic effect of aluminum ingestion on bone in calcium-deficient rats. *Basic Clin Pharmacol Toxicol* **78**: 429–434.

Kowalczyk E, Kopff A, Kędziora J, Błaszczyk J, Kopff M, Niedworok J, Fijałkowski P. (2004). Effect of long-term aluminium chloride intoxication on selected biochemical parameters and oxidative-antioxidative balance in experimental animals. *Pol J Environ Stud* **13**: 41–43.

Krewski D, Yokel RA, Nieboer E, Borchelt D, Cohen J, Harry J, Kacew S, Lindsay J, Mahfouz AM, Rondeau V. (2007). Human health risk assessment for aluminium, aluminium oxide, and aluminium hydroxide. *J Toxicol Environ Health* **10**: 251–269.

Kücük M, Kalayci RB, Cevik A, Elmas I, Kaya M. (2001). Effect of aluminum on the blood-brain barrier permeability in acute and chronically hyperglycaemic rats. *Biol Trace Elem Res* **80** (2): 181–189.

Kumar V, Gill KD. (2014). Oxidative stress and mitochondrial dysfunction in aluminium neurotoxicity and its amelioration. *Neurotoxicology* **41**: 154–166.

Lantzy RJ, MacKenzie FT. (1979). Atmospheric trace metals: global cycles and assessment of man's impact. *Geochim Cosmochim Acta* **43**: 511–525.

Lee REJ, Von Lehmden DJ. (1973). Trace metal pollution in the environment. *J Air Pollut Control Assoc* **23**: 853–857.

Lefcourt AM, Mesinger JJ. (2001). Effect of adding alum or zeolite to dairy slurry on ammonia volatilization and chemical composition. *J Dairy Sci* **84**: 1814–1821.

Lerner A. (2007). Aluminum is a potential envirnmental factor for Crohn's disease induction: extended hypothsesis. *Ann N Y Acad Sci* **1107**: 329–345.

Levine S, Saltzman A, Drakontides AB. (1992). Parenteral aluminum compounds produce a local toxic myopathy in rats: importance of the anion. *Toxicol Pathol* **20**(3–1): 405–415.

Levine SN, Sonnier GB, Abreo K. (1990). Effects of diabetes mellitus and aluminum toxicity on myocardial calcium transport. *Toxicology* **65**: 137–148.

Lewis RJ. (2001). *Hawley's Condensed Chemical Dictionary*, 14th edn, pp. 39–46, Wiley-Interscience, New Jersey, USA.

Li P, Luo W, Zhang H, Zheng X, Liu C, Ouyang H. (2016). Effects of aluminum exposure on bone stimulatory growth factors in rats. *Biol Trace Elem Res* **172**(1): 166–171.

Li X, Han Y, Guan Y, Zhang L, Bai C, Li Y. (2012). Aluminum induces osteoblast apoptosis through oxidative stress-mediated JNK signaling pathway. *Biol Trace Elem Res* **150**(1–3): 502–508.

Li Y, Liu J, Cao Z. (2015). Effect of sub-chronic aluminum exposure on renal structure in rats. *J Northeast Agric Univ* **22**(2): 47–51.

Liaquat L, Sadir S, Batool Z, Tabassum S, Shahzad S, Afzal A, Haider S. (2019). Acute aluminum chloride toxicity revisited: study on DNA damage and histopathological, biochemical and neurochemical alterations in rat brain. *Life Sci* **217**: 202–211.

Lidsky TI. (2014). Is the aluminum hypothesis dead? *J Occup Environ Med* **56**(5 suppl): S73–S79.

Lin CY, Hsiao WC, Huang CJ, Kao CF, Hsu GS. (2013). Heme oxygenase-1 induction by ROS-JNK pathway plays a role in aluminum-induced anemia. *J Inorg Chem* **128**: 221–228.

Lin JL, Yang YJ, Yang SS, Leu ML. (1997). Aluminum utensils contribute to aluminum accumulation in patients with renal disease. *Am J Kidney Dis* **30**: 653–665.

Linhart C, Talasz H, Morandi EM, Exley C, Lindner HH, Taucher S, Egle D, Hubalek M, Concin N, Ulmer H. (2017). Use of underarm cosmetic products in relation to risk of breast cancer: a case-control study. *EBioMedicine* **21**: 78–85.

Lione A. (1983). The prophylactic reduction of aluminum intake. *Food Chem Toxicol* **21**: 103–109.

Lione A. (1985). Aluminum toxicity and the aluminum-containing medications. *Pharmacol Ther* **29**: 255–285.

Liukkonen-Lilja H, Piepponen S. (1992). Leaching of aluminum from aluminum dishes and packages. *Food Addit Contam* **9**: 213–223.

Lukiw WJ, LeBlanc HJ, Carver LA, McLachlan DR, Bazan NG. (1998). Run-on gene transcription in human neocortical nuclei. Inhibition by nanomolar aluminum and implications for neurodegenerative disease. *J Mol Neurosci* **11**: 67–78.

Lukiw WJ, Percy ME, Kruck TP. (2005). Nanomolar aluminum induces pro-inflammatory and pro-apoptotic gene expression in human brain cells in primary culture. *J Inorg Biochem* **99**(9): 1895–1898.

Lukyanenko LM, Skarabahatava AS, Slobozhanina EI, Kovaliova SA, Falcioni ML. (2013). In vitro effect of $AlCl_3$ on human erythrocytes: changes in membrane morphology and functionality. *J Trace Elem Med Biol* **27**(2): 160–167.

Lyons-Weiler J, Ricketson R. (2018). Reconsideration of the immunotherapeutic pediatric safe dose levels of aluminum. *J Trace Elem Med Biol* **48**: 67–73.

Mahieu S, Contini MC, Gonzalez M, Millen N, Elias MM. (2000). Aluminum toxicity. Hematological effects. *Toxicol Lett* **111**(3): 235–242.

Mailloux RJ, Hamel R, Appanna VD. (2006). Aluminum toxicity elicits a dysfunctional TCA cycle and succinate accumulation in hepatocytes. *J Biochem Mol Toxicol* **20**: 198–208.

Mailloux RJ, Lemire J, Appanna VD. (2011). Hepatic response to aluminum toxicity: dyslipidemia and liver diseases. *Exp Cell Res* **317**: 2231–2238.

Maitani T, Kubota H, Hori N. (1994). Distribution and urinary excretion of aluminum injected with several organic acids into mice: Relationship with chemical state in serum studied by the HPLC-ICP method. *J Appl Toxicol* **14**: 257–261.

Malakoff D. (2000). Aluminum is put on trial as a vaccine booster. *Science* **288**: 1323–1234.

Malekshah AK, Torabizadeh Z, Naghshwar F. (2005). Developmental toxicity of aluminum from high doses of $AlCl_3$ in mice. *J Appl Res* **5**(4): 575–579.

Malluche HH, Smith AJ, Abreo K, Faugere MC. (1984). The use of deferoxarnme in the management of aluminum accumulation in bone in patients with renal failure. *N Engl J Med* **311**: 140–144.

Manello F, Ligi D, Canale M. (2013). Aluminium, carbonyls and cytokines in human nipple aspirate fluids: possible relationship between inflammation, oxidative stress and breast cancer microenvirnment. *J Inorg Biochem* **128**: 250–256.

Marítin-Llorens M, Jurado J, Hernández F, Avila J. (2014). GSK-3β, a pivotal kinase in Alzheimer's disease. *Front Mol Neurosci* **7**: 46.

Martin RB. (1992). Aluminum speciation in biology. *Ciba Found Symp* **16**: 95–125.

Martin RB, Savory J, Brown S, Bertholf RL, Wills MR. (1987). Transferrin binding to Al and Fe. *Clin Chem* **33**: 405–407.

Martinez CS, Escobar AG, Uranga-Ocio JA, Precanba FM, Vassallo DV, Exley C, Miguel M, Wiggers GA. (2017). Aluminum exposure for 60 days at human dietary levels impairs spermatogenesis and sperm quality in rats. *Reprod Toxicol* **73**: 128–141.

Martyn CN, Barker DJ, Osmond C, Harris EC, Edwardson JA, Lacey RF. (1989). Geographical relation between Alzheimer's disease and aluminum in drinking water. *Lancet* **1**: 59–62.

Mathiyazahan DB, Thenmozhi AJ, Manivasagam T. (2015). Protective effect of black tea extract against aluminium chloride-induced Alzheimer's disease in rats. A behavioural, biochemical and molecular approach. *J Funct Foods* **16**: 423–435.

Maya S, Prakash T, Madhu KD, Goli D. (2016). Multifaceted effects of aluminium in neurodegenerative diseases: a review. *Biomed Pharmacother* **83**: 746–754.

Mayor GH, Lohr TO, Sanchez TV. (1985). Aluminum metabolism and toxicity in renal failure: A review. *J Environ Pathol Toxicol Oncol* **6**: 43–50.

Mehrpour O, Alfred S, Shadnia S, Keyler DE, Soltaninejad K, Chalaki N, Sedaghat M. (2008). Hyperglycemia in acute aluminum phosphide poisoning as a potential prognostic factor. *Hum Exp Toxicol* **27**: 591–595.

Meliker JR, Wahi RL, Cameron LL, Nriagu JO. (2007). Arsenic in drinking water and cerebrovascular disease, diabetes mellitus, and kidney disease in Michigan: a standardized mortality ratio analysis. *Environ Health* **6**: 1–11.

Menke A, Casagrande S, Geiss L, Cowie CC. (2015). Prevalence of and trends in diabetes among adults in the United States, 1988–2012. *J Am Med Assoc* **314**(10): 1021–1029.

Mestaghanmi H, El Amrani S, Dauca M, Saile R. (2003). Effect of aluminium chloride on pregnant rats and their offspring. *Sciences et Techniques de l'Animal de Laboratoire* **28**(1): 43–51.

Miller RR, Churg AM, Hutcheon M, Lom S. (1984). Pulmonary aveolar proteinosis and aluminum dust exposure. *Am Rev Respir Dis* **130**(2): 312–315.

Miller ZN. (2016). Aluminum in childhood vaccines is unsafe. *J Am Phys Surg* **21**(4): 109–117.

Milnerowicz H, Ściskalska M, Dul M. (2015). Pro-inflammatory effects of metals in persons and animals exposed to tobacco smoke. *J Trace Elem Med Biol* **29**: 1–10.

Mirhashemi SM, Aarabi MH. (2011). To study various concentrations of magnesium and aluminium on amylin hormone conformation. *Pak J Biol Sci* **14**(11): 653–657.

Mirhashemi SM, Shahabaddin M-E. (2011). Evaluation of aluminium, manganese, copper and selenium effects on human islets amyloid polypeptide hormone aggregation. *Pak J Biol Sci* **14**(4): 288–292.

Mirza A, King A, Troakes C, Exley C. (2017). Aluminium in brain tissue in familial Alzheimer's disease. *J Trace Elem Med Biol* **40**: 30–36.

Miska-Schramm A, Kapusta A, Kruczek M. (2017). The effect of aluminum exposure on reproductive ability of the bank vole (Myodes glareolus). *Biol Trace Elem Res* **177**(1): 97–106.

Mitkus RJ, King DB, Hess MA, Forshee RA, Walderhaug MO. (2011). Updated aluminum pharmacokinetics following infant exposures through diet and vaccination. *Vaccine* **29**(51): 9538–9543.

Mittal K, Katare DP. (2016). Shared links between type 2 diabetes mellitus and Alzheimer's disease: A review. *Diabetes Metab Syndr* **10**(2 Suppl 1): S144–S149.

Miu AC, Benga O. (2006). Aluminum and Alzheimer's disease: a new look. *J Alzheimers Dis* **10**(2–3): 179–201.

Moghadamnia AA. (2012). An update on toxicology of aluminum phosphide. *DARU J Pharm Sci* **20**: 1–8.

Mohammed A, Mayyas I, Elbetieha A, Shoter A, Khamas W, Alnasser Z. (2008). Toxicity evaluation of aluminium chloride on adult female mice. *J Anim Vet Adv* **7**(5): 552–556.

Mold M, Umar D, King A, Exley C. (2018). Aluminium in brain tissue in autism. *J Trace Elem Med Biol* **46**: 76–82.

Moore PA, Daniel TC,Edwards DR. (1999). Reducing phosphorus runoff and improving poultry production with alum. *Poult Sci* **78**: 692–698.

Moore PA, Daniel TC,Edwards DR. (2000). Reducing phosphorus runoff and inhibiting ammonia loss from poultry manure with aluminum sulfate. *J Environ Qual* **29**: 37–49.

Morris G, Puri BK, Frye RE. (2017). The putative role of environmental aluminium in the development of chronic neuropathology in adults and children. How strong is the evidence and what could be the mechanism involved? *Metab Brain Dis* **32**(5): 1335–1355.

Morrissey J, Rothstein M, Mayor G, Slatopolsky E. (1983). Suppresion of parathyroid hormone secretion by aluminum. *Kidney Int* **23**(5): 699–704.

Mouro VGS, Menezes TP, Lima GDA, Domingues RR, Souza AC, Oiveira JA, Matta SLP, Machado-Neves M. (2017). How bad is aluminum exposure to reproductive parameters? *Biol Trace Elem Res* Sept 8. Doi: 10.1007/s12011-017-1139-3.

Mujika JI, Torre GD, Formoso E, Grande-Aztatzi R, Grabowski SJ, Exley C, Lopex X. (2018). Aluminum's preferential binding site in proteins: sidechain of amino acids versus backbone interactions. *J Inorg Biochem* **181**: 111–116.

Muselin F, Cristina RT, Iqna V, Dumitrescu E, Brezovan D, Trif A. (2016). The consequences of aluminium intake on reproductive function in male rats: a three-generation study. *Turk J Med Sci* **46**: 1240–1248.

Nam SM, Kim JW, Yoo DY, Kim W, Jung HY, Hwang IK, Seong JK, Yoon YS. (2014). Additive or synergistic effects of aluminum on the reduction of neural stem cells, cell proliferation and neuroblast differentiation in the dentate gyrus of high-fat diet-fed mice. *Biol Trace Elem Res* **157** (1): 51–59.

Nam SM, Kim JW, Yoo DY, Jung HY, Choi JH, Hwang IK, Seong JK, Yoon YS. (2016). Reduction of adult hippocampal neurogenesis is amplified by aluminium exposure in a model of type 2 diabetes. *Journal of Veterinary Science* **17**(1): 13–20.

Nasu T, Suzuki N. (1998). Effect of aluminum ions on K^+-induced contraction in ileal longitudinal smooth muscle. *Comp Biochem Physiol C Pharmacol Toxicol Endocrinol* **120**(1): 137–143.

Nayak P. (2002). Aluminum: impacts and disease. *Environ Res* **89**: 101–115.

Navas-Acien A, Silbergeld EK, Pastor-Barriuso R, Guallar E. (2009). Rejoinder: arsenic exposure and prevalence of type 2 diabetes: updated findings from the National Health Nutrition and Examination Survey, 2003–2006. *Epidemiology* **20**: 816–820.

Neiva TJC, Fries DM, Monteiro HP, D'Amico EA, Chamone DAF. (1997). Aluminum induces lipid peroxidation and aggregation of human blood platelets. *Braz J Med Biol Res* **30**: 599–604.

Nelson WO, Campbell PGC. (1991). The effects of acidification on the geochemistry of Al, Cd, Pb, and Hg in freshwater environments: a literature review. *Environ Pollut* **71**: 91–130.

Netterlid E, Hindsén M, Siemund I, Björk J, Werner S, Jacobsson H, Güner N, Bruze M. (2013). Does allergen-specific immunotherapy induce contact allergy to aluminim? *Acta Derm Venereol* **93**: 50–56.

Newairy AS, Salama AF, Hussien HM, Yousef MI. (2009). Propolis alleviates aluminum-induced lipid peroxidation and biochemical parameters in male rats. *Food Chem Toxicol* **47**: 1093–1098.

Ng M. (2004). Role of hydrogen peroxide in the aetiology of Alzheimer's disease: Implications for treatment. *Drugs Aging* **21**: 81–100.

Niemoeller OM, Kiedaisch V, Dreischer P, Wieder T, Lang F. (2006). Stimulation of eryptosis by aluminum ions. *Toxicol Appl Pharmacol* **217**(2): 168–175.

Nikolov IG, Joki N, Vicca S, Patey N, Auchere D, Benchitrit J. (2010). Tissue accumulation of lanthanum as compared to aluminum in rats with chronic renal failure: possible harmful effects after long-term exposure. *Nephron Exp Nephrol* **115**: 112–121.

Nordal KP, Dahl E, Albrechtsen D, Halse J, Leivestad T, Tretli S, Flatmark A. (1988). Aluminum accumulation and immunosuppressive effect in recipients of kidney transplants. *Br Med J* **287**: 1581–1582.

Obukhova T, Budkar' LN, Tereshina LG, Karpova EA. (2015). [Dissociation of disorders of carbohydrate and lipid metabolism in aluminum industry workers according to medical examination data] in Russian. *Gig Sanit* **94** (2): 67–69.

Ogborn MR, Dorcas VC, Crocker JF. (1991). Deferoxamine and aluminum clearance in pediatric hemodialysis patients. *Pediatr Nephrol* **5**: 62–64.

Ohsaka Y, Nomura Y. (2016). Rat white adipocytes activate p85/p110 P13K and induce PM GLUT4 response to adrenoceptor agonists or aluminum fluoride. *Physiol Int* **103**(1): 35–48.

Omar HM, Khadiga AH, Abd-Elghaffar SK, Ahmed EA. (2003). Aluminium toxicity in rats: the role of tannic acid as antioxidant. *Assiut Univ Bull Environ Res* **6**: 1–14.

Ondov JM, Zoller WH, Gordon GE. (1982). Trace element emissions of aerosols from motor vehicles. *Environ Sci Technol* **16**: 318–328.

Oneda S, Takasaki T, Kuriwaki K, Ohi Y, Umekita Y, Hatanaka S, Fujiyoshi T, Yoshida A, Yoshida H. (1994). Chronic toxicity and tumorigenicity study of aluminum potassium sulfate in B6C3F1 mice. *In Vivo* **8**: 271–278.

Orihuela D. (2007). Effect of aluminium on duodenal calcium transport in pregnant and lactating rats treated with bromocriptine. *J Inorg Biochem* **101**(9): 1270–1274.

Orihuela D. (2011). Aluminium effects on thyroid gland function: iodide uptake, hormone biosynthesis and secretion. *J Inorg Biochem* **105**(11): 1464–1468.

Osama A, Fatma A, Mohamed E, Huda S. (2014). Studies on the protective effects of ginger extract and in combination with ascorbic acid against aluminum toxicity induced hematological disorders, oxidative stress and hepatorenal damage in rats. *Ann Vet Anim Sci* **1**: 136–150.

Osman HM, Shayoub ME, Babiker EM, Osman B, Elhassan AM. (2012). Effect of ethanolic leaf extract of *Moringa oleifera* on aluminum-induced anemia in white albino rats. *Jordan J Biol Sci* **5**: 255–260.

Oteiza PI. (1994). A mechanism for the stimulatory effect of aluminum on iron-induced lipid peroxidation. *Arch Biochem Biophys* **308**: 374–379.

Oteiza PI, Fraga C, Keen CL. (1993a). Aluminum has both oxidant and antioxidant effects in mouse brain membranes. *Arch Biochem Biophys* **300**: 517–521.

Oteiza PI, Keen CL, Han B, Golub MS. (1993b). Aluminum accumulation and neurotoxicity in Swiss-Webster mice after long-term dietary exposure to aluminum and citrate. *Metabolism* **42**: 1296–1300.

Owen LM, Crews HM, Bishop NJ, Massey RC. (1994). Aluminum uptake from some foods by guinea pigs and the characterization of aluminum in *in vivo* intestinal digesta by SEC-ICP-MS. *Food Chem Toxicol* **32**: 697–705.

Oztürk B, Ozdemir S. (2015). Effects of aluminum chloride on some trace elements and erythrocyte osmotic fragility in rats. *Toxicol Ind Health* **31**(12): 1069–1077.

Pandey G, Jain GC. (2013). A review on toxic effects of aluminium exposure on male reproductive system and probable mechanisms of toxicity. *Intl J Toxicol Appl Pharmacol* **3**(3): 48–57.

Pappas RS. (2011). Toxic elements in tobacco and cigarette smoke: inflammation and sensitization. *Metallomics* **3**(11): 1181–1198.

Pennington JA. (1988). Aluminum content of foods and diets. *Food Addit Contam* **5**: 161–232.

Pennington JA,Schoen SA. (1995). Estimates of dietary exposure to aluminium. *Food Addit Contam* **12**: 119–128.

Perez G, Garbossa G, Nesse A. (2001). Disturbance of cellular iron uptake and utilization by aluminum. *J Inorg Biochem* **87**: 21–27.

Pettersen JC, Hackett DS, Zwicker GM,Sprague GL. (1990). Twenty-six week toxicity study with KASAL (basic sodium aluminum phosphate) in beagle dogs. *Environ Geochem Health* **12**: 121–123.

Pineau A, Fauconneau B, Sappino A-P, Deloncle R, Guillard O. (2014). If exposure to aluminium in antiperspirants presents health risk, its content should be reduced. *J Trace Elem Med Biol* **28**(2): 147–150.

Pivnick EK, Kerr NC, Kaufman RA, Jones DP, Chesney RW. (1995). Rickets secondary to phosphate depletion: a sequela of antacid use in infancy. *Clin Pediatr* **34**: 73–78.

Pogue AI, Jaber V, Zhao Y, Lukiw WJ. (2017). Systemic inflammation in C57BL/6J mice receiving dietary aluminum sulfate; up-regulation of the pro-inflammatory cytokines IL-6 and TNFα, C-reactive protein (CRP) and miRNA-146a in blood serum. *J Alzheimers Dis Parkinsonism* **7**(6): 403. doi: 10.4172/2161-0460.1000403.

Pogue Ai, Lukiw WJ. (2016). Aluminium, the genetic apparatus of human CNS and Alzheimer's disease. *Morphologie* **100**(329): 56–64.

Pratico D, Uryu K, Sung S, Tang S, Trojanowski JQ, Lee VM. (2002). Aluminum modulates brain amyloidosis through oxidative stress APP transgenic mice. *FASEB J* **16**: 1138–1140.

Priest ND, Talbot RJ, Austin JG, Day JP, King SJ, Fifield K, Cresswell RG. (1996). The bioavailability of ^{26}Al-labelled aluminium citrate and aluminium hydroxide in volunteers. *Biometals* **9**: 221–228.

Pun KK, Ho PWM, Lau P. (1990). Effect of aluminum on the parathyroid hormone receptors of bone and kidney. *Kidney Int* **37**(1): 72–78.

Que Hee SS, Finelli VN, Fricke FL,Wolnik KA. (1982). Metal content of stack emissions, coal and fly ash from some eastern and western power plants in the U.S.A. as obtained by ICP-AES. *Int J Environ Anal Chem* **13**: 1–18.

Qureshi N, Malmberg RH. (1985). Reducing aluminum residuals in finished water. *J Am Water Works Assoc* **77**: 1–18.

Ranau R, Oehlenschlager J, Steinhart H. (2001). Aluminium levels of fish fillets baked and grilled in aluminium foil. *Food Chem* **73**: 1–6.

Ranjbar A, Khani-Jazani R, Sedighi A, Jalali-Mashayekhi F, Ghazi-Khansari M, Abdollahi M. (2008). Alteration of body total antioxidant capacity and thiol molecules in human chronic exposure to aluminum. *Toxicol Environ Chem* **90**: 707–713.

Ravi SK, Ramesh BN, Mundugaru R, Vincent B. (2018). Multiple pharmacological activities of *Caesalpinia crista* against aluminium-induced neurodegeneration in rats: Relevance for Alzheimer's disease. *Environ Toxicol Pharmacol* **58**: 202–211.

Razniewska G, Trzcinka-Ochocka M. (2003). ET-AAS as a method for determination of aluminum in blood serum and urine. *Chem Anal* **48**: 107–113.

Reinke CM, Breitkreutz J, Leuenberger H. (2003). Aluminum in over the-counter drugs: risks outweigh benefits. *Drug Saf* **26**: 1011–1025.

Reto M, Figueira ME, Filipe HM, Almeida CM. (2007). Chemical composition of green tea (*Camellia sinensis*) infusions commercialized in Portugal. *Plant Foods Hum Nutr* **62**: 139–144.

Reza SM, Palan MJ. (2006). Effect of aluminium on testosterone hormones in male rat. *J Med Sci* **6**(2): 296–299.

Rigolet M, Aouizerate J, Couette M, Ragunathan-Thangarajah N, Aoun-Sebaiti M, Gherardi RK, Cadusseau C, Authier FJ. (2014). Clinical features in patients with long-lasting macrophagic myofasciitis. *Front Neurol* doi: 10.3389/fneur.2014.00230.

Rim K. (2007). Aluminum leaching using chelating agent as a composition food. *Food Chem Toxicol* **45**: 1688–1693.

Rodríguez J, Mandlunis PM. (2018). A review of metal exposure and its effects on bone health. *J Toxicol* **2018**, Article ID 4854152, 11 pages.

Rosseland BO, Eidhuset TD, Staurnes M. (1990). Environmental effects of aluminum. *Environ Geochem Health* **12**: 17–27.

Sadhana S. (2011). S-Allyl-Cysteines reduce amelioration of aluminum induced toxicity in rats. *Am J Biochem Biotechnol* **7**: 74–83.

Saiyed SM, Yokel RA. (2005). Aluminum content of some foods and food products in the USA, with aluminum food additives. *Food Addit Contam* **22**: 234–244.

Sakajiri T, Yamamura T, Kikuchi T, Ichimura K, Sawada T, Yajima H. (2010). Absence of binding between the human transferrin receptor and the transferrin complex of biological toxic trace element, aluminum, because of an incomplete open/closed form of the complex. *Biol Trace Elem Res* **136**: 279–286.

Sakamoto T, Saito H, Ishii K, Takahashi H, Tanabe S, Ogasawara Y. (2006). Aluminum inhibits proteolytic degradation of amyloid beta peptide by cathepsin D: a potential link between aluminum accumulation and neuritic plaque deposition. *FEBS Lett* **580**: 6543–6549.

Savory J, Exley C, Forbes WF, Huang Y, Joshi JG, Kruck T, McLachlan DR, Wakayama I. (1996). Can the controversy of the role of aluminum in Alzheimer's be resolved? What are the suggested approaches to this controversy and methodological issues to be considered? *J Toxicol Environ Health* **48**: 615–635.

Schroeder HA, Mitchener M. (1975a). Life-term studies in rats: effects of aluminum, barium, beryllium and tungsten. *J Nutr* **105**: 421–427.

Schroeder HA, Mitchener M. (1975b). Life-term effects of mercury, methylmercury, and nine other trace metals on mice. *J Nutr* **105**: 452–458.

Sedman AB, Klein GL, Merritt RJ, Weber KO, Gill WL, Anand H, Alfrey AC. (1985). Evidence of aluminum loading in infants receiving intravenous therapy. *N Engl J Med* **312**(21): 1337–1343.

Sepe A, Costantini S, Ciaralli L, Ciprotti M, Giordano R. (2001). Evaluation of aluminium concentrations in samples of chocolate and beverages by electrothermal atomic absorption spectrometry. *Food Addit Contam* **18**: 788–796.

Serdar MA, Bakir F, Hasimi A, Celik T, Akin O, Kenar L, Aykut O, Yildirimkaya M. (2009). Trace and toxic element patterns in nonsmoker patients with non-insulin-dependent diabetes mellitus, impaired glucose tolerance, and fasting glucose. *Int J Diabetes Dev Ctries* **29**: 35–40.

Shadnia S, Mehrpour O, Abdollahi M. (2008). Unintentional poisoning by phosphine released from aluminum phosphide. *Hum Exp Toxicol* **27**: 87–89.

Shahraki MR, Mony EYP, Asl SZ, Sarkaki AR, Shahraki AR. (2008). Effects of aluminium chloride injection in lateral ventricles on serum gonadothropines, testosterone and spermatogenesis in rats. *J Med Sci* **8**(4): 410–414.

Sharma DR, Wani WY, Sunkaria A, Kandimalla RJ, Sharma RK, Verma D, Bal A, Gill KD. (2016). Quercetin attenuates neuronal death against aluminum-induced neurodegeneration in rat hippocampus. *Neuroscience* **324**: 163–176.

Shati AA, Alamri SA. (2010). Role of saffron (*Crocus sativus* L.) and honey syrup on aluminum-induced hepatotoxicity. *Saudi Med J* **31**: 1106–1113.

Shaw CA, Li D, Tomljenovic L. (2014). Are there negative CNS impacts of aluminum adjuvants used in vaccines and immunotherapy. *Immunotherapy* **6**(10): 1055–1077.

She Y, Wang N, Chen C, Zhu Y, Xia S, Hu C, Li Y. (2012). Effects of aluminum on immune functions of cultured splenic T and B lymphocytes in rats. *Biol Trace Elem Res* **147**(1–3): 246–250.

Sherrard DJ, Ott SM, Andress DL. (1985). Pseudohyperparathyroidism syndrome associated with aluminum intoxication in patients with renal failure. *Am J Med* **79**(1): 127–130.

Shirley DG, Lote CJ. (2005). Renal Handling of Aluminium. *Nephron Physiol* **100**: 99–103.

Singh T, Goel RK. (2015). Neuroprotective effect of *Allium cepa L*. in aluminium chloride induced neurotoxicity. *NeuroToxicology* **49**: 1–7.

Skarabahatava AS, Lukyanenko LM, Slobozhanina EI, Falcioni ML, Orlando P, Silvestri S, Tiano L, Falcioni G. (2015). Plasma and mitochondrial membrane perturbation induced by aluminum in human peripheral blood lymphocytes. *J Trace Elem Med Biol* **31**: 37–44.

Song M, Huo H, Cao Z, Han Y, Gao L. (2017). Aluminum trichloride inhibits the rat osteoblast mineralization in vitro. *Biol Trace Elem Res* **175(1)**: 186–193.

Soni MG, White SM, Flamm WG, Burdock GA. (2001). Safety evaluation of dietary aluminum. *Regul Toxicol Pharmacol* **33**: 66–79.

Sorenson JRJ, Campbell IR, Tepper LB,Lingg RD. (1974). Aluminum in the environment and human health. *Environ Health Perspect* **8**: 3–95.

Sorgdrager B, Looff AJ, Monchy JG, Pal TM, Dubois AE, Rijcken B. (1998). Occurrence of occupational asthma in aluminum potroom workers in relation to preventative measures. *Int Arch Occup Environ Health* **71**: 53–59.

Stahl T, Taschan H, Brunn H. (2011). Aluminium content of selected foods and food products. *Environ Sci Eur* **23**(37): 1–11.

Steinhausen C, Kislinger G, Winklhofer C. (2004). Investigation of the aluminum biokinetics in humans: a ^{26}Al tracer study. *Food Chem Toxicol* **42**: 363–371.

Stone CJ, McLaurin DA, Steinhagen WH, Cavender FL, Haseman JK. (1979). Tissue deposition patterns after chronic inhalation exposures of rats and guinea pigs to aluminum chlorhydrate. *Toxicol Appl Pharmacol* **49**: 71–76.

Sun H, Hu C, Jia L, Zhu Y, Zhao H, Shao B, Wang N, Zhang Z, Li Y. (2011). Effects of aluminum exposure on serum sex hormones and androgen receptors expression in male rats. *Biol Trace Elem Res* **144**(1–3): 1050–1058.

Sun X, Cao Z, Zhang Q, Han L, Li Y. (2016a). Aluminum chloride inhibits osteoblast mineralization via TGF-β1/Smad signaling pathway. *Chem Biol Interact* **244**: 9–15.

Sun X, Cao Z, Zhang Q, Liu S, Xu F, Che J, Zhu Y, Li, Y, Pan C, Liang W. (2015). Aluminum trichloride impairs bone and downregulates Wnt/β-catenin signaling pathway in young growing rats. *Food Chem Toxicol* **86**: 154–162.

Sun X, Liu J, Zhuang C, Yang X, Han Y, Shao B, Song M, Li Y, Zhu Y. (2016b). Aluminum trichloride induces bone impairment through TGF-β1/Smad signaling pathway. *Toxicology* **371**: 49–57.

Sun X, Sun H, Yu K, Wang Z, Liu Y, Liu K, Zhu Y, Li Y. (2018). Aluminum chloride causes the dysfunction of testes through inhibiting ATPase enzyme activities and gonadotropin receptor expression in rats. *Biol Trace Elem Res* **183**(2): 296–304.

Sun X, Wang H, Huang W, Yu H, Shen T, Song M, Han Y, Li Y, Zhu Y. (2017). Inhibition of bone formation in rats by aluminum exposure via Wnt/β-catenin pathway. *Chemosphere* **176**: 1–7.

Sumathi T, Shobana C, Mahalakshmi V, Sureka R, Subathra M, Vishali A, Rekha K. (2013). Oxidative stress in brains of male rats intoxicated with aluminium and neuromodulating effect of *Celastrus paniculatus* alcoholic seed extract. *Asian J Pharm Clin Res* **6**: 80–90.

Sushma NJ, Sivaiah U, Suraj NJ, Rao KJ. (2007). Aluminium acetate: role in oxidative metabolism of albino mice. *Int Zool Res* **3**(1): 48–52.

Suwalsky M, Norris B, Villena F, Cuevas F, Sotomayor P, Zatta P. (2004). Aluminium fluoride affects the structure and functions of cell membrane. *Toxicology* **42**(6): 925–933.

Taïr K, Kharoubi O, Taïr OA, Hellal N, Benyettou I, Aoues A. (2016). Aluminium-induced acute neurotoxicity in rats: Treatment with aqueous extract of *Arthrophytum* (*Hammada scoparia*). *J Acute Dis* **5**(6): 470–482.

Taiwo OA. (2014). Diffuse parenchymal diseases associated with aluminium use and primary aluminum production. *J Occup Environ Med* **55**(5 suppl): S71–S72.

Taiwo OA, Sircar KD, Slade MD, Cantley LF, Vegso SJ, Rabinowitz PM, Fiellin MG, Cullen MR. (2006). Incidence of asthma among aluminum workers. *J Occup Environ Med* **48**(3): 275–282.

Tanabe K, Liu Z, Patel S, Doble BW, Li L, Cras-Méneur C, Martinez SC, Welling CM, White MF, Bernal-Mirzrachi E, Woodgett JR, Permutt MA. (2008). Genetic deficiency of glycogen synthase kinase-3β corrects diabetes in mouse models of insulin resistance. *PLoS Biology* **6**(2): e37.

Teraoka H. (1981). Distribution of 24 elements in the internal organs of normal males and the metallic workers in Japan. *Arch Environ Health* **36**: 155–164.

Thompson KH, Orvig C. (2006). Vanadium in diabetes: 100 years from phase 0 to phase I. *J Inorg Biochem* **100**: 1925–1935.

Thomson SM, Burnet DC, Bergmann JD, Hixson CJ. (1986). Comparative inhalation hazards of aluminum and brass powders using bronchopulmonary lavage as an indicator of lung damage *J Appl Toxicol* **6**: 197–209.

Tomasello MF, Sinopoli A, Pappalardo G. (2015). On the environmental factors affecting the structural and cytotoxic properties of IAPP peptides. *J Diabetes Res* **2015**: 918573.

Tomljenovic L, Shaw CA. (2011). Aluminum vaccine adjuvants: are they safe? *Curr Med Chem* **18**: 2630–2637.

Toyokuni S. (2002). Iron and carcinogenesis: From fenton reaction to target genes. *Redox Rep* **4**: 189–197.

Trieff NM, Romana LA, Esposito A, Oral R, Quiniou F, Iaccarino M, Alcock N, Ramanujam VMS, Pagano G. (1995). Effluent from bauxite factory induces developmental and reproductive damage in sea urchins. *Arch Environ Contam Toxicol* **28**: 173–177.

Türkez H, Geyikoglu F, Colak S. (2011). The protective effect of boric acid in aluminum-induced hepatotoxicity and genotoxicity in rats. *Turk J Biol* **35**: 293–301.

Türkez H, Yousef MI, Geyikoglu F. (2010). Propolis prevents aluminium-induced genetic and hepatic damages in rat liver. *Food Chem Toxicol* **48**(10): 2741–2746.

Valkonen S Aitio A. (1997). Analysis of aluminum in serum and urine for the biomonitoring of occupational exposure. *Sci Total Environ* **199**: 103–110.

van Landeghem GF, D'Haese PC, Lamberts LV, DebBroe ME. (1994). Quantitative HPLC/ETAAS hybrid method with an on-line metal scavenger for studying the protein binding and speciation of aluminum and iron. *Anal Chem* **66**: 216–222.

van Rensburg SJ, Carstens ME, Potocnik FCV, Aucamp AK, Taljaard JJF, Koch KR. (1992). Membrane fluidity of platelets and erythrocytes in patients with Alzheimer's disease and the effect of small amounts of aluminium on platelet and erythrocyte membranes. *Neurochem Res* **17**(8): 825–829.

Vandenplas O, Delwiche JP, Vanbilsen ML, Joly J, Roosels D. (1998). Occupational asthma caused by aluminum welding. *Eur Respir J* **11**: 1182–1184.

Vasanthan S, Joshi P. (2018). Effect of aluminum toxicity and *Bacopa monnieri* on plasma cortisol level in Wistar albino rats. *Natl J Physiol Pharm Pharmacol* **8**(8): 1088–1091.

Verma SK, Ahmad S, Shirazi N, Barthwal SP, Khurana D, Chugh M, Gambhir HS. (2007). Acute pancreatitis: a lesser-known complication of aluminum phosphide poisoning. *Hum Exp Toxicol* **26**: 979–981.

Vignal C, Desreumaux P, Body-Malapel M. (2016). Gut: An underestimated target organ for aluminium. *Morphologie* **100**(329): 75–84.

Vittori D, Garbossa G, Lafourcade C, Pérez G, Nesse A. (2002). Human erythroid cells are affected by aluminium. Alteration of membrane band 3 protein. *Biochim Biophys Acta Biomembr* **1558**(2): 142–150.

Vittori D, Nesse A, Pérez G, Garbossa G. (1999). Morphologic and functional alterations of erythroid cells induced by long-term ingestion of aluminum. *J Inorg Biochem* **76**: 113–120.

Vittori D, Pregi N, Pérez G, Garbossa G, Nesse A. (2005). The distinct erythropoietin functions that promote cell survival and proliferation are affected by aluminum exposure through mechanisms involving erythropoietin receptor. *Biochim Biophys Acta* **1743**(1–2): 29–36.

Vorbrodt AW, Trowbridge RS, Drobrogowska DH. (1994). Cytochemical study of the effect of aluminium on cultured brain microvascular endothelial cells. *Histochem J* **26**(2): 119–126.

Vota DM, Crisp RL, Nesse AB, Vittori DC. (2012). Oxidative stress due to aluminum exposure induces eryptosis which is prevented by erythropoietin. *J Cell Biochem* **113**(5): 1581–1589.

Wang N, She Y, Zhu Y, Zhao H, Shao B, Sun H, Hu C, Li Y. (2012). Effects of subchronic aluminum exposure on the reproductive function of female rats. *Biol Trace Elem Res* **145**(3): 382–387.

Wang X, Xi Y, Zeng X, Zhao H, Cao J, Jiang W. (2018). Effect of chlorogenic acid against aluminium neurotoxicity in ICR mice through chelation and antioxidant actions. *J Funct Foods* **40**: 365–376.

Wang Z, Wei X, Yang J, Suo J, Chen J, Liu X, Zhao X. (2016). Chronic exposure to aluminum and risk of Alzheimer's disease: a meta-analysis. *Neurosci Lett* **610**: 200–206.

Warady BA, Ford DM, Gaston CE, Sedrnan AB, Huffer WE, Lum GM. (1986). Aluminum intoxication in a child: treatment with intraperitoneal desferrioxamine. *Pediatrics* **78**: 651–655.

Ward R, Zhang Y, Crichton RR. (2001). Aluminum toxicity and iron homeostasis. *J Inorg Biochem* **87**: 9–14.

Wei H, Wang MD, Meng LX. (2012). Laurel West aluminum industial base residents trace element content in serum and its associated abnormal glucose metabolism (J). *Xian dai Yu fang Yi xue (Modern Prev Med)* **4**: 065.

Wei X, Wei H, Yang D, Li D, Yang X, He M, Lin E, Wu B. (2018). Effect of aluminum exposure on glucose metabolism and its mechanism in rats. *Biol Trace Elem Res* https: //doi.org/10.1007/s12011-018-1318-x First online 28 March 2018.

Wesdock JC, Arnold IMF. (2014). Occupational and environmental health in the aluminum industry. *J Occup Environ Med* **56**(5 suppl): S5–11.

Westermark P, Andersson A, Westermark GT. (2011). Islet amyloid polypeptide, islet amyloid and diabetes mellitus. *Physiol Rev* **91**(3): 795–826.

Willhite CC, Karyakina NA, Yokel RA, Yenugadhati N, Wisniewski TM, Arnold IMF, Momoli F, Krewski D. (2014). Systematic review of potential health risk posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminium, aluminum oxides, aluminum hydroxides and its soluble salts. *Crit Rev Toxicol* **44**(suppl 4): 1–88.

Wills MR, Savory J. (1983). Aluminum poisoning: Dialysis encephalopathy, osteomalacia and anaemia. *Lancet* **322**: 29–34.

Wills MR, Savory J. (1989). Aluminum and chronic renal failure: Sources, absorption, transport, and toxicity. *Crit Rev Clin Lab Sci* **27**: 59–107.

Wisniewski HM, Sturman JA, Shek JW. (1980). Aluminum chloride induced neurofibrillary changes in the developing rabbit: a chronic animal model. *Ann Neurol* **8**: 479–490.

Wisser LA, Heinrich BS, Leach RM. (1990). Effect of aluminum on performance and mineral metabolism in young chicks and laying hens. *J Nutr* **120**(5): 493–498.

Woodson GC. (1998). An interesting case of osteomalacia due to antacid use associated with stainable bone aluminum in a patient with normal renal function. *Bone* **22**: 695–698.

Xiea CX, Mattsonbc MP, Lovellcd MA, Yokelae RA. (1996). Intraneuronal aluminum potentiates iron-induced oxidative stress in cultured rat hippocampal neurons. *Brain Res* **743**(1–2): 271–277.

Xu F, Liu Y, Zhao H, Yu K, Song M, Zhu Y, Li Y. (2017). Aluminum chloride caused liver dysfunction and mitochondrial energy metabolism disorder in rat. *J Inorg Biochem* **174**: 55–66.

Xu F, Ren L, Song M, Shao B, Han Y, Cao Z, Li Y. (2018). Fas- and mitochondia-mediated signaling pathway involved in osteoblast apoptosis induced by $AlCl_3$. *Biol Trace Elem Res* **184**(1): 173–185.

Xu ZX, Fox L, Melethil S, Winberg L, Badr M. (1990). Mechanism of aluminum-induced inhibition of hepatic glycolysis: inactivation of phosphofructokinase. *J Pharmacol Exp Ther* **254**(1): 301–305.

Xu Z-X, Zhang Q, Ma G-L, Chen C-H, He Y-M, Xu L-H, Zhang Y, Zhou G-R, Li Z-H, Yang H-J, Zhou P. (2016). Influence of aluinium and EGCCG on fibrillation and aggregation of human islet amyloid polypeptide. *J Diabetes Res* **2016**, ID 1867059, 14 pages. http: //dx.org/10.1155/2016/1867059.

Yahaya T, Obaroh I, Oladele EO. (2017). The roles of environmental pollutants in the pathogenesis and prevalence of diabetes: a review. *J Appl Sci Environ Manag* **21**: 5–8.

Yamanaka K, Minato N, Iwai K. (1999). Stabilization of iron regulatory protein 2, IRP2, by aluminum. *FEBS lett* **462**: 216–220.

Yang AM, ChengN, Pu HQ, Liu SM, Li JS, Bassig BA, Dai M, Li HY, Hu XB, Wei X, Zheng TZ, Bai YN. (2015). Metal exposure and risk of diabetes and prediabetes among Chinese occupational workers. *Biomed Eviron Sci* **28**(12): 875–883.

Yang M, Jiang L, Huang H, Zeng S, Qiu F, Yu , Li X, Wei S. (2014). Dietary exposure to aluminium and health risk assessment in residents of Shenzhen, China. *PLoS One* **9**(3): e89715 https: //doi.org/10.1371/journalpone.0089715.

Yang S-J, Huh J-E, Lee JE, Choi SY, Kim TU, Cho S-W. (2003). Inactivation of human glutamate dehydrogenase by aluminum. *Cell Mol Life Sci* **60**(11): 2538–2546.

Yang X, Huo H, Xiu C, Song M, Han Y, Li Y, Zhu Y. (2016). Inhibition of osteoblast differentiation by aluminum trichloride exposure is associated with inhibition of BMP-2/Smad pathway component expression. *Food Chem Toxicol* **97**: 120–126.

Yang X, Yu K, Wang H, Zhang H, Bai C, Song M, Han Y, Shao B, Li Y, Li X. (2018). Bone impairment caused $AlCl_3$ is associated with activation of JNK apoptotic pathway mediated by oxidative stress. *Food Chem Toxicol* **116**(Part B): 307–314.

Yassa HA, George SM, Mohamed HK. (2017). Folic acid improves developmental toxicity induced by aluminum sulphates. *Environ Toxicol Pharmacol* **50**: 32–36.

Yokel RA. (2000). The toxicology of aluminum in the brain: a review. *Neurotoxicology* **21**: 813–828.

Yokel RA. (2012). Aluminum in food- The nature and contributions of food additives. *Food Additive* (El-Samragy Y ed), ISBN: 978-953-51-0067-6, InTech, http: //www.intechopen.com.

Yokel RA, Florence RL. (2006). Aluminum bioavailability from the approved food additive leavening agent acidic sodium aluminum phosphate, incorporated into a baked good, is lower than from water. *Toxicology* **227**: 86–93.

Yokel RA, Hicks CL, Florence RL. (2008). Aluminum bioavailability from basic sodium aluminum phosphate, an approved food additive emulsifying agent, incorporated in cheese. *Food Chem Toxicol* **46**: 2261–2266.

Yokel RA, McNamara PJ. (2001). Aluminum toxicokinetics: an updated minireview. *Pharmacol Toxicol* **88**: 159–167.

Yousef MI, Kamel KL, ElGuendi MI, El-Demerdash FM. (2007). An *in vitro* study on reproductive toxicity of aluminium chloride on rabbit sperm: The protective role of some antioxidants. *Toxicology* **239**: 213–223.

Yousef MI, Salama AF. (2009). Propolis protection from reproductive toxicity caused by aluminium chloride in male rats. *Food Chem Toxicol* **47**: 1168–1175.

Yu H, Zhang J, Ji, Q, Wang P, Song M, Cao Z, Zhang X, Li Y. (2019). Melatonin alleviates aluminium chloride-induced immunotoxicity by inhibiting oxidative stress and apoptosis associated with the activation of Nrf2 signaling pathway. *Ecotoxicol Environ Saf* **173**: 131–141.

Zatta P, Lain E, Cagnolini C. (2000). Effects of aluminum on activity of Krebs cycle enzymes and glutamate dehydrogenase in rat brain homogenate. *Eur J Biochem* **267**(10): 3049–3055.

Zatta P, Perazzolo M, Corain B. (1989). Tris acetylacetonate aluminium (III) induces osmotic fragility and acanthocyte formation in suspended erythrocytes. *Toxicol Lett* **45**(1): 15–21.

Zatta P, Ricchelli F, Drago D, Filipi B, Tognon G. (2005). Aluminum-triggered structural modification and aggregation of beta-amyloid. *Cell Mol Life Sci* **62**: 1725–1733.

Zatta P, Zambenedetti P, Milanese M. (1999). Activation of monoamine oxidase type B by aluminum in rat brain homogenate. *NeuroReport* **10(17)**: 3645–3648.

Zhang F, Sun X, Yu H, Yang X, Song M, Han Y, Li Y, Zhu Y. (2017). Effects of aluminum trichloride on cartilage stimulatory growth factor in rats. *Biometals* **30**(1): 143–150.

Zhang L, Lin X, Gu Q, Zhu Y, Zhao H, Li Y, Zhang Z. (2010). Effects of subchronic aluminum exposure on serum concentrations of iron and iron-associated proteins in rats. *Biol Trace Elem Res* **141**(1–3): 246–253.

Zhang Q, Cao Z, Sun X, Zuang C, Huang W, Li Y. (2016). Aluminum trichloride induces hypertension and disturbs the function of erythrocyte membrane in male rats. *Biol Trace Elem Res* **171**(1): 116–123.

Zhang Y, Song W. (2017). Islet amyloid polypeptide: another key molecule in Alzheimer's pathogenesis? *Prog Neurobiol* **153**: 100–120.

Zhou Y, Harris WR, Yokel RA. (2008). The influence of citrate, maltolate and fluoride on the gastrointestinal absorption of aluminum at a drinking water-relevant concentration: A 26Al and 14C study. *J Inorg Biochem* **102**: 798–808.

Zhou Y, Yokel RA. (2005). The chemical species of aluminum influence its paracellular flux across and uptake into Caco-2 cells, a model of gastrointestinal absorption. *Toxicol Sci* **87**: 15–26.

Zhu Y, Hu C, Zheng P, Miao L, Yan X, Li H, Wang Z, Gao B, Li Y. (2016a). Ginsenoside Rb1 alleviates aluminum chloride induced rat osteoblasts dysfunction. *Toxicology* **368–369**: 183–188.

Zhu Y, Li Y, Miao L, Wang Y, Liu Y, Yan X. (2014a). Immunotoxicity of aluminum. *Chemosphere* **104**: 1–6.

Zhu Y, Xu F, Yan X, Miao L, Li H, Hu C, Wang Z, Lian S, Feng Z, Li Y. (2016b). The suppressive effects of aluminum chloride on osteoblasts function. *Environ Toxicol Pharmacol* **48**: 125–129.

Zhu YZ, Sun H, Fu Y, Wang J, Song M, Li M, Li YF, Miao LG. (2014b). Effects of sub-chronic aluminium chloride on spermatogenesis and testicular enzymatic activity in male rats. *Life Sci* **102**(1): 36–40.

Zhuang C, Liu D, Yang X, Wang H, Han L, Li Y. (2016). The immunotoxicity of aluminum trichloride on rat peritoneal macrophages via β_2-adrenoceptors/cAMP pathway acted by norepinephrine. *Chemosphere* **149**: 34–40.

Zlatkovic J, Tsouchnikas G, Jarmer J, Koessi C, Stiasny K, Heinz FX. (2013). Aluminum hydroxide influences not only the extent but also the fine specificity and function activity of antibody responses to tick-borne encephalitis virus in mice. *J Virol* **87**(22): 12187–12195.