

## UC Irvine

### UC Irvine Previously Published Works

**Title**

Low levels of aluminum can lead to behavioral and morphological changes associated with Alzheimer's disease and age-related neurodegeneration

**Permalink**

<https://escholarship.org/uc/item/5c15r7xj>

**Author**

Bondy, Stephen C

**Publication Date**

2016

**DOI**

10.1016/j.neuro.2015.12.002

Peer reviewed



## Review

# Low levels of aluminum can lead to behavioral and morphological changes associated with Alzheimer's disease and age-related neurodegeneration



Stephen C. Bondy

*Environmental Toxicology Program, Center for Occupational and Environmental Health, Department of Medicine, University of California, Irvine, CA 92697-1830, USA*

## ARTICLE INFO

*Article history:*

Received 29 September 2015  
 Received in revised form 1 December 2015  
 Accepted 1 December 2015  
 Available online 12 December 2015

*Keywords:*

Aluminum toxicity  
 Brain senescence  
 Neurological disease  
 Neuroinflammation  
 Oxidative stress

## ABSTRACT

Aluminum (Al) is a very common component of the earth's mineral composition. It is not essential element for life and is a constituent of rather inert minerals. Therefore, it has often been regarded as not presenting a significant health hazard. As a result, aluminum-containing agents been used in the preparation of many foodstuffs processing steps and also in elimination of particulate organic matter from water. More recently, the reduced pH of bodies of water resulting from acid rain has led to mobilization of aluminum-containing minerals into a more soluble form, and these have thus entered residential drinking water resources. By this means, the body burden of aluminum in humans has increased. Epidemiological and experimental findings indicate that aluminum is not as harmless as was previously thought, and that aluminum may contribute to the inception and advancement of Alzheimer's disease. Epidemiological data is reinforced by indications that aluminum exposure can result in excess inflammatory activity within the brain. Activation of the immune system not initiated by an infectious agent, typifies the aging brain and is even more augmented in several neurodegenerative diseases. The origin of most age-related neurological disorders is generally not known but as they are largely not of genetic derivation, their development is likely triggered by unknown environmental factors. There is a growing and consistent body of evidence that points to aluminum as being one such significant influence. Evidence is presented that reinforces the likelihood that aluminum is a factor speeding the rate of brain aging. Such acceleration would inevitably enlarge the incidence of age-related neurological diseases.

© 2015 Elsevier Inc. All rights reserved.

## Contents

1. Aluminum in the Environment . . . . .	223
2. Transitory exposure to high levels of aluminum can result in neurological disturbance. . . . .	223
3. Inflammation is pronounced in the aging brain, and this is further elevated in several neurodegenerative disorders . . . . .	224
4. Epidemiological evidence of a relation between aluminum intake and the incidence of Alzheimer's disease . . . . .	224
5. Link between aluminum exposure and neurodegenerative conditions other than Alzheimer's disease . . . . .	225
6. Experimental results from animals support a causal relation between aluminum exposure and harmful effects on brain function . . . . .	225
7. Morphological and molecular changes produced in the brain by aluminum . . . . .	226
8. Is the passage of Al from the environment to the brain large enough to justify disquiet? . . . . .	226
9. Why does the neurological outcome of exposure to environmental levels of aluminum remain contested? . . . . .	226
10. Conclusions . . . . .	226
References . . . . .	227

*E-mail address:* [scbondy@uci.edu](mailto:scbondy@uci.edu).

<http://dx.doi.org/10.1016/j.neuro.2015.12.002>

0161-813X/© 2015 Elsevier Inc. All rights reserved.

## 1. Aluminum in the Environment

Aluminum (Al) is the third most abundant element in the earth's crust (Priest et al., 1988). It was only in 1825 that this metal was isolated in its elemental metallic form by the Danish physicist Hans Oersted (Sigel and Sigel, 1988). Al products have many modern applications. Adding aluminum sulfate and lime to water causes aluminum hydroxide formation, which leads to coagulation of pollutants. This procedure is used widely for water clarification in reservoirs. Al-containing materials are also commonly found in foods. These include emulsifying agents in processed cheese, firming agents in pickles, baking powder, and several food colorings. These aluminum-based colors also have cosmetic applications. Infant formulae can have a significant aluminum content (Dabeka et al., 2011; Burrell and Exley, 2010). Concentrations as high as 1.8 mM Al can be reached in the fruit juice resulting when acidic fruit is boiled in aluminum cookware (Fimreite et al., 1997). Drinking water has variable Al content. Several cities have reported concentrations as high as 0.4–1 mg/L of aluminum in their water. Although the health effects of aluminum on humans are not definitive, the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives lowered the allowable intake of aluminum in 2006 – from 7 mg/kg body weight to 1 mg/kg body weight per week. That is equivalent to 63 mg of aluminum per week for a 140-pound adult. The average commercial muffin alone has been reported to contain 28 mg of aluminum.

Many medicines contain Al salts, notably aluminum oxide is used as an effective adjuvant in vaccines in order to promote immune activation. Antiperspirants, buffered aspirin and antacids commonly contain Al (300–600 mg/tablet).

The most common form of human exposure to Al is by way of the gastrointestinal tract. The rate of absorption here is around 0.2% (Priest et al., 1988). Once Al salts are transferred to the vascular system in the blood, most of the metal is bound to transferrin (Harris et al., 2003). Al<sup>3+</sup> can enter the nervous system by transport across the blood–brain barrier using receptor-mediated endocytosis of transferrin. Approximately 0.005% of the aluminum-protein complexes enter the brain by this means (Yokel et al., 2001).

Al in the environment was originally considered to be innocuous, because Al salts form monomeric hydroxy compounds in water which start to form increasingly high molecular weight complexes as the solution ages. Because of the formation of these colloidal insoluble Al species, its absorption was thought to be restricted. However, Al compounds are known to be toxic to both plants (Kochian and Jones, 1997) and animals (Sparling and Campbell, 1997) and there has been an increased disquiet concerning the metal's potentially adverse effects on human health (LaZerte et al., 1997). While concerns about Al toxicity to humans have been expressed for over 80 years, the medical establishment has continuously tended to discount them. For example an article in the *Journal of the American Medical Association* in 1935 stated, "Propaganda as to possible dangers resulting from the use of aluminum cooking vessels is so persistent that one suspects ulterior motives in its background" (Monier-Williams, 1935).

The increasing prevalence of acid rain as a result of fossil fuel combustion can lead to the liberation of larger amounts of Al salts from insoluble minerals, resulting in greater bioavailability (Smith, 1996).

## 2. Transitory exposure to high levels of aluminum can result in neurological disturbance

The possibility of Al salts constituting a risk factor in enhancing the likelihood of neurological disease has been originally raised by

a number of clinical studies. Thus, hemodialysis of patients with severe kidney disease has led to toxic levels of Al in the blood, from exposure to aluminum in dialysis fluid and from the administration of high levels of aluminum-containing phosphate binders among patients who cannot excrete it. The resulting aluminum-induced dialysis encephalopathy following hemodialysis is accompanied by elevated levels of Al in the brain (Russo et al., 1992) and ingestion of Al salts can lead to the deposition of insoluble Al-containing materials within the brain (Bowdler et al., 1979). Clinical status is improved by therapeutic use of an Al chelator, desferrioxamine (Erasmus et al., 1995). Blood concentrations of Al as high as 7 μM, have been found in dialysis patients even in the absence of overt dementia (Altmann et al., 1987). Aluminum-induced encephalopathy also occurs in patients with kidney failure, treated with bladder irrigation using 1% alum (Phelps et al., 1999). A form of encephalopathy has been reported in workers in the aluminum industry, and this is characterized by intellectual deficits, loss of muscle control, tremor and spinocerebellar degeneration (Polizzi et al., 2002). A typical report concerns a chronic renal failure patient, who was treated phosphate-binding Al-hydroxy gels for a prolonged period. And then developed Al-induced encephalopathy nine months prior to death. Post-mortem neuropathology showed pronounced proliferation of microglia and astrocytes in specific brain areas (Shirabe et al., 2002).

Abnormal neurological signs have also been seen in some patients receiving intramuscular injections of Al-containing vaccines (Couette et al., 2009). In consequence, the World Health Organization (WHO) Vaccine Safety Advisory Committee has recognized that there may be a subset of predisposed individuals who may be sensitive to Al adjuvants (Authier et al., 2001). Overall, there is good evidence that high levels of aluminum exposure can have adverse effects on human health.

In the past, inhalation of Al in the form of the powdered oxide was used as a prophylactic agent against silicotic lung disease of miners (Crombie et al., 1944). The procedure was described as beneficial in an animal model of silicosis (Dubois et al., 1988) and continued despite the conclusion that humans suffering from silicosis, did not appreciably benefit from Al treatment (Kennedy, 1956). Harmful effects of inhaled Al, especially upon brain function, were later described (Rifat et al., 1990). More recently, a major accidental exposure of a rather large population to excessive amounts of Al occurred in Camelford, U. K. caused by the accidental release of large amounts of Al sulfate into a nearby reservoir. The neurological consequences from this mishap are being studied and there is already evidence of harmful effects on neurological function in some of the exposed population (Altmann et al., 1999). Pathological examination of the brain a person who was exposed to Al at Camelford and later died of an undetermined neurological condition, disclosed early-onset beta amyloid angiopathy in the cerebral cortical and leptomeningeal blood vessels. High Al concentrations were also present in the more seriously affected regions of the cortex (Exley and Esiri, 2006).

Correlative changes are never sufficient to irrefutably demonstrate causation and it has been suggested that that Al entry into the brain consequent to damage to the blood–brain barrier as a secondary event. However, dialysis encephalopathy can be treated with some success using the trivalent metal chelator desferrioxamine. This indicated that Al is directly neurotoxic (McLachlan et al., 1991). These results have not been followed up in recent years, perhaps partly due to the unfavorable side effects of desferrioxamine treatment that include muscle pain, nausea, and erythema and visual deficits. There may be a lack of interest by pharmaceutical companies in a promotion of a drug that is not patentable. Treatment of aluminum-related bone disease using desferrioxamine can mobilize Al from deposits in bone, has been reported to lead to elevated serum Al and to the appearance of

symptoms resembling dialysis dementia (Sherrard et al., 1988). While desferrioxamine is not a specific Al chelator, a causal relation between high circulating levels of Al and dementia is indicated by these reports. Other evidence of the neurotoxicity of relatively high levels of Al comes from various clinical reports. One such case resulting in a fatal outcome, implicated aluminum-containing cements used in resection of an acoustic neuroma (Reusche et al., 2001).

### 3. Inflammation is pronounced in the aging brain, and this is further elevated in several neurodegenerative disorders

Aging of the brain is characteristically attended by increased levels of inflammation (David et al., 1997; Sharman et al., 2004). Neuroinflammatory changes become more pronounced during normal aging in spite of the lack of identifiable immune stimuli (Sharman et al., 2008; Lucin and Wyss-Coray, 2009). A further worsening of inflammation appears to contribute to pathogenic changes associated with many age-related neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). The activated astrocyte count is elevated in AD and this is especially pronounced at the loci of senile plaques (Cullen, 1997). In the hippocampus of AD patients, there is an up-regulation of expression of pro-inflammatory genes (Colangelo et al., 2002), together with elevated concentrations of pro-inflammatory cytokines in brain (Zhao et al., 2003) and cerebrospinal fluid (Sun et al., 2003).

AD is accompanied by depositions of the toxic amyloid  $\beta$ -peptide ( $A\beta$ ), produced from amyloid- $\beta$  precursor protein ( $A\beta$ PP) by proteolytic processes. The AD brain contains reactive microglia, producing proinflammatory cytokines and acute phase proteins, in proximity to  $A\beta$ -containing neuritic plaques (Mrak et al., 1995; Styren et al., 1998). Nasally instilled aluminum nanoparticles have also been shown to reach the brain by way of the olfactory tract, and this leads to activation of both pro- and anti-inflammatory kinases (Kwon et al., 2013).

Aluminum salts can promote  $A\beta$  aggregation in vitro (Exley, 1997; Bondy and Truong, 1999; Bolognin et al., 2011), and treatment of transgenic mice over-expressing  $A\beta$ PP, with Al salts in the drinking water, leads to oxidative stress,  $A\beta$  deposition, and plaque formation in the brain (Pratico et al., 2002). However two recent studies on Al and the promotion of Alzheimer pathology or behavior has brought this finding into question (Poirier et al., 2011; Akiyama et al., 2012). An incipient generalization may be that aluminum's behavioral effects are clearest in normal aging animals while harder to detect in mutant strains of animals that are already predisposed to plaque formation and memory deficits (Ribes et al., 2008).

PD is a neurological disease whose hallmarks include abnormally elevated levels of both oxidative and inflammatory events (Selley, 2005). This disease is also characterized by activation of microglia activation and the presence of high levels of pro-inflammatory cytokines (Nagatsu and Sawada, 2005). The use of non-steroidal anti-inflammatory drugs (NSAIDs) may delay the onset and progression of PD (Hald et al., 2007).

When mice are treated with a wide-ranging inflammatory stimulus such as lipopolysaccharide (LPS), levels of inflammatory cytokines are rapidly elevated in serum and liver, but return to basal levels within 1 week. However, such treatment leads to inflammatory cytokine TNF- $\alpha$  being chronically maintained at high levels without returning to resting levels in the brain for over 10 months, a significant fraction of the mouse lifespan. This elevation is associated with both microglial activation and continuing neuronal death (Qin et al., 2007). In consequence, the aging brain can gradually accumulate evidence of prior insults

until a permanently damaging degree of inflammatory activity is reached and maintained. These findings offer a clue as to why the aged brain shows evidence of permanent inflammation with age (Bondy and Sharman, 2010). The responses to short-lived inflammatory events such as infections, which involve the whole body, may be prolonged in the CNS for an extended period (Shi et al., 2003; Bilbo et al., 2005; Galic et al., 2008). This chronic state of inflammation can be a self-promoting process may play an important role in advancing neurodegeneration (Block et al., 2007; Lucin and Wyss-Coray, 2009). Many age-related neurological diseases involve the appearance of an even higher level of inflammation than that found in normal brain aging (Bondy, 2010).

### 4. Epidemiological evidence of a relation between aluminum intake and the incidence of Alzheimer's disease

Early reports of the neurotoxicity of Al such as those with dialysis dementia involved relatively brief exposure to high levels of Al. More recently and more controversially, adverse effects of chronic exposures to lower levels of Al have been described. The finding of high levels of Al in the brains of patients with AD relative to controls has been reported [see above] and levels of Al are also found higher in less common neurological disorders including the Guamanian Parkinsonian-ALS complex and Hallervorden-Spatz disease (Eidelberg et al., 1987; Garruto et al., 1988). This has raised the question of whether Al plays a contributory role in the initiation and progression of a variety of neurological disorders (Kawahra and Kato-Negishi, 2011).

Chelation therapy in order to reduce the Al burden in AD patients has been reported as beneficial (McLachlan et al., 1991; Jansson, 2001) and new more Al-selective chelators for potential use in AD treatment have recently been developed (Shin et al., 2003).

A important indication of a link between exposure to Al and neurodegenerative diseases is the growing number of population studies linking the Al content of drinking water as being proportional to the degree of incidence of neurological disease. An early epidemiological study by McLachlan et al. (1996) correlated the risk of developing Alzheimer's disease with residing in areas where Al concentrations in the municipal drinking water are 100 mg/L or greater. A dose-response relationship between the concentration of Al in the drinking water and risk of developing AD was found. A more recent work, examining elderly populations, also reported a similar link between exposure and the prevalence of AD (Rondeau et al., 2009).

While the underlying mechanism by which Al exerts its effects is uncertain, in several instances Al has been shown to promote events connected to neurodegenerative changes in AD. Some occupational epidemiological studies have focused on specific groups of workers such as some groups of welders exposed to high levels of Al. While one report found no significant correlation between Al inhalation among welders and neurobehavioral performance (Kiesswetter et al., 2009), another group reported significant dose-related behavioral deficits in Al welders (Giorgianni et al., 2014). This latter paper emphasized that the tests most susceptible to Al exposure, involved complex attention and memory performance.

The relation between Al and Alzheimer's disease appears stronger than that for other neurological disorders but this may be because the much higher prevalence of AD than other neurodegenerative diseases facilitates epidemiological research. However, AD is also associated with other metal imbalances such as major depression of copper levels and the issue of causality remains elusive (Akatsu et al., 2012; Exley et al., 2012).

The case for a causal relation of the association between Al exposure and AD is reinforced by findings of excessive levels of Al

in post-mortem analyses of brain tissue from AD patients. The original description of this connection (Perl and Brody, 1980) was disputed due to the problem of obtaining accurate Al analyses and the probability of sample contamination (Bjertness et al., 1996). However, a wide range of more sophisticated analytical procedures including laser microprobe mass analysis (Bouras et al., 1997), instrumental neutron activation (Andrasi et al., 2005), an improved graphite furnace atomic absorption method (Xu et al., 1992) or energy-dispersive X-ray spectroscopy combined with transmission electron microscopy (Yumoto et al., 2009), have all basically confirmed the original findings. Laser microprobe mass analysis revealed the Al to be largely situated within the neurofibrillary tangles associated with AD (Bouras et al., 1997). Increased levels of Al have also been reported in the cerebral arteries of AD patients (Bhattacharjee et al., 2013).

Systemic aluminum can induce AD-like behavioral deficits in treated rats and this elevated has been correlated to  $\alpha$ - and  $\beta$ -secretase subtypes, together which appears to lead to increased levels of A $\beta$ 1–42 (Wang et al., 2014). In addition to leading to behavioral deficits, chronic exposure to dietary Al also leads to elevated levels of amyloid precursor protein (Walton and Wang, 2009).

The consequences of chronic exposure to rather low levels of Al are difficult to isolate as they involve seeking evidence of an altered incidence of relatively common neurological diseases such as sporadic AD. Many possible confounding environmental factors exist that may influence AD incidence. A survey, assembling results from many sources and many areas but focused on Al-containing antacid use, reported that this association is significant (Flaten, 2001). Another meta-analysis of nine studies concluded that there was evidence that urinary Al concentrations below 135 mg/l have an impact on cognitive performance (Meyer-Baron et al., 2007).

There are contradictory assertions on the hazard posed by levels of aluminum present in the environment. These range from the claims that “chronic aluminum intake can cause Alzheimer’s disease” (Walton, 2014) and “aluminum may be the single most aggravating and avoidable factor related to AD” (Tomljenovic, 2011), and the more qualified “exposure to aluminum dust may possibly increase the risk of cardiovascular disease and dementia of the Alzheimer’s type” (Peters et al., 2013). Negative reports include the lack of finding of any correlation between AD incidence and occupational exposure to aluminum (Santibáñez et al., 2007), and the conclusion that “lifetime occupational exposure to Al is not likely to be an important risk factor for AD” (Flaten, 2001). A recent review reports that “consideration of the published research concerning aluminum’s role in AD indicates that not one of the four Bradford Hill criteria deemed necessary to establish causation with respect to neurocognitive disorders such as AD has been satisfied” (Lidsky, 2014) while another review states that precisely these criteria have been met (Walton, 2014). This illustrates the need for more study rather than more polemics.

A recent overview suggests the possibility that conflicting results may in part be due to lack of consideration of silicate levels in drinking water in many reports. The presence of silicates in water can act to protect against the toxic effects of Al in the same water, presumably since the aluminosilicates do not readily cross the gut (Krewski et al., 2007; Foglio et al., 2012). It has been reported that aluminum in drinking water can increase the risk of cognitive impairment when the silica concentrations were low (Rondeau et al., 2009), and silicates may have utility in reducing aluminum hazards (Gillette Guyonnet et al., 2007).

In summary, despite a voluminous literature, the relation between AD and aluminum remains opacity. This is in part due to the great difficulty in unambiguous interpretation of epidemiological findings. Thus findings from laboratory results under well-defined conditions and those from population studies are

not yet sufficiently and conclusively correlated so as to result in a unanimous recognition of the hazards of environmental aluminum.

## 5. Link between aluminum exposure and neurodegenerative conditions other than Alzheimer’s disease

The connection between Al and less common neurological disorders is uncertain. Aluminum oxyhydroxide (alum) is widely used as a vaccine adjuvant (Girard, 2005; Sutton et al., 2009; Chang et al., 2010; Alvarez-Soria et al., 2011; Shoenfeld and Agmon-Levin, 2011), and phagocytosed alum particles can accumulate in the brain where they may then be re-solubilized by the acidic pH of lysosomes (Gherardi et al., 2015). Injection of alum into neonatal mice in amounts designed to correlate to those used in pediatric vaccination schedules, may lead to behavioral changes, persisting into adulthood (Shaw et al., 2013). There are still significant amounts of Al in most infant formulae (100–756 mg/l) and this has been proposed to constitute a developmental hazard (Chuchu et al., 2013).

There is a series of articles reporting that use of vaccines may be associated with increased incidence of multiple sclerosis. Al excretion has been reported as elevated in MS patients (Exley et al., 2006). On the other hand, Al-containing adjuvants within a vaccine have also been suggested to have prophylactic value in the treatment of MS (Wällberg et al., 2003).

There is also evidence linking Al and Parkinson’s disease, PD. An association has been made between the frequency of gastric ulcers, and PD, and it has been proposed that this linkage might be due to the higher usage of Al-containing antacids by those suffering from ulcers (Altschuler, 1999). Other indirect evidence in support of a connection between Al and PD is the ability of Al to activate monoamine oxidase B, an enzyme that is elevated with age and reaches even greater levels in PD (Zatta et al., 1999). Monoamine oxidase B is able to promote alpha-synuclein fibril formation and this may account for the observed association between neurotoxic metals and PD (Uversky et al., 2001). The initiation of inflammatory processes by activation of the transcription factor NF- $\kappa$ B was found to occur after simultaneous treatment of experimental animals with the dopaminergic neurotoxin, MPTP and low levels of Al in drinking water (Li et al., 2008), in a synergistic manner.

Neuropathological changes and behavioral deficits resembling those found in ALS have been found in animals treated with Al salts models. Specifically, injection of Al-containing adjuvants at levels comparable to those that are administered to human adults resulted in the death of motor neurons, impairments in motor function, decrements in spatial memory capacity in young mice and significant increases in activated astrocytes and microglia (Petrik et al., 2007; Shaw and Petrik, 2009). Blood and urine levels of Al may also be elevated in ALS (Perl et al., 1982) but there is disagreement concerning this (Qureshi et al., 2008).

## 6. Experimental results from animals support a causal relation between aluminum exposure and harmful effects on brain function

Clinical findings on aluminum neurotoxicity, are supported by numerous experimental animal models where systemically administered Al caused behavioral deficits. These include reports of in-coordination (Bowdler et al., 1979), changes in reactivity and neuropathological changes reminiscent of those found with brain aging (Miu et al., 2004).

These studies have entailed treatment with concentrations of Al that are not commonly encountered among human populations. However, other studies that better reflect common human exposures have been conducted using more extended treatment



with lower levels of Al resembling those found in some water supplies or exposures more closely paralleling human intake. One such study using Al in the drinking water, found indications of heightened inflammatory activity within brain tissue (Campbell et al., 2004) such as elevated levels of pro-inflammatory cytokines, and nitric oxide synthetase. These changes were found after Al salts had been in the drinking water of mice for three months at concentrations below those found in some residential water supplies. Other studies found that exposure to low levels of Al led to elevation of glial fibrillary astrocytic protein (GFAP) a marker of astrocytic activation (Yokel and O'Callaghan, 1998). Additional persuasive data on the probable harmfulness of Al, comes from observations of cognitive and neuropathological changes characteristic of AD in aged rats after chronic exposure to Al equivalent to that ingested by some human populations (Walton, 2009a,b; Walton and Wang, 2009; Walton, 2012).

If the gradual inflammatory changes that characterize neurosenescence were furthered by the extended presence of low levels of Al, this would reinforce the excess inflammatory events associated with the evolution of many age-related neurodegenerative disorders. Thus, Al may act predominantly by promoting the rate of brain aging. This acceleration could form a platform to then enable an increased incidence of a range of distinctive neurodegenerative diseases.

### 7. Morphological and molecular changes produced in the brain by aluminum

A clear mechanistic understanding of the molecular events underlying Al neurotoxicity remains elusive. Despite the chemical inertness of its salts, there are many potential mechanisms by which Al can promote neurotoxic events (Tomljenovic, 2011). The induction of glial activation and initiation of macrophage responsivity by Al complexes has been frequently described many times (Evans et al., 1992; Gorell et al., 1999; Platt et al., 2001) but the means by which Al salts promote inflammatory events are unclear. Aluminum salts can provoke inflammatory glial responses in isolated systems as well as in intact animals, and so it is likely that they can act directly upon responsive glial cells (Campbell et al., 2002).

Aluminum is also capable of promoting free radical generation, despite the fact that it is not a valence-labile metal and does not have a strong affinity for sulfhydryl radicals. It may achieve this by catalyzing the redox activity of trace amounts of iron. This ability of aluminum to potentiate the pro-oxidant properties of iron is evident even in the absence of biological tissue or proteins (Bondy et al., 1998). The mechanism of action may entail providing a colloidal surface for the sequestration of iron. This partial complexation allows iron to undergo Fenton transformations and such redox flux leads to production of reactive oxygen species (Alexandrov et al., 2005; Bondy, 2009; Ruipe rez et al., 2012; Bondy, 2009). A similar promotion of iron's pro-oxidant potential by an apparently inert mineral has been shown for silica fibers (Napierska et al., 2012). More recently it has been proposed that, since aluminum has an unusually high charge density  $Z^2/r$ , this can account for its ability to compact A-T rich chromatin domains leading to repression of specific genes (Lukiw, 2010).

### 8. Is the passage of Al from the environment to the brain large enough to justify disquiet?

The issue as to whether human aluminum intake from general environmental sources is sufficient for concern remains contentious. Drinking water can contain up to 2.7 mg Al/l, and foodstuffs up to 730 mg Al/kg (Agency for Toxic Substances and Disease Registry, 2008; Stahl et al., 2011). These estimates do not include

sources of unusually high aluminum intake such as antacid, baking powder and some acidic fruit drinks. Overall, around 10 mg/d Al from both water and food sources is estimated to be consumed (Agency for Toxic Substances and Disease Registry, 2008). Up to 0.3% of this may be absorbed from the gut leading to plasma concentrations in the region of 0.002 mgAl/l (Yokel, 2012). However, it is likely that the uptake of aluminum from food can vary at least 10-fold depending on the chemical forms present in the intestinal tract (Aguilar et al., 2008). Brain tissue can contain over 100 times the plasma concentration of Al (0.35 mg/kg, Yokel, 2012). This selective accumulation may result from major bioconcentration by the cerebral vasculature (Bhattacharjee et al., 2013). The ensuing content of Al in the brain (c. 0.1–0.4 mg/kg, Exley, 2014) is within molarity range of 4–15 mM. This is over ten times the concentration of Al that is toxic to isolated human neuronal and glial cells (Lukiw and Pogue, 2007). For this reason, while the exact chemical nature of Al is critical in determining the extent of toxicity, the cerebral content of Al in the population is sufficiently high to be a valid cause for concern.

### 9. Why does the neurological outcome of exposure to environmental levels of aluminum remain contested?

While interest in this topic is ongoing but there is not yet an explicit recognition of the hazards of environmental Al and for the need to take more regulatory action. Examination of the history of lead toxicity can give clues that may aid in comprehending of some of the reasons underlying this failure to reach a "critical takeoff velocity." Lead has been used in manufacturing for over 3000 years and has been intermittently known to be neurotoxic since 700 B. C. Its prevalence has risen greatly in the last 200 years and, in the last two decades the harmfulness of even low levels of lead has been widely accepted. As a result, legislative efforts to minimize lead exposure have been effective. However, this was preceded by a period of heated controversy during which the lead industry accused leading scientists conducting low level lead research, of bias and fraud (summarized in Needleman, 2008).

In contrast, Al has only had broad industrial use for just over a century. As in the case of lead, the neurotoxicity of high levels of Al is not disputed. However, also paralleling the situation for lead, the toxicity of low levels of Al is fiercely contested since major economic forces are concerned. Currently, no major efforts to minimize Al levels in food or drinking water are being legislatively considered. The considerably shorter history of Al use means that we are at an earlier stage of awareness of its threat to human health than is the case with lead. It is to be hoped that the next phase in the advancement of acknowledgment of the neurotoxicity of environmental aluminum, will soon occur.

### 10. Conclusions

Although the ability of absorbed aluminum to further the onset and progression of neurodegenerative disease remains unresolved, the following conclusions are relevant and incontrovertible.

- (i) Al is widespread in the environment, ingested by humans and can reach the brain.
- (ii) Short exposure to high levels of Al can lead to clear signs of neurological damage.
- (iii) Levels of basal inflammatory activity within the brain increase with age and this is worsened in many age-related neurodegenerative conditions.
- (iv) Low concentrations of Al in the drinking water of experimental animals that correspond to those found in some population exposures, can heighten inflammatory activity within the

brain and lead to pathological transformations, which resemble those found in AD.

- (v) Overall, there is a significant body of literature showing that Al exposure leads to higher levels of inflammatory activity within the brain.

The median age in the United States is becoming longer and an increasing prevalence of chronic neurodegenerative disorders including AD, PD ALS and MS can be expected. These diseases are in the main, non-genetic, idiopathic disorders implying that they are likely to be initiated by unknown environmental factors. The triggering agent of none of these diseases has been identified. Long latent periods may take place between exposure to a harmful environmental agent and the manifestation of clinical disease. This can complicate the identification of the factors originally responsible for initiating the disease process. Since aging forms an indispensable basis for the development of neurodegenerative disorders, an acceleration of changes taking place during normal brain aging, could speed up the time of the onset and thus the incidence of all such disorders. A postulated chain of events by which Al could accelerate the development of age-related neurological disease is presented in Fig. 1.

One of the most positive approaches to alleviation of progressive neurodegenerative diseases, lies in the identification and rectifying of those environmental factors, which can hasten those changes that accompany normal aging.

The simplest way of integrating much of the data concerning Al neurotoxicity is the concept that Al can accelerate the evolution of brain aging. This could account for the epidemiological relation between Al and Alzheimer's disease, which is increasingly prevalent in a large fraction of the very elderly. It could also explain the more tenuous connection that has been proposed for Al and several of less common age-related neurological diseases. The premise behind this concept is that a non-selective component of senescence, namely an elevated state of brain immune activity is propelled by Al, leading to prolonged and futile neuroinflammation. Such a chronic state could form a basis for the emergence and progression of more specific neurological conditions.

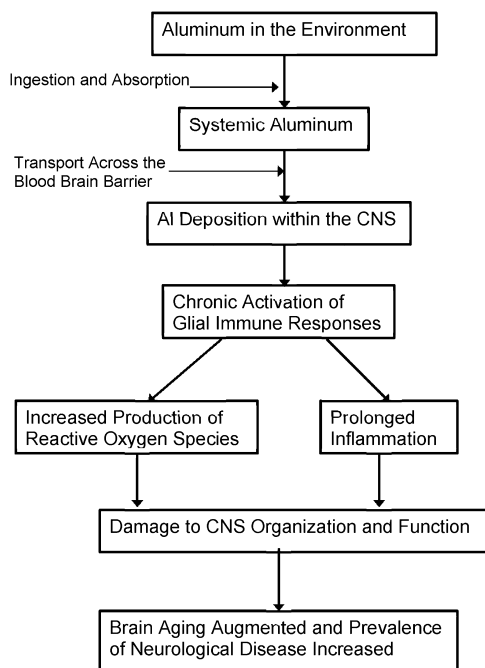


Fig. 1. Progression of events by which Al could promote age-related neurodegenerative changes.

## References

- Agency for Toxic Substances and Disease Registry, 2008. Potential for human exposure. In: *Toxicological Profile for Aluminum* US Dept. of Human Health Services, pp. 175–227.
- Aguilar, F., et al., 2008. Safety of aluminium from dietary intake. *EFSA J.* 754, 1–34.
- Akatsu, H., Hori, A., Yamamoto, T., Yoshida, M., Mimuro, M., Hashizume, Y., Tooyama, I., Yezdimer, E.M., 2012. Transition metal abnormalities in progressive dementias. *Biometals* 25, 337–350.
- Akiyama, H., Hosokawa, M., Kametani, F., Kondo, H., Chiba, M., Fukushima, M., Tabira, T., 2012. Long-term oral intake of aluminium or zinc does not accelerate Alzheimer pathology in A $\beta$ PP and A $\beta$ PP/tau transgenic mice. *Neuropathology* 32, 390–397.
- Alexandrov, P.N., Zhao, Y., Pogue, A.I., Tarr, M.A., Kruck, T.P., Percy, M.E., Cui, J.G., Lukiw, W.J., 2005. Synergistic effects of iron and aluminum on stress-related gene expression in primary human neural cells. *J. Alzheimers Dis.* 8, 117–127.
- Altmann, P., Al-Salihi, F., Butter, K., Cutler, P., Blair, J., Leeming, R., Cunningham, J., Marsh, F., 1987. Serum aluminum levels and erythrocyte dihydropteridine reductase activity in patients on hemodialysis. *N. Engl. J. Med.* 317, 80–84.
- Altmann, P., Cunningham, J., Dhanesha, U., Ballard, M., Thompson, J., Marsh, F., 1999. Disturbance of cerebral function in people exposed to drinking water contaminated with aluminum sulphate: retrospective study of the Camelford water incident. *Br. Med. J.* 319, 807–811.
- Altschuler, E., 1999. Aluminum-containing antacids as a cause of idiopathic Parkinson's disease. *Med. Hypotheses* 53, 22–23.
- Alvarez-Soria, M.J., Hernandez-Gonzalez, A., Carrasco-Garcia de Leon, S., Del Real-Francia, M.A., Gallardo-Alcaniz, M.J., Lopez-Gomez, J.L., 2011. Demyelinating disease and vaccination of the human papillomavirus. *Rev. Neurol.* 52, 472–476.
- Andrasi, E., Pali, N., Molnar, Z., Kosel, S., 2005. Brain aluminum, magnesium and phosphorus contents of control and Alzheimer-diseased patients. *J. Alzheimer's Dis.* 7, 273–284.
- Authier, F.J., Cherin, P., Creange, A., Bonnotte, B., Ferrer, X., Abdelmoumni, D., Ranoux, D., Pelletier, J., Figarella-Branger, D., Granel, B., Maisonneuve, T., Coquet, M., Degos, J.D., Gherardi, R.K., 2001. Central nervous system disease in patients with macrophagic myofasciitis. *Brain* 124, 974–983.
- Bhattacharjee, S., Zhao, Y., Hill, J.M., Culicchia, F., Kruck, T.P., Percy, M.E., Pogue, A.I., Walton, J.R., Lukiw, W.J., 2013. Selective accumulation of aluminum in cerebral arteries in Alzheimer's disease (AD). *J. Inorg. Biochem.* 126, 35–77.
- Bilbo, S.D., Biedenkapp, J.C., Der-Avakian, A., Watkins, L.R., Rudy, J.W., Maier, S.F., 2005. Neonatal infection-induced memory impairment after lipopolysaccharide in adulthood is prevented via caspase-1 inhibition. *J. Neurosci.* 25, 8000–8009.
- Bjertness, E., Candy, J.M., Torvik, A., Ince, P., McArthur, F., Taylor, G.A., Johansen, S.W., Alexander, J., Grønnesby, J.K., Bakkeiteig, L.S., Edvardson, J.A., 1996. Content of brain aluminum is not elevated in Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* 10, 171–174.
- Block, M.L., Zecca, L., Hong, J.S., 2007. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nat. Rev. Neurosci.* 8, 57–69.
- Bolognin, S., Messori, L., Drago, D., Gabbiani, C., Cendron, L., Zatta, P., 2011. Aluminum, copper, iron and zinc differentially alter amyloid-A $\beta$ (1–42) aggregation and toxicity. *Int. J. Biochem. Cell Biol.* 43, 877–885.
- Bondy, S.C., Guo-Ross, S.X., Pien, J., 1998. Mechanisms underlying the aluminum-induced potentiation of the pro-oxidant properties of transition metals. *Neurotoxicology* 19, 65–71.
- Bondy, S.C., 2009. Aluminum. In: Squire, L.R. (Ed.), *Encyclopedia of Neuroscience*, Vol. 1. Academic Press, Oxford, pp. 253–257.
- Bondy, S.C., 2010. The neurotoxicity of environmental aluminum is still an issue. *Neurotoxicology* 31, 575–581.
- Bondy, S.C., Truong, A., 1999. Potentiation of beta-folding of  $\beta$ -amyloid peptide 25–35 by aluminum salts. *Neurosci. Lett.* 267, 25–35.
- Bondy, S.C., Sharman, E.H., 2010. Melatonin, oxidative stress and the aging brain. In: Bondy, S.C., Maiese, K. (Eds.), *Oxidative Stress in Basic Research and Clinical Practice: Aging and Age-Related Disorders* Totowa. Humana Press, NJ, pp. 339–357.
- Bouras, C., Giannakopoulos, P., Good, P.F., Hsu, A., Hof, P.R., Perl, D.P., 1997. A laser microprobe mass analysis of brain aluminum and iron in dementia pugilistica: comparison with Alzheimer's disease. *Eur. Neurol.* 38, 53–58.
- Bowdler, N.C., Beasley, D.S., Fritze, E.C., Goulette, A.M., Hatton, J.D., Hessian, J., Ostman, D.L., Rugg, D.J., Schmittman, C.J., 1979. Behavioural effects of aluminum ingestion on animal and human subjects. *Pharmacol. Biochem. Behav.* 10, 505–512.
- Burrell, S.A., Exley, C., 2010. There is (still) too much aluminium in infant formulas. *BMC Pediatr.* 10, 63.
- Campbell, A., Yang, Y., Tsai-Turton, M., Bondy, S.C., 2002. Pro-inflammatory effects of aluminum in human glioblastoma cells. *Brain Res.* 933, 62–65.
- Campbell, A., Becaria, A., Lahiri, D.K., Sharman, K., Bondy, S.C., 2004. Chronic exposure to aluminum in drinking water increases inflammatory parameters selectively in the brain. *J. Neurosci. Res.* 75, 565–672.
- Chang, J., Campagnolo, D., Vollmer, T.L., Bomprezzi, R., 2010. Demyelinating disease and polyvalent human papilloma virus vaccination. *J. Neurol. Neurosurg. Psychiatry* 9, 1–3.

- Chuchu, N., Patel, B., Sebastian, B., Exley, C., 2013. The aluminium content of infant formulas remains too high. *BMC Pediatr.* 13, 162.
- Colangelo, V., Schurr, J., Ball, M.J., Pelaez, R.P., Bazan, N.G., Lukiw, W.J., 2002. Gene expression profiling of 12633 genes in Alzheimer hippocampal CA1: transcription and neurotrophic factor down-regulation and up-regulation of apoptotic and pro-inflammatory signaling. *J. Neurosci. Res.* 70, 462–473.
- Couette, M., Boisse, M.F., Maisson, P., Brugières, P., Cesaro, P., Chevalier, X., Gherardi, R.K., Bachoud-Levi, A.C., Authier, F.J., 2009. Long-term persistence of vaccine-derived aluminum hydroxide is associated with chronic cognitive dysfunction. *J. Inorg. Biochem.* 103, 1571–1578.
- Crombie, D.W., Blaisdell, J.L., MacPherson, G., 1944. The treatment of silicosis by aluminum powder. *Can. Med. Assoc. J.* 50, 318–328.
- Cullen, K.M., 1997. Perivascular astrocytes within Alzheimer's disease plaques. *NeuroReport* 8, 1961–1966.
- Dabeka, R., Fouquet, A., Belisle, S., Turcotte, S., 2011. Lead, cadmium and aluminum in Canadian infant formulae, oral electrolytes and glucose solutions. *Food Addit. Contam. Part A: Chem. Anal. Control Expo. Risk Assess.* 28, 744–753.
- David, J.P., Ghazali, F., Fallet-Bianco, C., Wattez, A., Delaire, S., Boniface, B., Di Menza, C., Delacourte, A., 1997. Glial reaction in the hippocampal formation is highly concentrated with aging in human brain. *Neurosci. Lett.* 235, 53–56.
- Dubois, F., Bégin, R., Cantin, A., Massé, S., Martel, M., Bilodeau, G., Dufresne, A., Perreault, G., Sébastien, P., 1988. Aluminum inhalation reduces silicosis in a sheep model. *Am. Rev. Respir. Dis.* 137, 1172–1179.
- Eidelberg, D., Sotrel, A., Joachim, C., Selkoe, D.I., Forman, A., Pendlebury, W.W., Perl, D.P., 1987. Adult onset Hallervorden-Spatz disease with neurofibrillary pathology. *Brain* 110, 993–1013.
- Erasmus, R.T., Kusnir, J., Stevenson, W.C., Lobo, P., Herman, M.M., Wills, M.R., Savory, J., 1995. Hyperaluminemia associated with liver transplantation and acute renal failure. *Clin. Transpl.* 9, 307–311.
- Evans, P.H., Peterhans, E., Burg, T., Klinowski, J., 1992. Aluminosilicate-induced free radical generation by murine brain glial cells in vitro: potential significance in the aetiopathogenesis of Alzheimer's dementia. *Dementia* 3, 1–6.
- Exley, C., 1997. ATP-promoted amyloidosis of an amyloid  $\beta$ -peptide. *NeuroReport* 8, 3411–3414.
- Exley, C., Esiri, M.M., 2006. Severe cerebral congophilic angiopathy coincident with increased brain aluminum in a resident of Camelford, Cornwall, UK. *J. Neurol. Neurosurg. Psychiatr.* 77, 877–879.
- Exley, C., Mamutse, G., Korchazhikina, O., Pye, E., Strekopytov, S., Polwart, A., Hawkins, C., 2006. Elevated urinary excretion of aluminum and iron in multiple sclerosis. *Mult. Scler.* 12, 533–540.
- Exley, C., House, E., Polwart, A., Esiri, M.M., 2012. Brain burdens of aluminum, iron, and copper and their relationships with amyloid- $\beta$  pathology in 60 human brains. *J. Alzheimer's Dis.* 31, 725–730.
- Exley, C., 2014. Why industry propaganda and political interference cannot disguise the inevitable role played by human exposure to aluminum in neurodegenerative diseases, including Alzheimer's disease. *Front. Neurol.* 5, 212.
- Fimreite, N., Hansen, O.O., Pettersen, H.C., 1997. Aluminum concentrations in selected foods prepared in aluminum cookware, and its implications for human health. *Bull. Environ. Contam. Toxicol.* 58, 1–7.
- Flaten, T.P., 2001. Aluminum as a risk factor in Alzheimer's disease, with emphasis on drinking water. *Brain Res. Bull.* 55, 187–196.
- Fogliò, E., Buffoli, B., Exley, C., Rezzani, R., Rodella, L.F., 2012. Regular consumption of a silicic acid-rich water prevents aluminium-induced alterations of nitrenergic neurons in mouse brain: histochemical and immunohistochemical studies. *Histol. Histopathol.* 27, 1055–1066.
- Galic, M.A., Riaz, K., Heida, J.G., Mouihate, A., Fournier, N.M., Spencer, S.J., Kalynchuk L.E., Teskey, G.C., Pittman, Q.J., 2008. Postnatal inflammation increases seizure susceptibility in adult rats. *J. Neurosci.* 28, 6904–6913.
- Garruto, R.M., Shankar, S.K., Yanagihara, R., Salazar, A.M., Amyx, H.L., Gajdusek, D.C., 1988. Low-calcium, high-aluminum diet-induced motor neuron pathology in cynomolgus monkeys. *Acta Neuropath. (Berlin)* 78, 210–219.
- Gherardi, R.K., Eidi, H., Crépeaux, G., Authier, F.J., Cadusseau, J., 2015. *Front. Neurol.* 6, 4.
- Gillette Guyonnet, S., Andrieu, S., Vellas, B., 2007. The potential influence of silica present in drinking water on Alzheimer's disease and associated disorders. *J. Nutr. Health Aging* 11, 119–124.
- Giorgianni, C.M., D'Arrigo, G., Brecciaroli, R., Abbate, A., Spataro, G., Tringali, M.A., Gangemi, S., De Luca, A., 2014. Neurocognitive effects in welders exposed to aluminium. *Toxicol. Ind. Health* 30, 347–356.
- Girard, M., 2005. Autoimmune hazards of hepatitis B vaccine. *Autoimmune Rev.* 4, 96–100.
- Gorell, J.M., Rybicki, B.A., Johnson, C., Peterson, E.L., 1999. Occupational exposure to specific metals (manganese, copper, lead, iron, mercury, zinc, aluminum and others) appears to be a risk factor for Parkinson's disease (PD) in some, but not all, case-control studies. *Neuroepidemiology* 18, 303–308.
- Hald, A., Van Beek, J., Lotharius, J., 2007. Inflammation in Parkinson's disease: causative or epiphenomenal? *Subcell. Biochem.* 42, 249–279.
- Harris, W.R., Wang, Z., Hamada, Y.Z., 2003. Competition between transferrin and the serum ligands citrate and phosphate for the binding of aluminum. *Inorg. Chem.* 42, 3262–3273.
- Jansson, E.T., 2001. Aluminum exposure and Alzheimer's disease. *J. Alzheimer's Dis.* 3, 541–549.
- Kawahra, M., Kato-Negishi, M., 2011. Link between aluminum and the pathogenesis of Alzheimer's disease: the integration of the aluminum and amyloid cascade hypotheses. *Int. J. Alzheimer's Dis.* 276393.
- Kennedy, M.C.S., 1956. Aluminum powder inhalations in the treatment of silicosis of pottery workers and pneumoconiosis of coal-miners. *Br. J. Ind. Med.* 13, 85–101.
- Kiesswetter, E., Schäper, M., Buchta, M., Schaller, K.H., Rossbach, B., Kraus, T., Letzel, S., 2009. Longitudinal study on potential neurotoxic effects of aluminum: II. Assessment of exposure and neurobehavioral performance of Al welders in the automobile industry over 4 years. *Int. Arch. Occup. Environ. Health* 82, 1191–1210.
- Kochian, L.V., Jones, D.L., 1997. Aluminum toxicity and resistance in plants. In: Yokel, R.A., Golub, M.S. (Eds.), *Research Issues in Aluminum Toxicity*. Taylor and Francis, Washington, pp. 69–90.
- Krewski, D., Yokel, R.A., Nieboer, E., Borchelt, D., Cohen, J., Harry, J., Kacew, S., Lindsay, J., Mahfouz, A.M., Rondeau, V., 2007. Human health risk assessment for aluminium, aluminium oxide, and aluminium hydroxide. *J. Toxicol. Environ. Health B Crit. Rev.* 10 (Suppl. 1), 1–269.
- Kwon, J.T., Seo Jo1, G.B., Lee, M., Kim, H.M., Shim, I., Lee, B.W., Yoon, B.I., Kim, P., Choi, K., 2013. Aluminum nanoparticles induce ERK and p38MAPK activation in rat brain. *Toxicol. Res.* 29, 181–185.
- LaZerte, B.D., Van Loon, G., Anderson, B., 1997. Aluminum in water. In: Yokel, R.A., Golub, M.S. (Eds.), *Research Issues in Aluminum Toxicity*. Taylor and Francis, Washington, DC, pp. 17–46.
- Li, H., Campbell, A., Ali, S.F., Cong, P., Bondy, S.C., 2008. Chronic exposure to low levels of aluminum alters cerebral cell signaling in response to acute MPTP treatment. *Toxicol. Ind. Health* 23, 515–524.
- Lidsky, T.I., 2014. Is the aluminum hypothesis dead? *J. Occup. Environ. Med.* 56 (5 Suppl.), S73–S79.
- Lucin, K.M., Wyss-Coray, T., 2009. Immune activation in brain aging and neurodegeneration: too much or too little? *Neuron* 64, 110–122.
- Lukiw, W.J., Pogue, A.I., 2007. Induction of specific micro RNA (miRNA) species by ROS generating metal sulfates in primary human brain cells. *J. Inorg. Biochem.* 101, 1265–1269.
- Lukiw, W.J., 2010. Evidence supporting a biological role for aluminum in chromatin compaction and epigenetics. *J. Inorg. Biochem.* 104, 1010–1012.
- McLachlan, D.R.C., Dalton, A.J., Kruck, T.P.A., Bell, M.Y., Smith, W.L., Kalow, W., Andrews, D.F., 1991. Intramuscular desferrioxamine in patients with Alzheimer's disease. *Lancet* 337, 1304–1308.
- McLachlan, D.R.C., Bergeron, C., Smith, J.E., Boomer, D., Rifat, S.L., 1996. Risk for neuropathologically confirmed Alzheimer's disease and residual aluminum in municipal drinking water employing weighted residential histories. *Neurology* 46, 401–405.
- Meyer-Baron, M., Schäper, M., Knapp, G., van Thriel, C., 2007. Occupational aluminum exposure: evidence in support of its neurobehavioral impact. *Neurotoxicology* 28, 1068–1078.
- Miu, A.C., Olteanu, A.I., Miclea, M., 2004. A behavioral and ultrastructural dissection of the interference of aluminum with aging. *J. Alzheimer's Dis.* 6, 315–328.
- Monier-Williams, G.W., 1935. Aluminum in Food. Report 78 on Public Health and Medical Subjects Ministry of Health, London.
- Mrak, R.E., Sheng, J.G., Griffin, W.S.T., 1995. Glial cytokines in Alzheimer's disease: review and pathogenic implications. *Hum. Pathol.* 26, 816–823.
- Nagatsu, T., Sawada, M., 2005. Inflammatory process in Parkinson's disease: role for cytokines. *Curr. Pharm. Des.* 11, 999–1016.
- Napierska, D., Rabolli, V., Thomassen, L.C., Dinsdale, D., Princen, C., Gonzalez, L., Poels, K.L., Kirsch-Volders, M., Lison, D., Martens, J.A., Hoet, P.H., 2012. Oxidative stress induced by pure and iron-doped amorphous silica nanoparticles in subtoxic conditions. *Chem. Res. Toxicol.* 25, 828–837.
- Needleman, H.L., 2008. The case of Deborah Rice: who is the Environmental Protection Agency protecting? *PLoS Biol.* 6, e129, <http://dx.doi.org/10.1371/journal.pbio.0060129>.
- Perl, D.P., Brody, A.R., 1980. Alzheimer's disease: X-ray spectrometric evidence of aluminum accumulation in neurofibrillary tangle-bearing neurons. *Science* 208, 297–299.
- Perl, D.P., Gajdusek, D.C., Garruto, R.M., Yanagihara, R.T., Gibbs, C.J., 1982. Intra-neuronal aluminum accumulation in amyotrophic lateral sclerosis and Parkinsonism-dementia of Guam. *Science* 217, 1053–1055.
- Peters, S., Reid, A., Fritsch, L., de Klerk, N., Musk, A.W., 2013. Long-term effects of aluminium dust inhalation. *Occup. Environ. Med.* 70, 864–868.
- Petrik, M.S., Wong, M.C., Tabata, R.C., Garry, R.F., Shaw, C.A., 2007. Aluminum adjuvant linked to Gulf War illness induces motor neuron death in mice. *Neuromol. Med.* 9, 83–100.
- Phelps, K.R., Naylor, K., Brien, T.P., Wilbur, H., Haqqie, S.S., 1999. Encephalopathy after bladder irrigation with alum: case report and literature review. *Am. J. Med. Sci.* 318, 181–185.
- Platt, B., Fiddler, G., Riedel, G., Henderson, Z., 2001. Aluminum toxicity in the rat brain: histochemical and immunocytochemical evidence. *Brain Res. Bull.* 55, 257–267.
- Poirier, J., Semple, H., Davies, J., Lapointe, R., Dziwienka, M., Hiltz, M., Mujibi, D., 2011. Double-blind, vehicle-controlled randomized twelve-month neurodevelopmental toxicity study of common aluminum salts in the rat. *Neuroscience* 193, 338–362.
- Polizzi, S., Pira, E., Ferrara, M., Bugiani, M., Papaleo, A., Albera, R., Palmi, S., 2002. Neurotoxic effects of aluminum among foundry workers and Alzheimer's disease. *Neurotoxicology* 23, 761–774.



- Pratico, D., Uryu, K., Sung, S., Tang, S., Trojanowski, J.Q., Lee, V.M., 2002. Aluminum modulates brain amyloidosis through oxidative stress in APP transgenic mice. *FASEB J.* 16, 1138–1140.
- Priest, N.D., Talbot, R.J., Newton, D., Day, J.P., King, S.J., Fifield, L.K., 1988. Uptake by man of aluminum in a public water supply. *Hum. Exp. Toxicol.* 17, 296–301.
- Qin, L., Wu, X., Block, M.L., Liu, Y., Breese, G.R., Hong, J.S., Knapp, D.J., Crews, F.T., 2007. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *Glia* 55, 453–462.
- Qureshi, M., Brown, R.H., Rogers, J.T., Cudkowicz, M.E., 2008. Serum ferritin and metal levels as risk factors for amyotrophic lateral sclerosis. *Open Neurol. J.* 2, 51–54.
- Reusche, E., Pilz, P., Oberascher, G., Lindner, B., Egensperger, R., Gloeckner, K., Trinka, E., Iglseder, B., 2001. Subacute fatal aluminum encephalopathy after reconstructive otoneurosurgery: a case report. *Hum. Pathol.* 32, 1136–1140.
- Ribes, D., Colomina, M.T., Vicens, P., Domingo, J.L., 2008. Effects of oral aluminum exposure on behavior and neurogenesis in a transgenic mouse model of Alzheimer's disease. *Exptl. Neurol.* 214, 293–300.
- Rifat, S.L., Eastwood, M.R., McLachlan, D.R., Corey, P.N., 1990. Effect of exposure of miners to aluminum powder. *Lancet* 336, 1162–1165.
- Rondeau, V., Jacqmin-Gadda, H., Commenges, D., Helmer, C., Dartigues, J.F., 2009. Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. *Am. J. Epidemiol.* 169, 489–496.
- Ruipérez F., Mujika, J., Ugalde, J.M., Exley, C., Lopez, X., 2012. Pro-oxidant activity of aluminum: promoting the Fenton reaction by reducing Fe(III) to Fe(II). *J. Inorg. Biochem.* 117, 118–123.
- Russo, L.S., Beale, G., Sandroni, S., Ballinger, W.E., 1992. Aluminum intoxication in undialysed adults with chronic renal failure. *J. Neurol. Neurosurg. Psychiatry* 155, 697–700.
- Santibáñez, M., Bolumar, F., García, A.M., 2007. Occupational risk factors in Alzheimer's disease: a review assessing the quality of published epidemiological studies. *Occup. Environ. Med.* 64, 723–732.
- Selley, M.L., 2005. Simvastatin prevents 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced striatal dopamine depletion and protein tyrosine nitration in mice. *Brain Res.* 1037, 1–6.
- Sharman, E., Sharman, K.G., Lahiri, D.K., Bondy, S.C., 2004. Age-related changes in murine CNS mRNA gene expression are modulated by dietary melatonin. *J. Pineal Res.* 36, 165–170.
- Sharman, E.H., Sharman, K.Z., Bondy, S.C., 2008. Melatonin causes gene expression in aged animals to respond to inflammatory stimuli in a manner differing from that of young animals. *Curr. Aging Sci.* 1, 152–158.
- Shaw, C.A., Petrik, M.S., 2009. Aluminum hydroxide injections lead to motor deficits and motor neuron degeneration. *J. Inorg. Biochem.* 103, 1555–1562.
- Shaw, C.A., Li, Y., Tomljenovic, L., 2013. Administration of aluminium to neonatal mice in vaccine-relevant amounts is associated with adverse long term neurological outcomes. *J. Inorg. Biochem.* 128, 237–244.
- Sherrard, D.J., Walker, J.V., Boykin, J.L., 1988. Precipitation of dialysis dementia by deferoxamine treatment of aluminum-related bone disease. *Am. J. Kidney Dis.* 12, 126–130.
- Shi, L., Fatemi, S.H., Sidwell, R.W., Patterson, P.H., 2003. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. *J. Neurosci.* 23, 297–302.
- Shin, R.W., Kruck, T.P., Murayama, H., Kitamoto, T., 2003. A novel trivalent cation chelator Feralex dissociates binding of aluminum and iron associated with hyperphosphorylated tau of Alzheimer's disease. *Brain Res.* 961, 139–146.
- Shirabe, T., Irie, K., Uchida, M., 2002. Autopsy case of aluminum encephalopathy. *Neuropathology* 22, 206–210.
- Shoenfeld, Y., Agmon-Levin, N., 2011. 'ASIA' Autoimmune/inflammatory syndrome induced by adjuvants. *J. Autoimmun.* 36, 4–8.
- Sigel, H., Sigel, A., 1988. Metal ions in biological systems. *Aluminum and Its Role in Biology*, Vol. 24. Marcel Dekker, New York.
- Smith, R.W., 1996. Kinetic aspects of aqueous aluminum chemistry: environmental implications. *Coord. Chem. Rev.* 149, 81–93.
- Sparling, D.W., Campbell, P.G.C., 1997. Ecotoxicology of aluminum to fish and wildlife. In: Yokel, R.A., Golub, M.S. (Eds.), *Research Issues in Aluminum Toxicity*. Taylor and Francis, Washington, DC, pp. 48–68.
- Stahl, T., Taschan, H., Brunn, H., 2011. Aluminium content of selected foods and food products. *Environ. Sci. Eur.* 23, 37.
- Styren, S.D., Kamboh, M.I., Dekosky, S.T., 1998. Expression of differential immune factors in temporal cortex and cerebellum: the role of  $\alpha$ -1-antichymotrypsin, Apolipoprotein E, and reactive glia in the progression of Alzheimer's disease. *J. Comp. Neurol.* 396, 511–520.
- Sun, Y.X., Minthon, L., Wallmark, A., Warkentin, S., Blennow, K., Janciauskiene, S., 2003. Inflammatory markers in matched plasma and cerebrospinal fluid from patients with Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* 16, 136–144.
- Sutton, I., Latoria, R., Tan, I.L., Clouston, P., Barnett, M.H., 2009. CNS demyelination and quadrivalent HPV vaccination. *Mult. Scler.* 15, 116–119.
- Tomljenovic, L., 2011. Aluminum and Alzheimer's disease: after a century of controversy, is there a plausible link? *J. Alzheimer's Dis.* 23, 567–598.
- Uversky, V.N., Li, J., Fink, A.L., 2001. Metal-triggered structural transformations, aggregation, and fibrillation of human alpha-synuclein. A possible molecular link between Parkinson's disease and heavy metal exposure. *J. Biol. Chem.* 276, 44284–44296.
- Wällberg, M., Wefer, J., Harris, R.A., 2003. Vaccination with myelin oligodendrocyte glycoprotein adsorbed to alum effectively protects DBA/1 mice from experimental autoimmune encephalomyelitis. *Eur. J. Immunol.* 33, 1539–1547.
- Walton, J.R., 2009a. Brain lesions comprised of aluminum rich cells that lack microtubules may be associated with the cognitive deficit of Alzheimer's disease. *Neurotoxicology* 30, 1059–1069.
- Walton, J.R., 2009b. Functional impairment in aged rats chronically exposed to human range dietary aluminum equivalents. *Neurotoxicology* 30, 182–193.
- Walton, J.R., Wang, M.X., 2009. APP expression, distribution and accumulation are altered by aluminum in a rodent model for Alzheimer's disease. *J. Inorg. Biochem.* 103, 1548–1554.
- Walton, J.R., 2012. Cognitive deterioration and associated pathology induced by chronic low-level aluminum ingestion in a translational rat model provides an explanation of Alzheimer's disease, tests for susceptibility and avenues for treatment. *Int. J. Alzheimer's Dis.*, <http://dx.doi.org/10.1155/2012/914947>.
- Walton, J.R., 2014. Chronic aluminum intake causes Alzheimer's disease: applying Sir Austin Bradford Hill's causality criteria. *J. Alzheimers Dis.* 40, 765–838.
- Wang, L., Hu, J., Zhao, Y., Lu, X., Zhang, Q., Niu, Q., 2014. Effects of aluminium on  $\beta$ -amyloid (1–42) and secretases (APP-cleaving enzymes) in rat brain. *Neurochem. Res.* 39, 1338–1345.
- Xu, N., Majidi, V., Markesbery, W.R., Ehmann, W.D., 1992. Brain aluminum in Alzheimer's disease using an improved GFAAS method. *Neurotoxicology* 13, 735–743.
- Yokel, R.A., O'Callaghan, J.P., 1998. An aluminum-induced increase in GFAP is attenuated by some chelators. *Neurotoxicol. Teratol.* 20, 55–60.
- Yokel, R.A., Rhineheimer, S.S., Sharma, P., Elmore, D., McNamara, P.J., 2001. Entry, half-life, and desferrioxamine-accelerated clearance of brain aluminum after a single (26)Al exposure. *Toxicol. Sci.* 64, 77–82.
- Yokel, R.A., 2012. Aluminum in food – the nature and contribution of food additives. In: El-Samragy, Y. (Ed.), *Food Additive*. Intech, Rijeka, Croatia, pp. 203–228.
- Yumoto, S., Kakimi, S., Ohsaki, A., Ishikawa, A., 2009. Demonstration of aluminum in amyloid fibers in the cores of senile plaques in the brains of patients with Alzheimer's disease. *J. Inorg. Biochem.* 103, 1579–1584.
- Zatta, P., Zambenedetti, P., Milanese, M., 1999. Activation of monoamine oxidase type-B by aluminum in rat brain homogenate. *NeuroReport* 10, 3645–3648.
- Zhao, M., Cribbs, D.H., Anderson, A.J., Cummings, B.J., Su, J.H., Wasserman, A.J., Cotman, C.W., 2003. The induction of the TNF alpha death domain signaling pathway in Alzheimer's disease brain. *Neurochem. Res.* 28, 307–318.