Aluminum
and
Alzheimer's Disease

The condition known as "senile dementia" has been recognized for hundreds of years. But in 1907 Alois Alzheimer reported on a patient who had the common symptoms of memory loss, confusion, and hallucinations yet was only 51 years old [4] – too young for this to be senile dementia, he thought. The patient died at age 55 and, curious, Dr. Alzheimer examined the brain microscopically. He found it loaded with tiny "neuritic plaques" and "neurofibrillary tangles." The tangles appeared to have originally formed within nerve cells but remained even after the cells had degenerated. A few years later, however, others found the brains of many people who had died with classical senile dementia had these same markers. We now call this condition Alzheimer's disease.

Later research has shown the plaques Dr. Alzheimer saw are made of a protein known as β-amyloid and the neurofibrillary tangles are formed from a protein known as tau. How this all comes about and results in nerve cell loss and the symptoms of dementia typical of Alzheimer's disease remains unclear. The most popular theory [27] is, after processing, the amyloid precursor protein is normally supposed to fold on itself to form a soluble protein. Occasionally, however, the parts that are supposed to stick to each other will instead stick to corresponding parts on other β-amyloid molecules, and once started the process continues. Eventually this "raft" of β-amyloid molecules will get too big and form the insoluble plaques seen in the microscope. Then, in some way that is not understood at all, the plaques cause the excessive phosphorylation of the tau protein and the resulting neurofibrillary tangles. Evidence suggests that it is the neurofibrillary tangles that actually cause the symptoms of Alzheimer's disease, since it is they rather than the plaques that correlate with the duration and severity of the disease [6, 55]. These tangles appear to produce the loss of nerve cells seen in Alzheimer's [23]. An additional point supporting a crucial role for neurofibrillary tangles is that a mutation in the tau protein leads to dementia and tangles very similar to those in Alzheimer's, but without amyloid plaques [60].

Where Does Aluminum Fit into Alzheimer's Disease?

Ever since the first reports of high levels of aluminum in brains of Alzheimer's victims [15], the idea of a possible role for aluminum has been controversial. The fact that senile dementia was common for many years before aluminum came into common use and that old age is by far the greatest risk factor for dementia suggest aluminum is not the primary cause of most Alzheimer's cases. It has been argued that aluminum is naturally present in surface waters and might gradually accumulate in the brain over the course of a lifetime [61]. Nevertheless, even if aluminum is not the primary cause of Alzheimer's disease it could still play a role. For example, it might speed progression of the disease, especially in its early stages before symptoms develop. This could result in people being diagnosed with Alzheimer's disease who would otherwise have died before anyone noticed the symptoms. Such accelerated progression could account for a weak but difficult to ignore link between aluminum exposure and Alzheimer's disease.

Aluminum Consumption and the Risk of Alzheimer's Disease

The epidemiological evidence, both positive and negative, for a possible connection between aluminum and Alzheimer's disease has been well reviewed by Frisardi and colleagues [21]. One reason for the continuing controversy is that not all studies of the subject agree. A 2008 systematic review of studies that included aluminum exposure through drinking water, diet, and occupation found 23 studies demonstrated an increased risk for Alzheimer's disease with elevated aluminum exposure, 3 found that there was no connection, and the data from 8 did not permit any firm conclusion [19]. Most of the positive studies looked at the amount of aluminum in drinking water. Four major studies have found that people living in areas where the drinking water had high aluminum concentrations were one-and-a-half to two times as likely to have Alzheimer's disease as those living where the amount was lower [20, 38, 41, 43], while two others that followed subjects for 7 and 8 years, respectively, found a similar connection to the risk of developing Alzheimer's disease during the study period [22, 52]. One of these studies was extended for a total of 15 years [53]. After adjusting for other known risk factors the direct connection to drinking water aluminum concentrations disappeared but there was still a significant connection to the amount of aluminum that each individual actually consumed. In other words, those who drank a lot of water with high aluminum concentrations were are greater risk of getting Alzheimer's than those who tended to drink wine or bottled water instead. These findings might appear to be contradicted by another study from one of these same research groups, which found no association between aluminum concentrations and Alzheimer's disease in men below age 75 [39]. The age cut-off, however, meant that many of their cases had early-onset disease of genetic origin where no connection to aluminum would be expected. All these studies defined "high aluminum concentrations" as at least twice the maximum amount permitted in US drinking water. (Higher amounts are allowed in other countries.)

The average person probably gets ten times as much aluminum from food as from their drinking water, although a smaller fraction of aluminum enters the body from food. Difficulty in measuring the amount of aluminum in a given individual's diet has made research in this area difficult. However, one small study found that, based on reports by spouses and relatives, patients with Alzheimer's disease were more likely than other residents of the same nursing home to have consumed pancakes, waffles, biscuits, cornbread, and corn tortillas [51]. These foods are known to be high in aluminum, but statistical analysis did not confirm significance for a larger group of aluminum-rich foods that also included American cheese, grain-based desserts,

> "A 2008 systematic review of studies that included aluminum exposure through drinking water, diet, and occupation found 23 studies demonstrated an increased risk for Alzheimer's disease with elevated aluminum exposure, 3 found that there was no connection…"

> **"The good news is that the Alzheimer's disease patients in this one study of deferoxamine had progress of their disease slowed to half that seen in control patients."**

and chocolate pudding. Because the small size of the study limited ability to reach statistical significance, it is difficult to draw any firm conclusions. This and other studies have also looked at the relationship to tea drinking. The tea plant has high concentrations of aluminum in the leaves [44]. However, the amount of aluminum in brewed tea can vary by a large amount. In any case, all three studies of possible association between tea drinking and age-related Alzheimer's disease have reached similar conclusions: There is a hint of a relationship, but it is too weak to reach statistical significance and thus allow any confidence that the possible association is real [1, 10, 51]. Notably, two studies found no connection at all between Alzheimer's disease and heavy use of aluminum-containing antacids [10, 51]. One might intuitively expect individuals who use antacids daily for extended periods to have much higher aluminum intakes than anyone else.

In summary, epidemiological studies appear to suggest that drinking-water aluminum levels higher than would be permitted in the US may increase the risk of an Alzheimer's diagnosis. Studies on exposure from other sources, however, do not confirm this suggestion. On balance, the jury is still out.

Aluminum in the Brain

Another reason the relationship between aluminum and Alzheimer's disease remains controversial is measurements of the amount in patients' brains have led to inconsistent results. These studies have two distinct methods of measure. First method like Crapper's initial study [15], measures the total aluminum in specific parts of the brain. Second method microscopically examines thin sections of brain tissue to locate aluminum in cells, neurofibrillary tangles, or β-amyloid plaques. In the first group, six studies in addition to Crapper's have found aluminum levels in brains or brain regions of Alzheimer's disease patients [5, 14, 16, 54, 62, 69]. Interestingly in view of results from the second group of studies, one of this group reported that aluminum levels were elevated specifically in brain regions where neurofibrillary tangles were common independently of the number of β-amyloid plaques that might be present [16]. However, these positive studies are contradicted by four studies that reported no difference in brain aluminum levels between individuals with Alzheimer's disease and other people the same age [7, 12, 26, 40]. It's difficult to say what these apparently conflicting results mean, since many different techniques were used and each method could lead to finding either higher or lower amounts of the metal than are actually present. However, one of the negative studies cited as a strength the fact that it had found similar results using two quite different techniques [26].

Several microscopic studies have explicitly reported finding aluminum in connection with neurofibrillary tangles [9, 45, 64]. Notably, one of these studies found still higher levels of aluminum associated with neurofibrillary tangles in brains of patients with dementia pugilistica ("punch-drunk" boxers) [9], suggesting aluminum accumulation is specific for tangles rather than Alzheimer's disease. There has also been a study reporting aluminum associated with the nuclei of nerve cells containing neurofibrillary tangles [46]. This was true even in the brains of non-demented seniors, although such brains naturally had far fewer neurofibrillary tangles than did those of people who had died with Alzheimer's disease. There has also been reports Alzheimer's disease is associated with elevated amounts of aluminum bound to a specific nuclear protein [36] and a microscopic study that did not report the subcellular location of the additional aluminum [59]. However, again, results have not been consistent. One study found no significant differences among nerve cells, with or without neurofibrillary tangles, from Alzheimer's disease patients, nerve cells from control subjects, or non-neural supporting tissues from the two groups [37]. Another study similarly reports no differences in either nuclear or cytoplasmic aluminum content among nerve cells with or without tangles or from control subjects [35]. Two other studies have looked specifically at β-amyloid plaques, with one stating that aluminum is associated with the amyloid fibers [70] while another reports that it is not [33]. There was also a study that found "no peculiarities in the distributions of aluminum" in brain slices taken from patients who had died of Alzheimer's disease [42].

Aluminum in Animal Models

Studies in animal models of Alzheimer's disease must be evaluated with a degree of caution. These models typically involve mice that have been genetically altered to incorporate the human amyloid precursor protein carrying mutations known to cause familial Alzheimer's disease, sometimes along with other mutated Alzheimer-associated proteins. None, however, have been shown to reproduce all major features of the human disease [56]. The only ones in which the original reports documented the presence of neurofibrillary tangles were those in which the animals also carried a mutated form of the tau protein, while the only ones in which loss of nerve cells was documented were those that also carried a mutated form of presenilin-1, mutations in which also produce familial Alzheimer's disease. Additionally, some studies looking at the effects of aluminum have injected the metal directly into the animals' brains, which is clearly different from the human situation, while others have measured the effects solely by declines in performance on memory tests such as water mazes without looking at the changes in the brain that define Alzheimer's disease. Although relevant to the general question of aluminum's bad effects on the brain, it is unclear whether such performance-only studies tell us anything about the disease.

Since these genetically altered ("transgenic") mice are a relatively recent development, many of the early studies used other animals. These models, however, do not reproduce the typical features of human Alzheimer's disease very well. In the first such study to be reported, aluminum was injected into the brains of cats, with the amount ending up in specific brain regions being associated both with the number of neurofibrillary tangles in those regions and with poorer performance on an avoidance test [15]. There was no mention of β-amyloid plaques, however. Another relatively early study injected aluminum into

rabbit brains, again finding many neurofibrillary tangles without mentioning plaques [31]. Still another study gave rabbits repeated injections of aluminum [63]. Neurofibrillary tangles appeared first in the spinal cord, then the brain stem, and finally the hippocampal region of the brain, with aluminum being found in the nuclei only of nerve cells containing tangles. However, the order in which these tangles appeared does not reflect the human disease, although this could be attributed to the way the aluminum was given. In a final set of recent non-mouse studies, rats were continuously given aluminum in their drinking water beginning at 12 or 16 months of age – middle-aged for a rat [65-67]. The amount of aluminum in the rats' diet was said to be comparable to human dietary intake. In the most comprehensive study [66], different groups of rats received low, medium, or high doses. Most but not all of those in the high-dose aluminum group, a few of those in the medium-dose group, and none of those in the low-dose group showed poorer performance on a T-maze test in old age than they had in middle age, suggesting a loss of spatial memory. Notably, however, none of the rats showed neurofibrillary tangles or β-amyloid plaques, although other types of brain lesions were seen and a related study [68] found that production of amyloid precursor protein was increased specifically in rats whose performance declined with age. Although these cat, rabbit, and rat studies suggest aluminum isn't good for you, it's hard to know whether they tell us anything about human Alzheimer's disease.

One intriguing study in transgenic mice found injecting aluminum into the brains of mice carrying mutated forms of both amyloid precursor protein and presenilin-1 resulted in greater loss of nerve cells and of ability to learn and remember a task than was seen in either transgenic animals not receiving aluminum or wild-type mice treated with aluminum [71]. Despite the unnatural way the aluminum was given, this tends to suggest that aluminum can accelerate the progress of Alzheimer's disease. However, another study employing a somewhat different transgenic mouse strain – this one containing mutated forms of amyloid precursor and tau proteins – found that high levels of aluminum in their drinking water did not increase the number of amyloid plaques or amount of over-phosphorylated tau in their brains [3]. This study did not examine effects on learning or memory. Two other studies did examine memory and learning, however. Both, from the same research group, used a strain with only mutated amyloid precursor protein. One study found very high levels of aluminum in the food (more than 1% of the entire diet), decreased ability to learn and remember a water maze, although there was no detectable loss of nerve cells [49]. The other fed aluminum at 1/10th the level employed in the previous study – still quite high by human standards – and found no effect on either plaque deposition or ability to recognize familiar objects [50]. By contrast, another study is interesting because it supports the theory that aluminum exerts its effects by increasing oxidant levels in the brain. Mice with a mutant form of amyloid precursor protein were fed high levels of aluminum, which increased both plaque formation and levels of a compound associated with the presence of oxidants [48]. Feeding the antioxidant vitamin E reversed these changes. Significantly, however, feeding aluminum had very little effect on oxidant levels in wild-type mice, again supporting an interaction of aluminum with Alzheimer's disease rather than aluminum as the direct cause.

Removing Aluminum from the Body

If aluminum is bad for you, can you get rid of it? Will that help? The only way to get rid of aluminum is with chelators – compounds that chemically "grab" aluminum and make it soluble so the urinary system can flush it out of the body. The FDA has not approved any chelators specifically for removing aluminum. However, the aluminum ion is very similar in size and charge to the ferric ion (the more highly charged form of iron) and two chelators have been approved for treatment of iron overload from diseases such as thalassemia.

Deferoxamine, also known as desferrioxamine and sold under the trade name Desferal, has been used to treat iron overload since 1963 [28]. In the 1980s a number of renal dialysis patients acquired excessive amounts of aluminum from their dialysis fluid, with symptoms that somewhat resembled those of Alzheimer's disease but without the diagnostic tangles and plaques. Deferoxamine was successfully used to remove this aluminum overload, with marked improvement in the symptoms [2, 25]. Deferoxamine use has been reported to cause a variety of side effects [18], with hearing loss and disturbances of vision being particularly common [11]. Official prescribing information for deferoxamine indicates that side effects are typically seen only with high dosages or prolonged use, but this is in the context of the officially approved use for iron overload. Evidence suggests that patients who do not have excessive amounts of iron in their systems may be more vulnerable [47]. Nevertheless, when patients with Alzheimer's disease were given low doses of deferoxamine for 2 years, the only side effect noted was loss of appetite [17].

Other drawbacks to deferoxamine are high cost and the fact that it is given by injection. The good news is that the Alzheimer's disease patients in this one study of deferoxamine had progress of their disease slowed to half that seen in control patients [17]. Critics have suggested, however, that this slowing may have been a result of seeing the doctor more often and the resulting increase in human interaction, since control patients did not get injections.

> **"A compound known as Feralex-G has drawn attention because it has been reported to be more effective than deferoxamine for removing aluminum from brain slices obtained at autopsy from Alzheimer's disease patients."**

Deferiprone, also known as L1 and sold under the trade name Ferriprox, has been under investigation for more than a decade but has only recently been approved for treatment of iron overload. A comparative study concluded that deferiprone and deferoxamine were more or less equally effective in removing either iron or aluminum and that, while they had different side effects, there was little to choose between them on this ground either [29]. A review from the same author, however, indicated that deferiprone's side effects were less significant [30]. Furthermore,

deferiprone is much cheaper and is given by mouth, so it is likely to be preferred.

A number of other iron/aluminum chelators were studied in the 1990s but have since been abandoned for various reasons. A compound known as Feralex-G has drawn attention because it has been reported to be more effective than deferoxamine for removing aluminum from brain slices obtained at autopsy from Alzheimer's disease patients [57]. No studies in live animals or humans have been reported, however. Other novel chelators are also being investigated [24] but appear unlikely to be available for human use in the near future. An innovative approach that has recently been suggested is attaching chelators to nanoparticles that can move freely back and forth through the blood-brain barrier [34], but much work still needs to be done to bring this idea to fruition.

Using more than one chelator in combination also appears to be an attractive idea. In aluminum-injected rats, however, the combination of deferoxamine and deferiprone was no better than deferoxamine alone [8]. There was similarly no advantage to combining deferiprone and the compound deferasirox [58]. On the other hand, combined use of two quite different types of chelators, both still largely in the "blue sky" stage, did provide superior results [13]. And in a highly artificial laboratory study, the combination of ascorbic acid (vitamin C) and Feralex-G was better than any of several other compounds or combinations for removing aluminum from nerve cell nuclei [32]. The authors suggest that ascorbic acid may enter the nucleus readily and chelate the aluminum there, then transfer it to the Feralex-G for disposal. The antioxidant effects of ascorbic acid may also be relevant. The possibility that ascorbic acid might enhance the effectiveness of deferoxamine or deferiprone needs to be tested in a more realistic setting.

> **"And in a highly artificial laboratory study, the combination of ascorbic acid (vitamin C) and Feralex-G was better than any of several other compounds or combinations for removing aluminum from nerve cell nuclei."**

Conclusions

The Alzheimer's Association says, "Since [the 1970s], studies have failed to confirm any role for aluminum in causing Alzheimer's" (http://www.alz.org/alzheimers_disease_myths_about_alzheimers.asp, accessed May 23, 2012). This seems somewhat overstated. Although the evidence is not entirely convincing, there is too much data supporting a role for aluminum in Alzheimer's disease for it to be entirely ignored. However, the evidence best fits with that role being to speed progression of the disease rather than constituting a direct cause.

References

[1] The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada. *Neurology* 44: 2073-2080, 1994.

[2] Ackrill P, and Day JP. Desferrioxamine in the treatment of aluminum overload. *Clin Nephrol* 24 Suppl 1: S94-97, 1985.

[3] Akiyama H, Hosokawa M, Kametani F, Kondo H, Chiba M, Fukushima M, and Tabira T. Long-term oral intake of aluminium or zinc does not accelerate Alzheimer pathology in AbetaPP and AbetaPP/tau transgenic mice. *Neuropathology* 2011.

[4] Alzheimer A, Stelzmann RA, Schnitzlein HN, and Murtagh FR. An English translation of Alzheimer's 1907 paper, "Uber eine eigenartige Erkankung der Hirnrinde". *Clinical Anatomy* 8: 429-431, 1995.

[5] Andrasi E, Pali N, Molnar Z, and Kosel S. Brain aluminum, magnesium and phosphorus contents of control and Alzheimer-diseased patients. *J Alzheimers Dis* 7: 273-284, 2005.

[6] Arriagada PV, Growdon JH, Hedley-Whyte ET, and Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology* 42: 631-639, 1992.

[7] Bjertness E, Candy JM, Torvik A, Ince P, McArthur F, Taylor GA, Johansen SW, Alexander J, Gronnesby JK, Bakketeig LS, and Edwardson JA. Content of brain aluminum is not elevated in Alzheimer disease. *Alzheimer Dis Assoc Disord* 10: 171-174, 1996.

[8] Blanusa M, Prester L, Varnai VM, Pavlovic D, Kostial K, Jones MM, and Singh PK. Chelation of aluminium by combining DFO and L1 in rats. *Toxicology* 147: 151-156, 2000.

[9] Bouras C, Giannakopoulos P, Good PF, Hsu A, Hof PR, and Perl DP. A laser microprobe mass analysis of brain aluminum and iron in dementia pugilistica: comparison with Alzheimer's disease. *Eur Neurol* 38: 53-58, 1997.

[10] Broe GA, Henderson AS, Creasey H, McCusker E, Korten AE, Jorm AF, Longley W, and Anthony JC. A case-control study of Alzheimer's disease in Australia. *Neurology* 40: 1698-1707, 1990.

[11] Cases A, Kelly J, Sabater F, Torras A, Grino MC, Lopez-Pedret J, and Revert L. Ocular and auditory toxicity in hemodialyzed patients receiving desferrioxamine. *Nephron* 56: 19-23, 1990.

[12] Chafi AH, Hauw JJ, Rancurel G, Berry JP, and Galle C. Absence of aluminium in Alzheimer's disease brain tissue: electron microprobe and ion microprobe studies. *Neurosci Lett* 123: 61-64, 1991.

[13] Chaves S, Dron PI, Danalache FA, Sacoto D, Gano L, and Santos MA. Combined chelation based on glycosyl-mono- and bis-hydroxypyridinones for aluminium mobilization: solution and biodistribution studies. *J Inorg Biochem* 103: 1521-1529, 2009.

[14] Corrigan FM, Reynolds GP, and Ward NI. Hippocampal tin, aluminum and zinc in Alzheimer's disease. *Biometals* 6: 149-154, 1993.

[15] Crapper DR, Krishnan SS, and Dalton AJ. Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration. *Science* 180: 511-513, 1973.

[16] Crapper DR, Krishnan SS, and Quittkat S. Aluminium, neurofibrillary degeneration and Alzheimer's disease. *Brain* 99: 67-80, 1976.

17. Crapper McLachlan DR, Dalton AJ, Kruck TP, Bell MY, Smith WL, Kalow W, and Andrews DF. Intramuscular desferrioxamine in patients with Alzheimer's disease. *Lancet* 337: 1304-1308, 1991.

18. Domingo JL. Adverse effects of aluminium-chelating compounds for clinical use. *Adverse Drug React Toxicol Rev* 15: 145-165, 1996.

19. Ferreira PC, Piai Kde A, Takayanagui AM, and Segura-Munoz SI. Aluminum as a risk factor for Alzheimer's disease. *Rev Lat Am Enfermagem* 16: 151-157, 2008.

20. Frecker MF. Dementia in Newfoundland: identification of a geographical isolate? *J Epidemiol Community Health* 45: 307-311, 1991.

21. Frisardi V, Solfrizzi V, Capurso C, Kehoe PG, Imbimbo BP, Santamato A, Dellegrazie F, Seripa D, Pilotto A, Capurso A, and Panza F. Aluminum in the diet and Alzheimer's disease: from current epidemiology to possible disease-modifying treatment. *J Alzheimers Dis* 20: 17-30, 2010.

22. Gillette-Guyonnet S, Andrieu S, Nourhashemi F, de La Gueronniere V, Grandjean H, and Vellas B. Cognitive impairment and composition of drinking water in women: findings of the EPIDOS Study. *Am J Clin Nutr* 81: 897-902, 2005.

23. Gomez-Isla T, Hollister R, West H, Mui S, Growdon JH, Petersen RC, Parisi JE, and Hyman BT. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Ann Neurol* 41: 17-24, 1997.

24. Grazina R, Gano L, Sebestik J, and Amelia Santos M. New tripodal hydroxypyridinone based chelating agents for Fe(III), Al(III) and Ga(III): Synthesis, physico-chemical properties and bioevaluation. *J Inorg Biochem* 103: 262-273, 2009.

25. Hernandez P, and Johnson CA. Deferoxamine for aluminum toxicity in dialysis patients. *ANNA J* 17: 224-228, 1990.

26. Jacobs RW, Duong T, Jones RE, Trapp GA, and Scheibel AB. A reexamination of aluminum in Alzheimer's disease: analysis by energy dispersive X-ray microprobe and flameless atomic absorption spectrophotometry. *Can J Neurol Sci* 16: 498-503, 1989.

27. Karran E, Mercken M, and De Strooper B. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat Rev Drug Discov* 10: 698-712, 2011.

28. Keberle H. The Biochemistry of Desferrioxamine and Its Relation to Iron Metabolism. *Ann N Y Acad Sci* 119: 758-768, 1964.

29. Kontoghiorghes GJ. Comparative efficacy and toxicity of desferrioxamine, deferiprone and other iron and aluminium chelating drugs. *Toxicol Lett* 80: 1-18, 1995.

30. Kontoghiorghes GJ. New concepts of iron and aluminium chelation therapy with oral L1 (deferiprone) and other chelators. A review. *Analyst* 120: 845-851, 1995.

31. Kowall NW, Pendlebury WW, Kessler JB, Perl DP, and Beal MF. Aluminum-induced neurofibrillary degeneration affects a subset of neurons in rabbit cerebral cortex, basal forebrain and upper brainstem. *Neuroscience* 29: 329-337, 1989.

32. Kruck TP, Cui JG, Percy ME, and Lukiw WJ. Molecular shuttle chelation: the use of ascorbate, desferrioxamine and Feralex-G in combination to remove nuclear bound aluminum. *Cell Mol Neurobiol* 24: 443-459, 2004.

33. Landsberg JP, McDonald B, and Watt F. Absence of aluminium in neuritic plaque cores in Alzheimer's disease. *Nature* 360: 65-68, 1992.

34. Liu G, Men P, Perry G, and Smith MA. Nanoparticle and iron chelators as a potential novel Alzheimer therapy. *Methods Mol Biol* 610: 123-144, 2010.

35. Lovell MA, Ehmann WD, and Markesbery WR. Laser microprobe analysis of brain aluminum in Alzheimer's disease. *Ann Neurol* 33: 36-42, 1993.

36. Lukiw WJ, Krishnan B, Wong L, Kruck TP, Bergeron C, and Crapper McLachlan DR. Nuclear compartmentalization of aluminum in Alzheimer's disease (AD). *Neurobiol Aging* 13: 115-121, 1992.

37. Makjanic J, McDonald B, Li-Hsian Chen CP, and Watt F. Absence of aluminium in neurofibrillary tangles in Alzheimer's disease. *Neurosci Lett* 240: 123-126, 1998.

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

39. Martyn CN, Coggon DN, Inskip H, Lacey RF, and Young WF. Aluminum concentrations in drinking water and risk of Alzheimer's disease. *Epidemiology* 8: 281-286, 1997.

40. McDermott JR, Smith AI, Iqbal K, and Wisniewski HM. Brain aluminum in aging and Alzheimer disease. *Neurology* 29: 809-814, 1979.

41. McLachlan DR, Bergeron C, Smith JE, Boomer D, and Rifat SL. Risk for neuropathologically confirmed Alzheimer's disease and residual aluminum in municipal drinking water employing weighted residential histories. *Neurology* 46: 401-405, 1996.

42. Murray FE, Landsberg JP, Williams RJ, Esiri MM, and Watt F. Elemental analysis of neurofibrillary tangles in Alzheimer's disease using proton-induced X-ray analysis. *Ciba Found Symp* 169: 201-210; discussion 210-206, 1992.

43. Neri LC, and Hewitt D. Aluminium, Alzheimer's disease, and drinking water. *Lancet* 338: 390, 1991.

44. Pennington JA, and Schoen SA. Estimates of dietary exposure to aluminium. *Food Addit Contam* 12: 119-128, 1995.

45. Perl DP. Relationship of aluminum to Alzheimer's disease. *Environ Health Perspect* 63: 149-153, 1985.

46. Perl DP, and Brody AR. Alzheimer's disease: X-ray spectrometric evidence of aluminum accumulation in neurofibrillary tangle-bearing neurons. *Science* 208: 297-299, 1980.

47. Porter JB, and Huehns ER. The toxic effects of desferrioxamine. *Baillieres Clin Haematol* 2: 459-474, 1989.

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

49. Ribes D, Colomina MT, Vicens P, and Domingo JL. Impaired spatial learning and unaltered neurogenesis in a transgenic model of Alzheimer's disease after oral aluminum exposure. *Curr Alzheimer Res* 7: 401-408, 2010.

50. Ribes D, Torrente M, Vicens P, Colomina MT, Gomez M, and Domingo JL. Recognition Memory and beta-amyloid Plaques in Adult Tg2576 Mice are not Modified After Oral Exposure to Aluminum. *Alzheimer Dis Assoc Disord* 26: 179-185, 2012.

51. Rogers MA, and Simon DG. A preliminary study of dietary aluminium intake and risk of Alzheimer's disease. *Age Ageing* 28: 205-209, 1999.

52. Rondeau V, Commenges D, Jacqmin-Gadda H, and Dartigues JF. Relation between aluminum concentrations in drinking water

and Alzheimer's disease: an 8-year follow-up study. *Am J Epidemiol* 152: 59-66, 2000.

53. Rondeau V, Jacqmin-Gadda H, Commenges D, Helmer C, and Dartigues JF. 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, 2009.

54. Rusina R, Matej R, Kasparova L, Kukal J, and Urban P. Higher aluminum concentration in Alzheimer's disease after Box-Cox data transformation. *Neurotox Res* 20: 329-333, 2011.

55. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, and Brayne C. Age, neuropathology, and dementia. *N Engl J Med* 360: 2302-2309, 2009.

56. Schaeffer EL, Figueiro M, and Gattaz WF. Insights into Alzheimer disease pathogenesis from studies in transgenic animal models. *Clinics (Sao Paulo)* 66 Suppl 1: 45-54, 2011.

57. Shin RW, Kruck TP, Murayama H, and Kitamoto T. 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, 2003.

58. Shokooh Saljooghi A. Chelation of aluminum by combining deferasirox and deferiprone in rats. *Toxicol Ind Health* 2011.

59. Solomon B, Koppel R, and Jossiphov J. Immunostaining of calmodulin and aluminium in Alzheimer's disease-affected brains. *Brain Res Bull* 55: 253-256, 2001.

60. Spillantini MG, Crowther RA, and Goedert M. Comparison of the neurofibrillary pathology in Alzheimer's disease and familial presenile dementia with tangles. *Acta Neuropathol* 92: 42-48, 1996.

61. Tomljenovic L. Aluminum and Alzheimer's disease: after a century of controversy, is there a plausible link? *J Alzheimers Dis* 23: 567-598, 2011.

62. Trapp GA, Miner GD, Zimmerman RL, Mastri AR, and Heston LL. Aluminum levels in brain in Alzheimer's disease. *Biol Psychiatry* 13: 709-718, 1978.

63. Uemura E. Intranuclear aluminum accumulation in chronic animals with experimental neurofibrillary changes. *Exp Neurol* 85: 10-18, 1984.

64. Walton JR. Aluminum in hippocampal neurons from humans with Alzheimer's disease. *Neurotoxicology* 27: 385-394, 2006.

65. Walton JR. 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, 2009.

66. Walton JR. Functional impairment in aged rats chronically exposed to human range dietary aluminum equivalents. *Neurotoxicology* 30: 182-193, 2009.

67. Walton JR. A longitudinal study of rats chronically exposed to aluminum at human dietary levels. *Neurosci Lett* 412: 29-33, 2007.

68. Walton JR, and Wang MX. APP expression, distribution and accumulation are altered by aluminum in a rodent model for Alzheimer's disease. *J Inorg Biochem* 103: 1548-1554, 2009.

69. Xu N, Majidi V, Markesbery WR, and Ehmann WD. Brain aluminum in Alzheimer's disease using an improved GFAAS method. *Neurotoxicology* 13: 735-743, 1992.

70. Yumoto S, Kakimi S, Ohsaki A, and Ishikawa A. 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, 2009.

71. Zhang QL, Jia L, Jiao X, Guo WL, Ji JW, Yang HL, and Niu Q. APP/PS1 transgenic mice treated with aluminum: an update of Alzheimer's disease model. *Int J Immunopathol Pharmacol* 25: 49-58, 2012.