Chapter 1
Overview of the Relationship Between Aluminum Exposure and Health of Human Being

Qiao Niu

Abstract Aluminum is a type of ubiquitously existing naturally and widely used metal in our world. It is combined with other elements and forms different compounds. In different pH and due to other conditions, it can be released into ions of different valence states. Our century is an "aluminum age"; aluminum is used in many fields of our daily life, such as vaccine adjuvant, antacids, food additives, skin care products, cosmetics, and cooking wares, and may be as elements or contaminants appeared in a lot of foods, including infant formulae, milk products, juice, wine, sea foods, and tea. It also appears in drinking water due to the water treatment process, or naturally coming from weathering rocks and soils, or released from rocks and soils caused by pollution-induced acid rain. Due to good physical and chemical property, aluminum is being tremendously utilized in many industries. In a lot of production and process procedures, aluminum particulates are seriously exposed by workers. Many factors, such as silicon, citrate, iron, calcium, fluoride, etc., can affect absorption of aluminum in human body. Human being ingests aluminum through the respiratory and digestive system and skin. Aluminum can affect our health, especially impair central nervous system. The important damage is cognitive impairment in Al-exposed peoples, Alzheimer's disease and other neurodegenerative disorders have been related with aluminum exposure, and aluminum has been proposed as etiology.

Keyword Aluminum · Dietary intake · Occupational exposure · Adverse effect · Cognitive impairment

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1.1 Aluminum in the Environment

Aluminum is a type of widely used light metal with the second position in utilization ranking of metals. It is ubiquitous, the third most common element, and the first rich metal in the earth, accounting for about 8% of the earth's crust. It is combined with oxygen, fluorine, silicon, sulfur, and other species, does not appear naturally in the elemental state [4, 11, 93], and mainly exists as bauxite rock and other aluminum salts, such as silicates and cryolite. With centuries and centuries weathering of rocks and volcanic activity as natural processes for most part of aluminum redistribution in the environment [4, 44, 93], it is released to the environment naturally as aerosols, settled in surface water and earth. From the nineteenth century, aluminum was found and extracted from rocks, and due to its excellent chemical and physical property, such as low gravity, ductility, malleability, reflectivity, high tensile strength, corrosion resistance, readily machined into shapes, and high electrical conductivity, it was quickly utilized at an incredible quantity for many purposes; we got into an "aluminum age." Bauxite is a type of aluminum salt and the most important raw material to be refined to produce alumina, from which aluminum metal is recovered by electrolytic reduction; aluminum is also recycled from scrap. Industrial activities of aluminum production and use performed by human being such as exploration, mining, smelting, manufacturing, and polishing also result in the anthropogenic release of great amount of aluminum to the environment. Only from January 2015 to September 2017, the total production of alumina over the world is 327,156 thousand metric tonnes (Fig. 1.1), and metal aluminum is 163,464 metric tonnes (Fig. 1.2). China is the greatest contributor for aluminum mining, refining, production, fabrication, manufacturing, and use (Fig. 1.3) (http://www.world-aluminium.org/).

The biggest utilizations for aluminum metal and its alloys are in production of transportation vehicles, such as cars, buses, high-speed trains, and aircrafts, materials of building and construction, packaging, and electrical equipment. Transportation vehicle uses are one of the fastest growing areas for aluminum use due to the surprisingly growing need from China and other emerging economies. Aluminum powders are used in a lot of industrial fields, such as pigments and paints, fuel additives, explosives, and propellants. Aluminum oxides are not only used as raw materials to produce metal aluminum but also as food additives and in the manufacturing of abrasives, refractories, ceramics, electrical insulators, catalysts, paper, spark plugs, light bulbs, artificial gems, alloys, glass, and heat-resistant fibers. Aluminum hydroxide is used widely in pharmaceutical and personal care products, for example, as adjuvant in vaccine, main constituent of antacids. Aluminum compounds are used in food industries as preservatives, fillers, coloring agents, anticaking agents, emulsifiers, and baking powders; soy-based infant formula can contain aluminum. Natural aluminum minerals especially bentonite and zeolite are used in water purification, sugar refining, brewing, and paper industries.

In recent decades, with the fast industrialization and burning of fossil fuel, great amount of NO, NO_2, SO_2, SO_3, and CO_2 is emitted into the air, combines with water

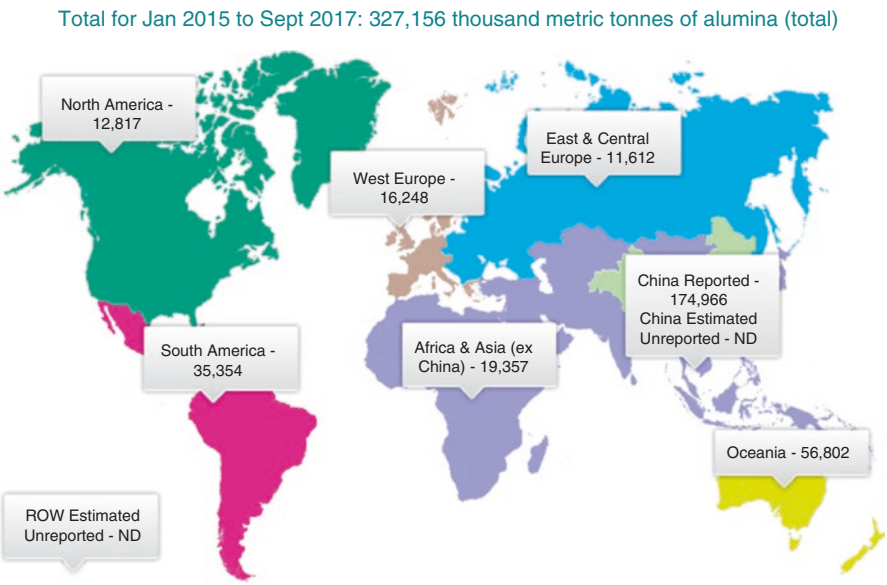

Fig. 1.1 Total quantity of alumina produced globally from January 2015 to September 2017 is 327,156 thousand metric tonnes. China is the biggest producer with the production quantity of 174,966 thousand metric tonnes, accounting for 53.48% of the global production quantity. Oceania and South America stand at the second and third positions with production quantity of 56,802 and 35,354 thousand metric tonnes, respectively, accounting for 17.36% and 10.80%, respectively. The production quantity in North America, West Europe, East and Central Europe, and Africa and Asia (ex., China) are between 10,000 and 20,000 metric tonnes

vapor, and then forms acidic rain that falls into ground earth and results in bauxite resolving and Al^{3+} releasing into soil and surface water.

In general, the forms of aluminum in metal, oxide, and hydroxide are hardly soluble in water and organic solvents, but some aluminum compounds, such as aluminum alkyls, alkyl halides, hydrides, bromide, chloride, iodide, carbide, chlorate, nitride, and phosphide, are active to react with water.

Aluminum levels in environmental media vary tremendously depending upon the location where geochemical constituents are different, the degree of industrialization, the severity of pollution, and sampling site. Generally, background levels of aluminum in the atmosphere are different, ranging from about 0.6 to 7.0 μg/m^3 [49]. Much higher levels can be routinely observed in urban and industrial areas, especially heavily industrialized cities and seriously polluted regions. Aluminum levels in surface water is usually very low (<0.1 mg/L); however, in acidic waters or water with high content of humic or fulvic acid, the concentration of soluble aluminum increases due to the increased solubility of aluminum oxide and aluminum salts [95]. Its concentration in soils and rocks varies greatly, ranging from about 7 to over 100 g/kg in different geographical and geological locations. Some natural aluminum minerals especially bentonite and zeolite are used in water purification; this process is thought

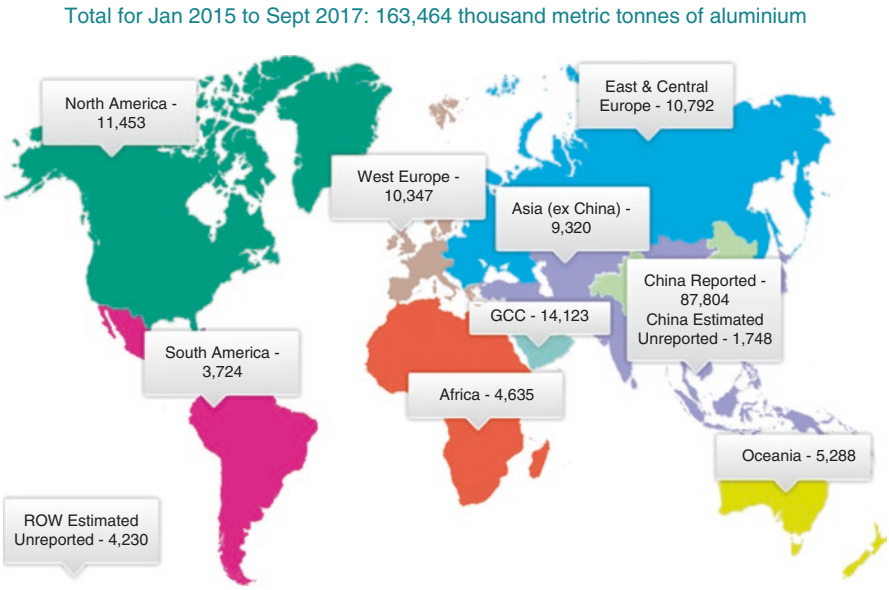

Fig. 1.2 Total quantity of metal aluminum produced globally from January 2015 to September 2017 is 163,464 thousand metric tonnes. China is still the biggest producer with the production quantity of 89,552 thousand metric tonnes, accounting for 54.78% of the global production quantity. Gulf Cooperation Council (GCC) stands at the second position with production quantity of 14,123 thousand metric tonnes, accounting for 8.64%. The production quantity in North America, West Europe, East and Central Europe, and Africa and Asia (ex., China) all are around 10,000 thousand metric tonnes, respectively. Oceania, Africa, and South America are small producers of metal aluminum; their production quantity together is 13,647 thousand metric tonnes, accounting for only 8.35% of global quantity

to leave behind Al ions in the treated water that we drink everyday. In the environment, only one oxidation state of aluminum exists, Al^{+3}, and it does not undergo oxidation reduction reactions. Al^{+3} is a type of reactive ion and can react with other matters in the environment to form various complexes. Environmental factors, such as pH, salinity, and the presence of various species with which aluminum may form complexes, can largely control the fate and transport of aluminum. In general, when the soil is rich in organic matters which are capable of forming aluminum-organic complexes and when the pH is low, such as in areas prone to acid rain or in acidic mine tailings, the solubility and mobility of aluminum in soil are greatest.

1.2 Exposure of Aluminum by Human Being

The general population is primarily exposed to aluminum through the consumption of food items, taking in antacids, ingestion of aluminum in drinking water, and inhalation of ambient air, though the latter two exposure ways are believed as only minor parts. There are other ways in which the people are exposed to aluminum.

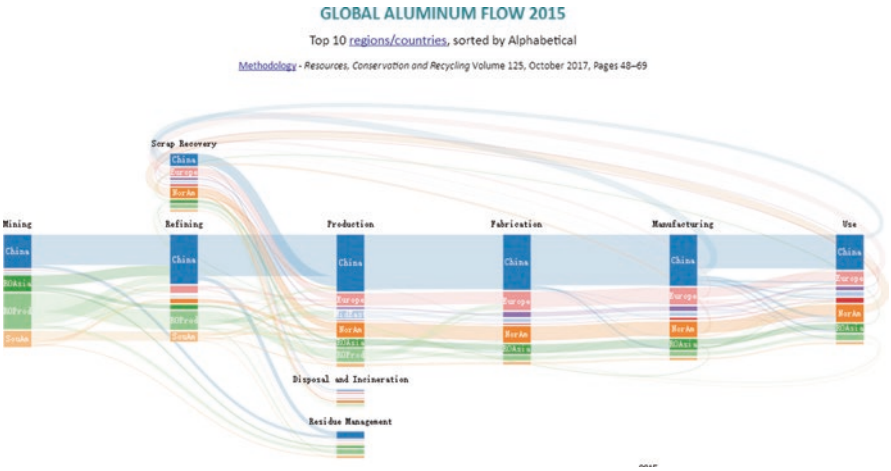

Fig. 1.3 From the global aluminum flow 2015, it is clearly showed that China is the biggest aluminum producer and user through whole production-utilization chain: mining, refining, scrap recovery, production, fabrication, manufacturing, and use

1.2.1 Dietary Aluminum Exposure

Aluminum oxides are used as food additives, such as preservatives, fillers, coloring agents, anticaking agents, emulsifiers, and baking powders. The concentration of aluminum in foods and beverages varies widely, depending upon the type of food product, the technology or type of processing performed, and the geographical areas in which food crops are grown. Based on the FDA's 1993 Total Diet Study dietary exposure model and the 1987–1988 US Department of Agriculture (USDA) Nationwide Food Consumption Survey, the investigators estimated daily aluminum intakes of 0.10 mg Al/kg/day for 6–11-month-old infants, 0.30–0.35 mg Al/kg/day for 2–6-year-old children, 0.11 mg Al/kg/day for 10-year-old children, 0.15–0.18 mg Al/kg/day for 14–16-year-old males and females, and 0.10–0.12 mg Al/kg/day for adult (25–30- and 70+-year-old) males and females. In Wuhan, Central China, 59 samples of youtiao were taken and analyzed; the aluminum contents were from 514.6 to 1578.6 mg/kg, much higher than China National Standard (GB) 2760–2014 [51]. Both the mean and median aluminum contents of youtiao, a typical, traditional, and widely consumed fried dough food in China, exceeded 100 mg/kg, which is the limit value for aluminum regulated by China National Standard (GB) 2760–2014 [87], though the median and 97.5th percentile of weekly dietary intake of aluminum from youtiao did not exceed the provisional tolerable weekly intake (PTWI) set by the joint FAO/WHO Expert Committee on Food Additives. If an adult eats 327.10 g of youtiao per week, which is very possible in China, the weekly dietary intake of aluminum would exceed the PTWI [50]. Like most substances ingested into the digestive tract, aluminum is absorbed from the upper intestine more than from the stomach. The stomach is lined by a thick, mucus-covered membrane which has a much smaller surface area than the intestine membrane has.

Aluminum absorption in the digestive tract seems to be a two-step process, a mucosal cell uptake of Al as initial and then a much slower release into the blood following. The mechanisms mediating aluminum absorption in the digestive tract have been suggested to include both passive (diffusion) and active (carrier- and vesicular-mediated) transport across intestinal cells, as well as paracellular diffusion between these cells.

1.2.1.1 Aluminum in Tea and Cookwares

Depending upon regional tea consumption habit, especially in China, Japan, eastern Asia countries, and the United Kingdom, tea may be a major source of Al ingestion. The Al concentration in fermented tea (794 ± 140 mg/kg) was higher in some degree than that in raw tea (594 ± 129 mg/kg). According to the tea consumption investigation in residents of two main cities of Yunnan, China, a main tea plantation and consumption area, mean daily Al doses taking from tea were 99–60 μg/kg bw/day [12]. Consumption of tea infusions can account for up to 50% of one's daily Al exposure [106]. Aluminum minerals bentonite and zeolite are also used in sugar refining and brewing and left in sugar which often be used in food. In developing countries, the aluminum cookwares made from scrap metal are widely used in many families; an investigation [96] reported that the mean exposure estimate for aluminum was 125 mg per serving (250 ml) with aluminum cookware, more than six times the World Health Organization's provisional tolerable weekly intake of 20 mg/day for a 70 kg adult, and 40 of 42 cookwares tested exceeded this level. Besides, the artisanal aluminum cookwares tested also released great amount of lead, cadmium, and arsenic. Apart from aluminum cookwares, some other metallic, glass, stainless steel, and ceramic utensils can leach considerable quantities of aluminum.

1.2.1.2 Aluminum Exposure from Infant Milk and Formula

Infant formula can contain aluminum; a survey in EU market [63] revealed that all 30 infant formulas sampled, both ready-to-drink milks and milk powders, were contaminated with aluminum, especially the concentration of aluminum in 2 soya-based milk products was as high as 656 and 756 μg/L. The data from other countries vary greatly, such as 440 and 730 mg/L in ready-to-use milk and soy-based formulas and 3442 μg/L in a milk-based iron-fortified ready-to-use formula, in Canada [14]; aluminum concentrations might be as low as 6 μg/L and as high as 1152 μg/L (particularly for soy-based, lactose-free, and hypoallergenic formula) in Britain, the European continent countries, Nigeria, Saudi Arabia, and the United States. The Al concentrations in milk vary greatly depending upon source, location, and local practice. The concentrations in milk are increased in a rank of complexity of processing: 0.004 ± 0.001 mg/L in raw cow's milk, 0.081 ± 0.010 mg/L in "small market" milk, 0.732 ± 0.270 mg/L in powdered milk, and 0.027–5.7 mg/kg in processed cheese which is thought to be due to the addition of anticaking additives including sodium

aluminosilicate while making cheese [1]. So the major part of aluminum in milk products should be contaminants while being processed depending to the complexity of processing technology.

1.2.1.3 Aluminum in Other Foods

High aluminum concentrations were found in a lot of foods in Europa and Japan. 21.09 mg/kg in molluscs and crustaceans, 25.5 mg/kg in shrimp and 42.9 mg/kg in mussel, 116 mg/kg in shellfish, and 88.4 mg/kg in sea urchin [3]. Millour et al. found Al up to 116 mg/kg in shellfish [60], and the edible portions of 159 species of saltwater organisms collected from 4 French coastal areas were reported a mean Al content at 1.35 mg Al/kg [38]. Aluminum were also found in market-sold fruit juices, wines, alcohol, coffee, beer, bottled water, meat, sweats, oils and fats, rice, cereals and potatoes, fruit, green and yellow vegetables, pasta, pastries, and cakes. In Brazilian market-sold juices, Al concentrations in grape juice were reported ranging from less than 0.1 to 0.19 mg/L, in peach juice ranging from 0.15 to 0.31 mg/L, in mango juice varying from less than 0.1 to 0.25 mg/L, in passion fruit ranging from less than 0.11 to 0.37 mg/L, and in guava juice ranging from less than 0.19 to 0.3 mg/L [10]. Tariba summarized the Al concentrations in wines from different countries, 0.017–0.018 mg/L from Argentina, 0.132–1.67 mg/L from the Czech Republic, 0.244–0.81 mg/L from Croatia, 0.01–1.5 mg/L from Hungary, and 0.36–9.5 mg/L from Greece [85]. Two types of German sweets the Westerner like most cocoa powders contained the highest mean Al (165 mg/kg) and chocolate contained a mean 48 mg Al/kg [83]. It can be concluded that aluminum can be found in almost all the foods no matter what they come from or what type they are and what technology they are made or processed.

1.2.1.4 Aluminum in Drinking Water

The mean Al concentrations in finished municipal tap water were reported as 20–174 μg/L in Canada [41]. Polish scientists carefully measured Al in potable water from the area of the city of Poznań using three frequently used analytical techniques (GFAAS, ICP-MS, and ICP-AES) and found that the water source pH, the temperature, the concentrations of organic carbon, and the nature of the suspended particulates together decided the chemical forms of aluminum in water [30]. The data from adults living in six Japanese cities indicated that an adult consuming 2 L of water each day could receive 80 ± 7 μg Al/day, accounting 2.2% of their total mean daily Al dietary intake (3600 ± 1370 μg/day) [68]. A median Al concentration in finished municipal drinking water (0.112 mg/L) was reported in the United States, which corresponded to a daily ingested dose of 160 μg Al/kg for a 70-kg adult (assuming water consumption of 1.4 l/day) or about 1% of the ingested Al amount by food [49]. In Taiyuan city, China, the mean Al concentration was reported as 0.014 mg/l, lower than the China National Standard and WHO recommended standard [115].

1.2.2 Aluminum Exposure by Medication and Personal Care Products

Aluminum hydroxide is used widely in pharmaceutical and personal care products. Aluminum is rich in over-the-counter medicines, such as antacids and buffered aspirin, and in a number of topically applied consumer products such as antiperspirants, first aid antibiotic and antiseptics, diaper rash and prickly heat, insect sting and bite, sunscreen and suntan, and dry skin products. Aluminum-containing adjuvants have been used in vaccines to enhance the immune response against killed, inactivated, and subunit antigens for more than nine decades, and almost whole population in the world, except for peoples living in very poor and remote areas, get many times vaccinations not only in childhood but also in adulthood. The healthy people with normal renal function can ingest much larger amounts of aluminum taking from aluminum-containing medications than from the diet and drinking water, possibly as high as 12–71 mg Al/kg bw/day from antacid/anti-ulcer products and 2–10 mg Al/kg bw/day from buffered analgesics when taken at recommended dosages, equals 3500–5200 mg/day [49], but the absorption rate is low (0.07–0.2%) [109]. Absorption of aluminum in human gastrointestinal tract is generally low, about 0.1–0.4%, although absorption of particularly bioavailable forms such as aluminum citrate and aluminum maltolate may be higher at about 0.5–5%. Although for the patients who are under antacid therapy, big doses of as much as half a gram of aluminum in the form of aluminum hydroxide can be ingested throughout the day, absorption of aluminum hydroxide is usually less 0.01% of the intake dose. Bioavailability of aluminum in human gastrointestinal tract varies greatly based mainly on the chemical form of the ingested compound (i.e., type of anion) and the concurrent exposure to some dietary compounds which can chelate aluminum, such as citric acid, ascorbic acid, or lactic acid.

1.2.3 Aluminum Exposure by Occupation

Bauxite is the most important raw material used in the production of metal aluminum, and is refined to produce alumina (aluminum oxide), which is put into electrolytic reduction process, and aluminum metal is recovered. Aluminum metal can be also recycled from aluminum-containing scraps. Aluminum hydroxide is produced from bauxite too. Along with the fast industrialization in China, Russia, India, and other developing countries, due to the need for products lightweight, the demand for aluminum in construction, shipbuilding, aircraft, automobile, high-speed train production, packaging, and electrical equipment increases in an incredible quantity over the world. China, Russia, Canada, and the United States are the main producers and users of primary aluminum. Only in 2016, China produced 57,960,000 tonnes of aluminum, more than half of production quantity of the total world. A huge occupational population is exposed to aluminum in China; though we have not got the

exact number, it is estimated in four to six million workers employed in aluminum production, processing, and manufacturing and aluminum-related industries. Aluminum powders are used in pigments and paints, fuel additives, explosives, and propellants. Besides as the material for producing aluminum metal, aluminum oxides are also used in the production of abrasives, refractories, ceramics, electrical insulators, catalysts, paper, spark plugs, light bulbs, artificial gems, alloys, glass, and heat-resistant fibers. Natural aluminum minerals especially bentonite and zeolite are also used in paper industries.

Occupational exposure to aluminum happens in industries in the form of McIntyre powder, aluminum oxide, aluminum sulfate, aluminum dust and fumes in potrooms, and aluminum fumes during welding aluminum plate while manufacturing automobiles, aircraft, trains, and ships. Aluminum hydroxide and aluminum fluoride are the main exposure source in the aluminum fluoride plant, aluminum oxide and a small amount of aluminum fluoride are exposed in the smelter potroom, and aluminum oxide and a small amount of oxidized aluminum metal fume are exposed by workers in the foundry. The air inside aluminum potrooms, smelters, foundries, welding places, and remelting plants can contain appreciable concentrations of Al oxides and Na3AlF6 [98]. According to the investigations, the aluminum dust or fume concentrations in the air of workplaces vary from 0 to several tens mg/m^3, the diameters of aluminum particles for aluminum dust can be at nanometer to micrometer scales, but those for aluminum fume are mostly at nanometer scales. During routine operations, total and respirable Al dust concentrations measured in workers' breathing zones were 0.08–2.1 mg/m^3 and 0.03 mg/m^3, respectively. The Al oxides generally constitute approximately 25–44% of the total Al in these dusts [97]. The occupational exposure of aluminum is mainly by inhalation, while the inhaled aluminum particulate can enter CNS via several ways. First, the inhaled aluminum particulates deposit in alveoli and pass through "respiratory membrane" and be delivered into the bloodstream and are transferred to organs and tissues with the systemic circulation; second, are transferred from the nasal cavity via the olfactory neuron into brain tissue [16]; and, third, are absorbed into systemic circulation by the vasculature of the nasal cavity.

1.3 Aluminum Bioavailability and Influencing Factors

Aluminum bioavailability is critically important for its absorption, transportation, metabolism, and toxic effect in creatures including human being. Oral aluminum bioavailability is increased by citrate, acidic pH, and uremia and may be decreased by silicon-containing compounds. Oral aluminum bioavailability is also inversely related to iron status. Water perhaps contribute significantly for the aluminum body burden, oral aluminum bioavailability from water has been reported to be 0.1% to 0.4% and much more than that in food, but some researchers believed the similar oral aluminum availability between water and food. Surprisingly, aluminum bioavailability from occupational inhalation exposure is ~2% [76], significantly higher

than those from water and foods. Though food provides the primary source (>90%) of aluminum for the general human, a few data on oral aluminum bioavailability from foods or beverages can be obtained. Oral aluminum bioavailability from food has been assumed to be less than that from water because the aluminum may be incorporated in high-molecular-weight, relatively insoluble complexes in foods. Oral aluminum bioavailability from milk was estimated to be <1% in rabbits [107]. Though tea leaves contain considerable quantity of aluminum and some people described tea leaves as accumulator of aluminum, the aluminum in tea leaves having low oral bioavailability has been suggested. In tea leaves, 91–100% of aluminum is combined with organic complexes which may interfere with the bioavailability of aluminum [32]. Oral aluminum bioavailability from medication is dependent on aluminum species from the drugs; the bioavailability of aluminum from ingested aluminum hydroxide seems being less than those from aluminum chloride, nitrate, citrate, and lactate from which the aluminum ions are released more than aluminum hydroxide; and sucralfate, another type of aluminum compound, just like aluminum hydroxide, almost can't solve in water but can solve in acid and base and shows oral bioavailability similar with that of aluminum hydroxide and lower than that of soluble aluminum compound such as aluminum chloride, nitrate, citrate, and lactate [108]. In conclusion, the oral absorption or availability of aluminum is mainly affected by the solubility of aluminum compound, pH, and carboxylic acids.

1.3.1 Some Important Influencing Factors on Oral Aluminum Absorption

Citrate Citrate may be one of the most important factors that affect oral aluminum absorption; it may form coordination complexes with aluminum and enhance oral aluminum absorption. Amount of studies revealed that aluminum citrate is more bioavailable than other aluminum chemical species, while oral ingested, it can increase oral absorption of aluminum and also increase aluminum distribution into and out of tissues and discharge from the creature body through renal elimination [54].

Silicon-Containing Compounds Some studies, both epidemiological investigation and animal experiments in drinking water, suggested that increased dietary intake of silicon (Si)-containing compounds could reduce aluminum absorption and facilitate aluminum excretion [7].

Fluoride Fluoride seems to increase aluminum absorption; the mechanism may be it forming numerous complexes with aluminum. In a study with speciation calculations, the authors suggested that fluoride could solubilize more than 60% of aluminum in the stomach [36]. But contradictorily, some authors believed that fluoride might decrease aluminum absorption or enhance its clearance [69].

Iron Iron (Fe) is a very active metal and have different status, which may have impacts on the absorption of aluminum and its accumulation in the brain due to its competitiveness with aluminum; thus aluminum absorption was generally increased in the deficiency of iron. Rats fed with an iron-deficient diet showed greater (0.0065%) aluminum bioavailability, and rats fed with an iron-supplemented diet manifested lower (0.0028%) oral aluminum bioavailability than controls (0.0040%) [66]. In general iron shows two valent status, divalent iron Fe(II) and trivalent iron Fe(III). Fe(II), not Fe(III), decreased the absorption of aluminum hydroxide from the intestinal tract and hence decreased the content of aluminum in portal and systemic blood, in which the authors proposed the mechanism may be Fe(II)-enhancing transferrin (Tf)-mediated aluminum uptake first and then ferritin binding the aluminum in mucosal cells [91].

Calcium and Sodium Calcium is a type of very important ion in creature. Just like iron, calcium (Ca) status influences aluminum absorption and accumulation. In a study on aluminum-treated rat, deficient dietary calcium content increased the aluminum absorption rate and extent, aluminum accumulation in tissue, and aluminum-induced neuropathology [86]. There may be a negative effect of sodium (Na) on aluminum absorption, and an increment of aluminum uptake induced by reduction of sodium has been reported [90].

Ethanol In an in vivo study, rats were combinedly treated with ethanol and aluminum chloride, the results revealed that ethanol elevates the effects of aluminum, but the mechanism on how ethanol affects aluminum toxicokinetics was not provided [77]. In our study on occupationally Al-exposed workers, it seems that the workers with alcohol drinking habit displayed more serious cognitive impairment than workers without alcohol drinking habit (unpublished data). We still cannot distinguish that is it the effect of aluminum or ethanol, because longtime and high-quantity alcohol consumption impairs cognition too.

Age There were reports that aluminum concentration was increased with the aging, not only in Alzheimer's disease patients but also in normal people [56]. Age-related aluminum content increases in the blood, bone, brain, and other soft tissues were reported in human being. Aluminum contents were ~160 mg/kg (in ash) in the lung of 0–3-month-old, ~625 in 1–12-year-old, and >2000 in 19–89-year-old adults, ~100 in the liver in 0–3-month-old, ~150 in 1–12-year-old, and ~550 in 19–89-year-old adults, and ~150 in the kidney in 0–3-month-old, ~300 in 1–12-year-old, and ~350 in 19–89-year-old adults [84]. Brain and bone aluminum increases too with age, up to ~40 years old, then showing a plateau or slight decrease to age 70 and then an increase later in life. Shimizu reported mean hippocampal and frontal cortex aluminum concentrations as 0.014 and 0.020 mg/kg (wet tissue) in 32–46-year-old and 0.402 mg/kg and 0.373 mg/kg in 75–101-year-old [81]. Serum aluminum levels in healthy 20–80-year-old people increased with age too [114]. The increment of aluminum in human body with aging may be the accumulation of aluminum getting from environment including air, water, food, medication, vaccine, and skin care products (Fig. 1.4).

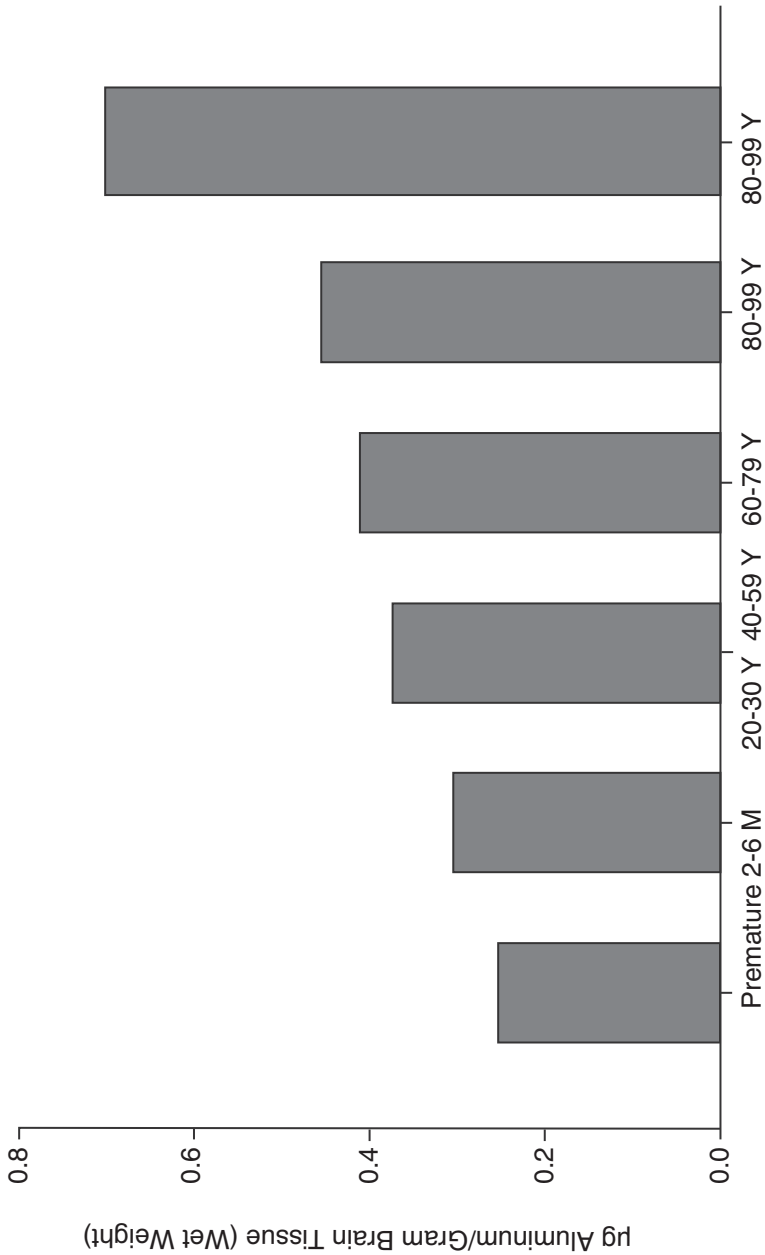

Fig. 1.4 Aluminum concentrations in brain tissues of different ages. (Quoted from Ref. [56])

Foods and Dietary Components Organic ligands in food may associate with aluminum, so presence of food in the stomach may inhibit aluminum absorption. In a study to assess influence of beverages and foods on oral absorption of aluminum, Australian scientists separately co-administered orange juice, or coffee, or wine, or meat, or carbohydrate/cereal products with aluminum sulfate solution and found that orange juice, coffee, and wine increased aluminum absorption by increasing peak serum aluminum concentrations and urinary aluminum excretion and, in contradictory, meat and carbohydrate/cereal products decreased aluminum absorption [94]. Some dietary components, such as phytate and polyphenols, can chemically associate with aluminum and affect aluminum absorption [73, 74].

1.4 Adverse Effect of Aluminum on Human Being

In biological systems including human body, Al^{3+}, like all the metal cations, looks for carboxylate and phosphate groups connected to macromolecules (i.e., proteins, RNA, and DNA) or linked into low-molecular-mass ligands, such as amino acids, nucleotides, citrates, phytates, lactates, carbonates, phosphates, and sulfates as constituents [39], and the phenolic group of the amino acid tyrosine in proteins. Most of the Al^{3+} in human serum is bound to the protein Tf, a recognized carrier of trivalent metal ions, and, in its citrate complex form, can bind to a deprotonated alcohol group and then exerts its biological effects. As regards the aluminum particles, their reactivity and related adverse effect are dependent on their size, shape, surface area, bulk density, and aluminum content. Nanoparticles of aluminum powders displayed maximal oxidation (combustion) rates than microparticles [43] and showed severer oxidative impairment on neural cells [75]. Tiny aluminum flakes are also more reactive due to their thinness and corresponding high surface area. The size of aluminum aerosols in environment air is critical for what part of respiratory system they are deposited in and where they exert their adverse effects. In occupational locations, three aerosol fractions are now thought to be health-related; they are inhalable, thoracic, and respirable fractions [65]. The inhalable fraction refers to the total amount of airborne particulates to enter the nose and/or mouth during breathing (aerodynamic diameters (dae) $\leq$100 μm); the thoracic fraction passes through the tracheoalveolar region of the lung (dae <28 μm), while the respirable fraction (dae <10 μm) goes into and deposits in the alveolar region of the lung (includes the respiratory bronchioles, the alveolar ducts, and the sacs). In recent years, exposure to tiny particles (dae <2.5 μm) has been put under spotlight for their possible relation with cardiovascular and respiratory diseases [17, 18]. The workers employed in aluminum powder processing and producing are probable to be exposed to some or all of the aerosol fractions, based on the different production process used. The aluminum refinery workers that use alumina powders and are exposed to aluminum fumes may encounter the same situation [42, 88]. The Al^{3+} ions on the aluminum particle surface possess strong Lewis acids property and react strongly with water, while hydroxyl groups on the particle surface are Lewis bases which interact with metal

ions [19]. Hence, the reactivity of Al_2O_3 particles is based on its specific crystal structure and hydrophilic/hydrophobic surface properties and the surface hydration degree. Adsorption capacity of Al_2O_3, $Al(OH)_3$, and aluminum phosphate is important for its adverse health effect; the inhalation of Al_2O_3 particles and related oxyhydroxide particles in aluminum smelting process can serve as a delivery vehicle for hydrogen fluoride adsorbed on the particle surface; in addition, the release of volatile by-products including polycyclic aromatic hydrocarbons (PAH), generated by carbon electrodes in the electrolytic reduction process, may exert additional adverse effect [4, 42, 52], and Jinzhu et al. have in vitro demonstrated the cooperative effects of aluminum and benzopyrene, a major constituent of PAH [45].

1.4.1 Neurotoxic Effects Induced by Occupational Aluminum Exposure

Workers in aluminum industries can be occupationally exposed to airborne aluminum particulate at concentrations exceeding to which the general population was exposed by approximately 350 times. Occupational aluminum intake was estimated to be 21 mg/day (6×10^{-3} mg/kg bw/day), much higher than 0.06 mg/day (1.7×10^{-5} mg/kg bw/day) of the general population's intake. Many studies have shown that these types of occupational exposures could produce elevated urine aluminum concentration, elevated serum aluminum concentration, and elevated bone aluminum content. The serum and urine of workers employed in the electrolytic aluminum production for average 3.8 years, the production of aluminum powder for 10.2 years, and the production of aluminum sulfate for 7.4 years, and in aluminum welding for 10.7 years, were compared with a control group [82]. All of the aluminum-exposed workers displayed higher (significantly or nonsignificantly) serum aluminum concentrations than that of the controls. And all of them showed significantly higher urine aluminum concentrations than that of the controls, and a significant correlation was found between weekly mean air aluminum concentration and weekly average urine aluminum content. A positive correlation was found between serum and urine aluminum concentrations. The plasma and urine aluminum concentrations of the aluminum-exposed workers measured end-of-shift were higher than those measured beginning-of-shift and higher on last workday than on first workday in a week [62]. Both plasma and urine aluminum concentrations were higher after exposure to aluminum fume than exposure to aluminum dust in similar concentrations. The reason might be that the dust particles were larger than fume particles. Post-of-shift urinary aluminum concentrations were correlated significantly with workshop air aluminum concentration. Inhaling nanoparticles of alumina is an increasing problem due to the large usage of nano-aluminum. In the in vivo and in vitro studies, Zhang et al. indicated that nano-alumina impaired neurobehavioral functions in rats and induced cell necrosis and apoptosis, likely mediated by the reduction in MMP and ROS and the induction of the caspase-3 gene. The ability of the nano-alumina

particles caused cell death, ultrastructural lesions, mitochondrial damage, and mitochondrial membrane integrity in vitro. Nanoparticles of alumina were much more toxic compared to micro-alumina particles, indicating a particle size-induced toxicity of nano-alumina; one key mechanism may be the ability of alumina to damage the mitochondria [75, 117]. In recent report, Zhang et al. also found the genotoxicity of nano-alumina, inducing DNA damage [116].

In industrial environment, workers mainly inhale aluminum fumes, dusts, and flakes via respiratory tract, though they are exposed to aluminum particulate by skin too. Several studies have reported adverse effects in respiratory tract of aluminum-exposed workers, such as asthma-like symptoms, widely known as potroom asthma, wheezing, dyspnea, and lung function impairment. But the cause of potroom asthma has been suggested to be the exposure to fluorides in the workplace air [48]. Some studies debated if there was an association between allergic status and the development of potroom asthma symptoms in aluminum-exposed workers. Furthermore, occupational exposure to aluminum dust was directly associated with the development of aluminum pneumoconiosis [13], a type of aluminum dust-induced pulmonary fibrosis in aluminum industry workers. Contact dermatitis and irritant dermatitis were symptoms reported in workers exposed to aluminum alloys and aluminum dust too. Epidemiological investigations have revealed a higher risk of developing lung cancer [55] or bladder cancer in aluminum-exposed workers compared with controls, but, the risk was ascribed to the inhalation or dermal exposure to the PAHs which are generated during aluminum production, other than exposure to aluminum compound particles.

Extensive occupational health and occupational epidemiological investigations have reported adverse neurological symptoms or signs as results of occupational aluminum exposure, even related to Alzheimer's disease [92]. An important even critical issue in these investigations is aluminum exposure assessment, otherwise the exposure-response relationship could not be achieved. The researchers utilized a number of different methods to assess the aluminum exposure, including exposure scaling for different job types, estimation for aluminum body burden, or simply years working in the aluminum industry, and even having worked or having not worked in the aluminum industry. In the aluminum-exposed workers, a variety of neuropyschiatric or neurological symptoms, including angry, depression, confusion, loss of coordination, loss of memory, and balancing problems were significantly correlated with occupational aluminum exposure, both exposure duration and exposure level or estimated exposure dose.

In a cross-sectional study [40], 33 occupationally aluminum-exposed Al electrolytic workers, who were 35.16 ± 2.95 (mean ± S.D) years old and exposed to aluminum for 14.91 ± 6.31 (mean ± S.D) years, were investigated. Air aluminum concentration in workplaces and their urinary aluminum concentration were measured by means of graphite furnace atomic absorption spectrophotometer. Matched normal reference group were selected from a flour plant. Neurobehavioral core test battery (NCTB) recommended by WHO was performed. Autonomic nervous function test battery recommended by Ewing DJ was conducted. FAC SCAN was used

to measure the lymphocyte subsets of peripheral blood. The mean air aluminum concentration in the workshop was 6.36 mg/m^3 (2.90–11.38 mg/m^3). Urinary aluminum concentration of the Al electrolytic workers (40.08 ± 9.36 μg/mg.cre) was significantly higher than that of the controls (26.84 ± 8.93 m/mg.cre). Neurobehavioral test results revealed that the scores of DSY, PAC, and PA in Al electrolytic workers were significantly lower than those of the controls and the score of POMSC, POMSF, and SRT among Al-exposed workers were significantly raised compared to those of the controls. Autonomic nervous function test results displayed that R-R interval variability of maximum ratio of immediately standing up in Al electrolytic workers were decreased compared with the control group, while the BP-IS, HR-V, HR-DB, and R30:15 did not show significant change.

In a cross-sectional case-control study conducted in Northern Italy, 64 former aluminum dust-exposed workers were compared with 32 unexposed controls from other companies matched for age, professional training, economic status, and educational and clinical features. Cognitive functions were assessed by the Mini Mental State Examination (MMSE), the Clock Drawing Test (CDT), and the auditory evoked Event-Related Potential (ERP-P300), and the time required to solve the MMSE (MMSE-time) and CDT (CDT-time) was also measured to detect early signs of mild cognitive impairment (MCI). Significantly higher internal doses of serum Al and blood Fe were found in the ex-aluminum dust-exposed workers compared to the controls. The results of neuropsychological tests displayed a significant difference in the latency of P300, MMSE score, MMSE-time, CDT score, and CDT-time between the former Al-exposed workers and the controls. P300 latency was correlated positively with Al-s and MMSE-time. Al-s concentration showed significant effects on all the tests: a negative relationship was observed between internal Al concentrations, MMSE score and CDT score; a positive relationship was found between internal Al concentrations, MMSE-time and CDT-time. All the potential confounders such as age, height, weight, blood pressure, schooling years, alcohol, coffee consumption, and smoking habit were taken into account, and their affections were ruled out by statistical analysis. Based on the findings, the authors suggest a possible role played by the inhalation of aluminum dust in preclinical mild cognitive disorder which might prelude Alzheimer's disease (AD) or AD-like neurological deterioration [67].

A total of 66 retired Al potroom workers and 70 unexposed controls were investigated by Xiaoting Lu and colleagues [53]. The cognitive functions were assessed with the Mini Mental State Examination. Since tau protein hyperphosphorylation and expression are pathological markers of Alzheimer's disease, and due to unacceptability of brain tissue of workers, the tau protein expression in peripheral blood lymphocyte of workers was analyzed with Western blot. The cognitive functions of the Al-exposed workers were significantly decreased compared to the controls. Twelve mild cognitive impairment cases in the exposed group and 14 mild cognitive impairment cases in the control group were diagnosed, and the difference is significant. Significantly higher p-tau181 and p-tau231 levels, which are somewhat similar with AD patients, were detected in the Al-exposed workers than in the control group. The study suggests that long-term exposure to Al may cause cognitive disor-

ders and that p-tau181 and p-tau231 might be useful indicators for monitoring cognitive decline in Al-exposed workers.

Some other groups of scientists performed investigations which specifically examined the relationship between occupational aluminum exposure and occurrence of AD, but significant correlation was not found. However, negative conclusion can't be drawn. The results of these investigations are limited due to the complicated exposure situations in workplaces. Hardly can a worker be only exposed to aluminum particulate without exposure to other hazards, and the workers' exposure estimation is often not clear, adequate, and accurate due to the long-term, often changing, and complicated exposure situations. There coexist many toxic substances in the air of workplaces due to the production process and material needs; other toxic substances other than aluminum as the cause of the observed effect can't be ruled out. Additionally, frequently appeared defects in epidemiological studies, such as small sample sizes, relatively young age of exposed workers, misclassification bias, inappropriate selection of exposed group and comparison group, and unable strictly controlling confounding factors, are usual weaknesses under criticism in these occupational epidemiological investigations [79].

1.4.2 Aluminum Exposure in Drinking Water and Neurological Disorders

The neurotoxic features of aluminum are well displayed in mounting of investigations in non-occupational populations, and associations between aluminum exposure and neurological disorders even Alzheimer's disease have been reported; however, the strong evidence demonstrating causality of aluminum on human neurological disorders is still not clear.

Since bioavailability of aluminum in water is higher than in other form in normal living conditions, though it was thought to be lower than that of inhaled aluminum particles that occurs in occupational settings [33], the relationship of aluminum exposure level in drinking water and prevalence of Alzheimer's disease has been extensively investigated. Though the data collected for this relationship is difficult to reach a sounded conclusion because of the big variation of study designs, the difficulty to maintain big and long-term cohort, and the unbalanced study quality in these investigations, the majority, though not all, of the epidemiological investigations identified, reported, and at least implied a positive relationship between aluminum levels in drinking water and risk of cognitive impairment, dementia, or AD [21]. Silica in drinking water has been identified as a protective agent against the development of dementia, and fluoride has also been suggested to have a potential protective effect against AD. Due to methodological issues, the results drawn from many of the epidemiological investigations studying the association between aluminum in drinking water and the risk of developing AD are limited in some degree. These methodological issues mainly include: almost all the detailed individual Al

exposure information from longtime drinking water and from other exposure ways are lacked; disease diagnosis and ascertainment are poor due to the incomplete disease records, inconsistent "diagnosis scale," and poor recall of family members; unable to adjust important confounding factors; and in general the investigated sample sizes are not large enough. A study performed in France [59] is better than other studies performed to date in methodology. The strong evidence drawn from a significant positive relationship between aluminum levels in drinking water and the development of AD in this large-scaled prospective study, plus the weak evidences drawn from positive relationships in numerous studies that have some methodological deficiency, may propose the positive and probable causality relationship between aluminum and AD and certainly can be used to encourage further investigations with well designing and better methodology.

Ferreira et al. have systematically selected and reviewed 34 existing study papers exploring evidence on relationship between Al exposure (mainly through drinking water) and the risk of developing AD and showed in their review article that 68% of them established a relationship between Al and AD, 23.5% did not get conclusion, and 8.5% did not establish a relationship between Al and AD [20]. From Ferreira PC's review article, it is clear that the majority of the investigators got the positive relationship between Al exposure and AD.

Two groups of Norwegian scientists led by Flaten [21, 22] performed ecological investigations using basically the same sources of data to measure exposure and outcome and got almost the same results. The municipalities included in the investigations were grouped according to Al contents in drinking water, and the mortality with dementia was outcome measure, which were coded from death certificates as the underlying or a contributory cause of death. After analysis, they found a dose-response relationship. The Al contents in drinking water were <0.05 (control), 0.05–0.20, and >0.20 mg/l, and age-adjusted mortality rates showed relative risks for dementia of 1.00, 1.15, and 1.32 in men and 1.00, 1.19, and 1.42 in women.

Wood et al. [100] analyzed mental test scores of 386 patients with hip fracture, while they were admitted into hospital and tested mental state between 1982 and 1985. Almost all the patients with reduced mental test scores were identified between one health district with high Al concentration (0.18–0.25 mg/l) in drinking water and two districts with low Al concentration (<0.05 mg/l) in drinking water. In general, Al treatment is a standard process for "purifying water" in water supply plants and elevates Al concentrations in the drinking water; the water supply in the high-Al district in this study had only "been treated with Al since 1982," that is, for only 0–3 years before the mental tests were performed; so considering the short term of high level Al exposure from drinking water, this study does not provide much evidence both pro and against the Al–AD hypothesis.

Martyn et al. [58] selected 88 county districts in England and Wales, integrated them as 7 computerized tomography scanning units, and utilized the records of these computerized tomography scanning units to estimate incidence rates of AD. They found that the relative risk of AD was 1.5 times higher in districts with mean Al concentration >0.11 mg/l than districts with mean Al concentration <0.01 mg/l. No obvious dose-response relationship was observed, but when the

analysis was restricted to subjects under 65 years of age, a tendency for dose response appeared.

In Ontario of Canada, Neri and Hewitt [64] performed a large-scaled case-control study. They matched 2232 patients who had been diagnosed as AD or presenile dementia and discharged from hospital, with an equal number of age and sex comparable patients discharged with a nonpsychiatric diagnosis, analyzed the data, and calculated the relative risk of AD. A dose-response relationship appeared, with the increasing of Al concentrations in drinking water (>0.01 mg/l (control), 0.01–0.10 mg/l, 0.10–0.20 mg/l, and >0.20 mg/l). The relative risks of AD increased too (1.00, 1.13, 1.26, and 1.46).

Frecker [31] examined the birthplaces of 40 individuals in 7 communities around Bonavista Bay in Newfoundland, who had died with a diagnosis of dementia recorded on their death certificates. The relative risks for dementia in these communities seemed to increase with increasing Al concentrations in drinking water. But, due to the small number of patients and defect of the ecological design, to draw the conclusions from this study was limited.

Wettstein et al. [99] selected two groups of 80–85-year-old residents who had a long-term (>15 years) residing in Zürich, Switzerland, according to the mean Al concentration in drinking water of their residence area, one group with a mean approximately 0.10 mg/l Al concentration in drinking water and the another group with <0.01 mg/l, and measured their cognitive impairment and compared the mnestic and naming skills. No difference in cognitive impairment between the two groups was found. But, we should note that a concentration of 0.10 mg Al/l is not very high. Also, the limitation in this study in contrast to most other epidemiological studies is that the data came from only two sources of drinking water and the bioavailability of Al is probable to vary with water qualities due to different Al speciation and the only high-Al source in this study might contain a low fraction of bioavailable Al.

A series of papers have been published based on the Ontario Longitudinal Study of Aging that may be the most long-term observation till now on the relationship between Al content in drinking water and AD, in which about 2000 men have been followed for about 30 years and Forbes et al. studied the relationship between cognitive function and Al, fluoride, and other constituents in drinking water [23–28]. In the initial report of the study, the OR for impaired cognitive function was 1.14 (not significant) for median Al concentration (>0.085 mg/l) in drinking water compared to lower Al concentrations. In later analyses, they took in consideration other water constituents and adjusted data, using two different logistic regression models, found significantly elevated odds ratios (OR = 1.97, 95% confidence interval [CI] 1.21–3.22, $p < 0.05$ and OR = 2.27, 95% CI 1.27–4.02 for Al $p < 0.01$) [28]. Also, they compared individuals with high Al (>0.085 mg/l) and low fluoride (<0.88 mg/l) concentrations in their drinking water with those with low Al and high fluoride in drinking water, and the OR was as high as 2.72 ($p < 0.01$).

The Paquid cohort [2, 5, 6, 15, 80] in southwestern France, which was composed of 3777 elderly men and women in the parishes of Gironde and Dordogne, left puzzle for us. The investigators used mental impairment as the outcome variable in the first three papers published from this cohort and used AD in the last paper. In the

preliminary report of the study, when an increase of 0.1 mg/l of Al in drinking water was calculated, an unbelievable high relative risk of 4.5 (95% CI 3.4–6.1) was shown. But, then the archival data from the individual waterworks were rechecked, and it was found that the Al measurements, based which the study data were analyzed and conclusion was drawn, were erroneously high. Because of these big errors, the investigators resampled all of the water sources and analyzed samples with up-to-date methods and thorough quality control in the same laboratory, after analysis, the new values of Al content in drinking water were surprisingly many times lower than the old ones. It is likely that the unbelievable high relative risk for mental impairment in preliminary report was in a great part due to using erroneous exposure data. The results got from epidemiological study using the new drinking water data were ambiguous: There was a weak positive relationship between Al content in drinking water and cognitive impairment in the elderly who drank the water with pH less than 7.3; but when the pH of drinking water was above 7.3, the relationship was negative. In the most recent analysis of the Paquid cohort, the authors used AD, diagnosed using the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, in spite of cognitive impairment, as outcome variable. The results seemed reasonable; the relative risk of AD adjusted for age, sex, education level, residence place, and wine consumption was 2.14 (95% CI 1.21–3.80) for individuals whose drinking water Al content was >0.10 mg/l, while the relative risk of dementia was 1.99 (95% CI 1.20–3.28). Furthermore, in a subcohort whose information on bottled mineral water consumption was available, the relative risk of dementia adjusted for age, sex, education level, residence place, wine consumption, silica in drinking water, and mineral water consumption significantly increased to 3.36 (95% CI 1.74–6.49).

Forster et al. performed a case-control study composed of 109 cases of clinically diagnosed presenile AD patients (<65 years of age) in Northern England, relative risks of presenile AD for different Al concentrations varied from 0.8 to 1.3, and no significant relationship between the disease and Al contents in drinking water was found [29]. However, the Al concentrations in this study were relatively low compared to other studies, the highest concentration was only 0.125 mg/l, and few concentrations were above 0.050 mg/l. This may be the reason of low relative risk of presenile AD in this study. Another reason may be that gastrointestinal absorption of Al increases with age. Perhaps the cases in this study were not old enough. And the effect of Al on AD may be smaller in presenile stage than in senile stage.

AD was listed as the underlying cause of death in Ontario, Canada; Forbes et al. examined death certificates there [27] and reported an AD death rate ratio of 2.42 (95% CI 1.42–4.11) for Al concentration >0.336 mg/l relative to <0.067 mg/l in drinking water. Then they restricted the analysis to individuals over 75 years of age, and the rate ratio increased to 3.15 (95% CI 1.85–5.36). Furthermore, while they repeated the analysis on individuals >85 years only, the rate ratio was raised to 4.76, and they adjusted the data for drinking water source (groundwater vs. surface water) and the water contents of silicon, iron, pH, fluoride, and turbidity, and the rate ratio

surprisingly increased to 9.95. The Al concentrations in this study were higher than in other published studies, and the effect of Al in drinking water was higher too.

A case-control study on autopsy-verified material from a brain bank in Ontario was conducted by McLachlan et al. on the basis of strict neuropathologic criteria [59], with 385 AD cases (296 pure AD and 89 with other coexisting pathology) and 295 controls (125 with no brain histopathology and 170 with neurodegenerative diseases but has never been implicated with Al). The authors compared all AD cases with all non-AD controls, took the Al concentration in drinking water at last residence before death as the exposure level, and got the OR 1.7 (95% CI 1.2–2.5) associated with Al concentration >0.10 mg/l. Then they used 10-year weighted residential histories to improve the data for Al exposure, and the estimates of ORs increased to 2.5 or greater. Furthermore, when they calculated ORs using increasing Al cutoff points, ORs increased gradually: the OR was 3.6 (95% CI 1.4–9.9) at 0.125 mg/l, 4.4 (95% CI 0.98–20) at 0.150 mg/l, and 7.6 (95% CI 0.98–61) at 0.175 mg/l. The diagnostic quality of the data in this study might be ideal, but potential bias might exist due to using brain tissue from a brain bank. The brain tissues stored in a brain bank are possibly not representative of the general population whose brains generally may not sampled and stored in brain bank, but this shortcoming seems not having substantially distorted the results.

As a part of a large, multidisciplinary study of AD, Gauthier et al. [35] performed a case-control study (68 cases) in Québec, Canada, and diagnosed AD using the NINCDS-ADRDA criteria. Exposure level was calculated from water Al contents sampled at four different seasons, combined with the individual's residential locations from 1945 to onset of AD. Furthermore, they adjusted the ORs for educational level, family AD history, and presence of at least one apolipoprotein E e4 allele. Notably, the specificity of this study is that it focused on speciation of Al, the exposure data including total Al, total dissolved Al, monomeric organic Al, monomeric inorganic Al, polymeric Al, Al_{31}, and complexes of Al with hydroxide, fluoride, silicon, and sulfate. The ORs were elevated to 2.10 for onset exposure and 1.52 for long-term exposure in total Al concentration in drinking water (>0.077 mg/l), but not significantly. The monomeric organic Al measured at disease onset is the only fraction of Al that was associated with AD (OR = 2.67, 95% CI 1.04–6.90). The threshold concentration used in this study was 0.012 mg/l (measured as elemental Al). Though this study has high-quality disease data; very detailed and specific water chemistry data, especially the Al speciation; and adjustment for till now-known risk factors, the small number of subjects (only 68 cases) seriously restricts the conclusions to be drawn.

Martyn et al. performed a case-control study composed of 106 clinically diagnosed male AD cases below 75 years old in 8 regions of England and Wales and did not found evidence of an association between AD and higher Al concentrations in drinking water; also no association was found when the analyses were restricted to water supplies with low concentrations of silicon [57]. The authors used three comparison groups (other dementia, brain cancer, and other diagnoses) to match the AD cases and performed analyses using three different methods for computing Al exposure (Al concentrations averaged from age 25 years to diagnosis, from age 25 years

to 10 years before diagnosis, and over 10 years before diagnosis). Most of the 54 ORs for increased Al concentrations were below unity, 8 of them significantly so. This is a study providing the strongest evidence against the Al–AD hypothesis in all the studies published so far.

1.4.3 Antacids Ingestion and Development of AD

A typical heavily aluminum-exposed population is that who regularly ingest antacids for stomach problems. In one study [37], researchers found a significantly elevated odds ratio for AD between regular antacid ingesters and irregular ingesters; but, when only aluminum-containing acids were taken into consideration and put into analysis, the association became not significant. There was no other study that reported a significant positive association between antacid ingest and AD till now. Reports on the relationship between aluminum content in food and the risk of developing AD are limited and controversial. This situation may be due to difficulty to measure aluminum content in foods and to get accurate exposure information in dietary studies. A positive relationship between the consumption of foods with high aluminum content and the risk of developing AD was reported in a small-scaled case-control study, but the results need to be confirmed in larger-scaled cohort investigations.

1.4.4 Aluminum-Related ALS and PDT in Specific Regions

In 1945 until 1960, two syndromes featuring amyotrophic lateral sclerosis (ALS) and a parkinsonism-dementia (PD) developed in some natives in some regions of the world, including indigenous people in several western Pacific foci; the Chamorro on Guam; Japanese on the Kii peninsula of Honshu Island, Japan; and the Auyu and Jakai of southern West New Guinea. The incidence of this special ALS was 50–150 times higher than elsewhere in the world [47]. High aluminum and low calcium and magnesium concentration in the environment has been proposed to contribute to these syndromes [101]. Scientists observed carefully specific localization of manganese, aluminum, and calcium in the spinal cord of ALS patients [111]. High aluminum content in soil was found, but was not found in food [59]. Using neutron activation analysis, Yoshimasu et al. found higher concentrations of aluminum and calcium in the brain of victims of ALS than in controls whereas not elevated magnesium concentration [111, 112]. The average aluminum concentrations in brains were 33.1 mg/kg in 6 ALS cases and 36.8 mg/kg in 4 PD cases compared to 17.7 mg/kg in controls, determined by neutron activation analysis. Aluminum concentration in the ALS and PD patients was statistically higher than in the controls, and calcium concentration was elevated too in the ALS and PD patients. Similar aluminum, calcium, and manganese distribution in spinal cord of ALS patients was found with

X-ray microanalysis [110]. Increased brain aluminum contents in two Guamian ALS cases (1.7 and 8.9 mg/kg) and in two Guamian PD cases (2.0 and 3.9 mg/kg) compared to an average of 1.38 mg/kg in 4 normal subjects were measured with EAAS and reported by Traub et al. [89]. Compared with normal subjects and PD patients, aluminum, silicon, calcium, vanadium, iron, and zinc contents were increased in the frontal cortex of ALS patients [61]. Measured in 26 brain regions, aluminum contents were markedly elevated in 2 of 6 ALS patients compared to 5 patients who did not showed neurological abnormalities. Mean aluminum concentrations in brain were 88 and 136 mg Al/kg dry weight in the two ALS cases, while 26 and 23 mg Al/kg in the other four cases and controls [103, 104]. High aluminum concentrations were found, using SEM with energy-dispersive spectrometry, in NFT-bearing neurons from ALS-PD and nonafflicted patients [70], and aluminum and calcium were co-localized in the NFT-bearing neurons. Utilizing wavelength-dispersive spectrometry coupled with electron beam X-ray microprobe analysis, Garruto found co-localized aluminum and calcium in the NFTs of two Guamian PD patients but not in the non-NFT-containing regions in brain of either PD patients or two normal lifelong Guamian residents [34]. The highest calcium and aluminum concentrations were semiquantitatively estimated as 7200 and 500 mg/kg dry weight, respectively. The average brain aluminum concentration (179 mg/kg dry weight) in six Guam PD cases was higher than seven Chamorro controls (57 mg/kg dry weight) [113]. Using laser microprobe mass spectroscopy, aluminum and calcium were found in the cytoplasm of hippocampal neurons bearing NFTs [71]. Also, using secondary ion mass spectrometry, aluminum and calcium were found to be associated with NFT-bearing hippocampal neurons of PD patients [34]. Using histochemical staining, Piccardo visualized aluminum in the hippocampus, spinal cord, and frontal cortex in most of three Guamian ALS patients and five PD patients who had NFTs in brains, but not in the five neurologically and neuropathologically normal Guamian or Caucasian patients [72]. Staining for aluminum was observed in the cytoplasm, nucleoli, neuropil, white matter, and some endothelial cells and walls of cerebral vessels, and X-ray microanalysis confirmed the existence of aluminum in aforementioned tissue and cell organelles. Neutron activation analysis results showed that aluminum contents in brains were higher in three Guamian demented cases than in four non-demented controls. High calcium contents in gray and white matter and low zinc contents in gray matter were also observed in the Guamian demented cases [105]. Using PIXE, extremely high aluminum contents were detected in the lumbar spinal cord and hippocampus of ALS patients from Guam and the Kii peninsula of Japan, compared with those in sporadic ALS cases and controls [46]. Aluminum content positively correlated with iron and copper contents, negatively correlated with zinc content in the neural tissue, and negatively correlated with calcium and magnesium concentrations in the birthplace area's rivers [105]. Toenail aluminum contents, often used as an indicator of metal exposure, did not show difference between 22 ALS patients and 40 controls; the median values were 34.5 mg Al/kg in the former and 37.5 in the latter, respectively [8]. Aluminum contents of the hippocampal gyrus, caudate nucleus, globus pallidus, and substantia nigra, as well as in the liver, kidney, and spleen, in four Parkinson's

disease cases were significantly higher than those in the five patients without neurological abnormalities [102].

1.4.5 Aluminum and Neurodevelopmental Toxicity

Aluminum, due to its ubiquitous existence everywhere, may contaminate everything, including commercial intravenous-feeding solutions for premature infants, and induce potential neurotoxicity. Bishop et al. randomly assigned 227 premature infants whose gestational ages were less than 34 weeks and birth weights were less than 1850 g into 2 groups and received either standard or specially constituted, aluminum-depleted intravenous-feeding solutions before they could begin enteral feeding. The authors assessed neurologic development of the 182 surviving infants who could be tested using the Bayley Scales of Infant Development at 18 months of age. The 90 infants intravenously fed with standard feeding solution showed a mean (±SD) Bayley Mental Development Index of 95 ± 22, while 92 infants intravenously fed with aluminum-depleted solution showed 98 ± 20 ($P = 0.39$). In a planned subgroup analysis on infants, whose intravenous-feeding duration exceeded the median and who did not show neuromotor impairment, the mean value of the Bayley Mental Development Index for the 39 infants intravenously fed with the standard solutions were 92 ± 20, and that of the 41 infants intravenously fed with the aluminum-depleted solutions were 102 ± 17 ($P = 0.02$). The infants intravenously fed with the standard solutions were significantly more likely than the infants intravenously fed with the aluminum-depleted solutions to show a Mental Development Index of less than 85 (39%, vs. 17%; $P = 0.03$), increasing their risk of subsequent educational problems. In all 157 infants without neuromotor impairment, increasing aluminum exposure was associated with reducing Mental Development Index ($P = 0.03$), with an adjusted loss of one point per day for infants intravenously fed with the standard solutions. The authors concluded that, in preterm infants, prolonged intravenous feeding with solutions containing aluminum is associated with impaired neurologic development [9].

María de Jesús Ramírez-Altamirano et al. conducted a study on newborns including 8 infants with neural tube defect and 15 infants without this defect. The parents of infants with neural defects confirmed their exposure to aluminum and other 18 inorganic elements. The aluminum content in hair samples was measured with inductively coupled plasma spectroscopy (ICP-MAS). In the hair of infants with neural tube defects, the aluminum content was 152.77 ± 51.06 μg/g, doubled the value of normal infants (76.24 ± 27.89 μg/g). Association between hair metal contents (aluminum plus silver, aluminum plus potassium, silver plus potassium, and potassium plus sodium) and neural tube defects was found at 75th percentile. The authors thought the metals including aluminum may be risk factors in inducing neural tube defects [76].

1.5 Conclusions

Aluminum is a certain neurotoxic agent which exists widely in the environment, including air, water, processed foods, vaccines, medications, and skin protection products, causes neuropsychological and neurological impairment which displays cognitive impairment and even dementia, and is thought to be related to occurrence of Alzheimer's disease (AD), Parkinson's disease (PD), and even other neurodegenerative diseases such as ALS. It may affect neurodevelopment too. The aluminum exposure in living environment is associated with pollution conditions and industrialization levels and influenced by a lot of factors, while the occupational aluminum exposure depends on the air aluminum concentration in workplace. AD prevalence and incidence are increased in populations exposed to high aluminum concentrations compared to those exposed to low aluminum levels. Though the exact etiology–disease relation between aluminum and AD is still not assured, large and rigorously controlled or less rigorously controlled prospective and retrospective human studies have examined the aluminum levels in drinking water supplied to different geographic regions. Those studies have shown significantly increased risk for AD in human populations that routinely consume water containing $\geq$0.1 mg/l aluminum compared to those that routinely consume water in regions with aluminum levels below 0.1 mg/l. Though only one case of AD in occupationally Al-exposed workers was reported both clinically and pathologically, cognitive impairment in aluminum-exposed workers was widely reported in a lot of countries by many authors. In conclusion, aluminum can impair central nervous system and induce cognitive impairment and even Alzheimer's disease.

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