# The Revised Aluminum Hypothesis: Possible Role of Inorganic and Organic Silicon

Bernhard Buchter, Alberta
Bertastrasse 18a, CH-8003 Zürich, buchter@alberta.ch
Margrit Dunkel, Centre of Occupational Therapy Wiedikon OTCW
Zurlindenstrasse 214, CH-8003 Zürich, dunkel@ergowiedikon.ch

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aluminosilicates, amyloid-β peptide, autoimmune diseases, α-synuclein, dimethylsilanediol, fibrils, monomethylsilanetriol, plaques, tangles

Abbreviations:

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|---|---|
| Al | aluminum (all forms) |
| AlH | aluminum hypothesis |
| AlSiH | aluminum-silicon hypothesis |
| AID | autoimmune disease |
| DMSD | dimethylsilanediol |
| PDMS | polydimethylsilanediol |
| HH | hygiene hypothesis |
| MF | macroscopic feature |
| MMST | monomethylsilanetriol |
| Si | silicon (all forms) |

## Abstract

### *Common findings*

The aluminum hypothesis (AlH) is based on the reasoning that the aluminum in the environment influences the amount of aluminum in the human body. Al and Si are taken up by the human body where their concentrations are mutually reduced as they are deposited as aluminosilicates within macroscopic features (MFs). However, the correlation between Al in the environment and Al in the human body has been inconsistent, as the amount of Al in the blood has been regarded as too low to explain the extent of MFs found in the brain. Additional Al fluxes have not been observed, and no clear explanations for the precipitation of Al in the central nervous system have been offered. Thus, the AlH has never become operational.

### *Specific finding*

Most aluminosilicates exhibit a permanent negative surface charge, similar to microbes, and this charge triggers the human immune system to attack precipitated aluminosilicates. Macrophages cannot eliminate aluminosilicates, so their electrical load persists. MFs contain Al, Si, and misfolded fragments of 18 polypeptides that show no sequential or structural similarities. Misfolding seems to be the observable immune response of the human body to the electrically charged aluminosilicate particles. The prevalence of single autoimmune diseases (AIDs) is quite different worldwide; most cases of AIDs have increased over time, the number of cases is much lower in Eastern Europe than in Western Europe, and the diseases affect various ethnic groups differently and usually affect women more than men. Some AIDs may have a single primary cause. To date, organic Si has not been considered to play a role in the formation of MFs. The most frequently used organic Si compounds are polydimethylsiloxanes (PDMSs, silicones), two of which are highly soluble in water. This property allows organic Si concentrations to be 70 to 200 times greater than those of inorganic (ionic) Si in blood. Organic silicon does not interfere with (ionic) Al. PDMSs are taken up through the dermis, by inhalation, and via oral consumption.

### *Collating new findings and combining them with the existing knowledge*

Al reacts with Si to form aluminosilicate, thus greatly reducing the Al and Si concentrations. Therefore, a valid AlH must always consider Si. If PDMSs are metabolized, they produce ionic silicon, which interferes with aluminum. Despite the low aluminum concentration in the blood, nearly all Al is precipitated. Aluminosilicate particles constitute the kernel of MFs, and their negative charges cause permanent misfolding of protein molecules. A valid AlH should also consider organic Si. Only the AlH and the hygiene hypothesis (HH) can explain the variety of AIDs and their variable prevalence. The HH is based on the reasoning that a clean environment denies the human body the opportunity to become sufficiently immunized. However, a lot of cleaning products are harmful to the human body. In this way, the HH would provide a simple approach and would fit well with the aluminum-silicon hypothesis (AlSiH). The inclusion of both inorganic and organic silicon could explain the additional flux necessary for the extent of MFs found in the human neurological system. PDMSs are a group of chemical compounds whose consumption depends on a person's lifestyle.

## Introduction

The current scientific community has gathered abundant knowledge about relevant processes; however, the information is often redundant, sometimes containing irrelevant details, and continues to accumulate with a lack of order. The main research problems appear to be solved, but the solutions are buried under a plethora of confusing results. In our view, the problem of aluminum within the biosphere is such a case. For decades, new findings have been continually discovered, and solutions have been perpetually proposed, but the issue of aluminum in the environment remains.

## Aim

The aim of this study was to formulate a clear and concise aluminum hypothesis (AlH) based on chemical and physical data capable of explaining the observed pathological symptoms and epidemiological findings (Buchter, Dunkel, & Li, 2011; Sullivan, 1990).

## Materials and methods

We performed a literature search, browsed a great number of articles, read a wide range of these articles, discussed their findings, interpreted their informative value and combined a selection of scientifically significant publications. The compilation of the scientific findings provided the basis for the new Al-Si hypothesis (AlSiH).

## Common findings

### *The current aluminum hypothesis*

The current AlH is based on the reasoning that the aluminum (Al) in the environment influences the amount of aluminum in the human body. Al and Si are taken up by the human body and specifically deposited within macroscopic features (MFs) of the nervous system, colocalized with Si (Candy et al., 1986; Garruto et al., 1986; Tokutake et al., 1995). The diagnosis of neurological autoimmune diseases (AIDs) is based on a clinical examination and observation of the MFs, which contain amyloid-β peptides and are commonly known as plaques, tangles, Lewy bodies, α-synuclein, and τ-proteins (Serrano-Pozo et al., 2011). The deposits are visualized by staining cross-sectional samples of nervous tissue with silver, Congo red, and thioflavin S.

Al in the MFs exhibits tetrahedral and octahedral coordination, indicating that Al is precipitated together with Si as aluminosilicates. Al and Si strongly interact with each other and mutually reduce their concentrations (Iler, 1979), forming aluminosilicates with solubility product constants $pK_{sp}$ (= - log $K_{sp}$) between 12.8 and 13.3 (Iler, 1979; Jugdaohsingh et al., 2000; Lindsay, 1979). No clear, constant correlation exists between Al in the environment and Al in the human body.

Al and Si are both ubiquitous in natural and man-made environments. Unsurprisingly, both elements are also present in the blood. For a healthy subject, the Al concentration in blood serum is 0.25 μmol/L (Birchall & Chappell, 1988), which is 5 % of the calculated Al concentration in water in equilibrium with solid-phase $Al(OH)_3^0$ (Lindsay, 1979). The concentration of Si in blood serum is 4 – 20 μmol/L (Dobbie and Smith, 1982; Mauras et al., 1980; Van Dyck et al., 2000; Jugdaohsingh et al., 2013), which is 0.2 – 1 % of the calculated Si concentration in water in equilibrium with solid-phase amorphous $SiO_2$ (Iler, 1979; Lindsay, 1979).

The amount of precipitable Al in blood has been regarded as being too low to explain the extent of MFs found in the brain (Farmer et al., 1991). Thus, researchers have searched for additional Al fluxes. Because Al can pass through the blood-brain barrier only in a complexed form, the existing studies have focused on naturally occurring complex-forming compounds, such as citric acid, transferrin and albumin (Fatemi, Kadir, & Moore, 1991; Roskams & Connor, 1990). These studies did not reveal an additional, sufficiently large Al flux (Tokutake et al., 1995).

Even if the Al concentrations were adequate to produce MFs to the observed extent, there is currently no clear explanation for the precipitation of Al in the human body after it has passed through the blood-brain barrier.

Due to these problems, the AlH has never become operational and has become less accepted in the scientific community over the last two decades. However, the AlH remains accepted by the general public because there are no convincing etiologies or successful treatments for most AIDs and neurodegeneration diseases (Lidsky, 2014).

### *Aluminosilicate-microbe interactions*

In aluminosilicates, isomorphous substitution, which involves the substitution of $Si^{4+}$ by $Al^{3+}$ within tetrahedrally coordinated layers and the substitution of $Al^{3+}$ by divalent cations within octahedrally co-ordinated layers, causes a permanent shortage of positive electrical loads, resulting in a permanent negative surface charge (Lindsay, 1979; Perrott, 1977).

Aluminosilicates and microbes have negative surface charges (SiO-OH vs. CO-OH) and similar particle sizes (cf. fig 1A in Candy et al., 1986). These similarities in electrical load and size trigger the human immune system to attack precipitated aluminosilicates. Amyloid-β peptides, associated with antimicrobial activities (Soscia et al., 2010), are misfolded by the Coulomb forces of the negative surface charges of microbes (Smith et al., 1991). The cell membranes of the attacked microbes are destroyed, and the electrical load and misfolding disappear.

Macrophages, however, cannot eliminate aluminosilicates; their electrical load persists along with the misfolding. The aggregated remnants are deposited and are visible as MFs (Haustein & Herrmann, 1994). The MFs include the aluminosilicate kernel (cf. fig. 1A in Candy et al., 1986) that contains Al and Si as well as fragments of amyloid-β peptides and 17 other polypeptides (Ramirez-Alvarado, 2000).

The divergent impact of the permanent and transient electrical loads was unintentionally observed in an experiment performed by Banin and Meiri (1990). Three different negatively charged aluminosilicates created holes within the cell membranes and eventually destroyed the membranes. In contrast, Al added as a salt did not disrupt the cell membranes. If stained with thioflavin S, the MFs caused by Alzheimer's disease showed a strong fluorescence due to the strong electrical load of the aluminosilicates, whereas MFs induced by Al salts did not have a strong fluorescence (Lidsky, 2014).

### *Epidemiology*

The worldwide prevalence of AIDs with a single primary cause is quite different (Buchter, Dunkel, & Li, 2012), and the prevalence of most AIDs has increased over time (Lerner, Jeremias & Matthias, 2015). The prevalence of many AIDs is much lower in Eastern Europe than in Western Europe, most clearly visible in Karelia (Kondrashova, 2013). AIDs usually affect women more than men (Hayter & Cook, 2012). The prevalence of AIDs with a single primary cause for native inhabitants usually differs from that of immigrants and other ethnic groups (Buchter, Dunkel, & Li, 2011). Findings concerning comorbidity suggest that certain AIDs may have a single primary cause that can induce different reactions in the human body at different locations (Somers et al., 2009; Sardu et al., 2012).

## Collating new findings and combining them with the existing knowledge

### *Organic silicon*

In addition to the well-known inorganic (ionic) Si, organic Si also exists, which is composed of chemical compounds containing covalent carbon-Si bonds. Despite their name, organic Si compounds are entirely synthetic. The commercial production of these compounds increased after World War II. To our knowledge, organic Si compounds are not considered to be involved in the formation of MFs. The most frequently used organic Si compounds are polydimethylsiloxanes (PDMSs), also called silicones. PDMSs are linear or cyclic polymers of siloxanes with a base unit of dimethylsilanediol (DMSD; $(CH_3)_2Si(OH)_2$). DMSD can penetrate the skin and pass through the blood-brain barrier (Buchter & Dunkel, 2013), similar to dimethylsulfoxide (Marren, 2011; Perlman & Wolfe, 1966). Monomethylsilanetriol (MMST; $(CH_3)Si(OH)_3$) is the smallest molecule containing both carbon and Si, which have been described as being poorly soluble in water (Mazzoni, Roy, & Grigoras, 1997). However, in contrast to all other PDMSs, DMSD and MMST are highly soluble in water (with solubilities of 0.7 mmol/L and 20 mmol/L, respectively; Jugdaohsingh et al., 2013; Xu & Kropscott, 2012). This property allows organic Si concentrations to be 70 to 200 times greater than those for ionic (inorganic) Si in blood. In contrast to ionic silicon, organic Si is not known to interact with Al.

Due to their widespread daily use, PDMSs are taken up through the dermis, by inhalation, and via oral consumption. PDMSs are used *inter alia* in personal care products, including hairsprays (Horii & Kannan, 2008), as antifoaming agents in detergents, in the food and beverage processing industry as a component of antifoaming and anticaking agents (DMSD), and as a food additive (MMST, Jugdaohsingh et al., 2013). Daily supplementation of 10.5 mg Si in the form of MMST resulted in an MMST-Si concentration in the blood serum of 100 µg/L (≈ 4 µmol/L) in addition to the 6 µmol/L of inorganic Si that was already present (Jugdaohsingh et al., 2013).

### *Aluminum, aluminosilicates, silicon, and proteins*

$Al^{3+}$ and $Fe^{3+}$ compete for the same enzymes; however, in contrast to $Fe^{3+}$, $Al^{3+}$ has no oxidative function. The competition between these ions causes enzymes to be blocked. If $Si^{4+}$ is present, $Al^{3+}$ reacts with it to form aluminosilicate and does not interfere with $Fe^{3+}$. Hence, studying the impact of the aluminum concentration in drinking water on human health without determining the Si concentration is of no value (Birchall, 1992). Although this fact was not completely unknown, disregarding the Si concentration was a common practice. As a result, despite numerous studies and a multitude of publications, the applicability of the AlH could never be clarified.

Al is the main suspect as a disease-causing agent because it is considered to be an "artificial" metal that humans were not originally exposed to routinely. However, this reasoning falls short. All terrestrial beings inevitably come into contact with Si, Al, and oxygen, the three most abundant elements in Earth's crust; therefore, humans have always been exposed to these elements. For ages, humans lived in caves and then in dwellings with natural, unsurfaced ground. They were exposed to dust containing Al in the form of aluminosilicates throughout their lives. From prehistoric times to the present, however, the prevalence of AIDs has been low, indicating that Al has not historically been harmful to the human body.

$Si^{4+}$, like $Al^{3+}$, is naturally occurring. Despite the chemical similarity of $Si^{4+}$to $Al^{3+}$, Si has never been suspected of being harmful. Organic Si, which is artificial, is considered to be beneficial to health. Si is considered to be essential, even though the Si-C bond, which makes the Si "organic", has never been found in nature. The essentiality of silicon seems to be based only on its precipitation reaction with Al, which reduces its bioavailability (Birchall, 1992).

At the beginning of the last century, proteins within MFs were suspected to cause neurodegenerative diseases; this was later disputed. By the middle of the last century, scientists researched the correlation between Al and MFs, which was also later disputed. Since the turn of the century, most scientists have switched their attention back to proteins. However, explaining the occurrence of MFs with only amyloid-β peptide and not including Al and Si in the hypothesis does not appear to be the correct approach. The inclusion of additional proteins also does not appear to solve the problem regarding the causes of neurodegenerative diseases.

According to Ramirez-Alvarado, Merkel and Regan (2000), MFs contain amyloid-β peptide and 17 additional polypeptides. The 18 proteins show no sequential or structural similarities; however, they all react with the same dye and are stable over a wide pH range. The pH stability appears to be an additional indication of the presence of aluminosilicates, whereas the lack of structural similarities supports our assumption that MFs are caused by electrical loads. In principle, all electrically charged particles are expected to be attracted to the electrical load of the aluminosilicate kernel. In that case, most polypeptides, rather than only 18, are expected to be misfolded.

If folding is irreversible, then the protein is trapped and unable to return to its native state (Ramirez-Alvarado, Merkel & Regan, 2000). If the Coulomb forces are due to the negative surface charges on microbes, then the MFs may eventually disappear. However, if the Coulomb forces are due to aluminosilicates, then the MFs will remain (Smith et al., 1991), and the therapeutic approach of destroying amyloid-β peptide deposits (Karran & Hardy, 2014) will not be useful. Presumably, misfolding is a common feature of the human immunological response against foreign particles bearing electrical loads. Hence, electrically charged particles like aluminosilicate particles are the cause of diseases, whereas all other components of the MFs are the effect.

### *Metabolism of PDMSs and a hidden Al-Si flux*

The disproportionately large but stable energy demand of the brain (Raichle & Gusnard, 2002) may initiate the metabolism of PDMS-producing ionic Si (Jugdaohsingh et al., 2013), which immediately interferes with Al by inducing the formation of aluminosilicate deposits and reducing the Al and Si concentrations. A substantial part of even a low concentration of Al can be precipitated this way. A blood volume of approximately 4 L contains 10 µg of Al and is circulated once per minute. Assuming that a local equilibrium exists, the reduced Al content in blood is replenished during circulation through the human body. In this manner, a reduction of 50 % enables a deposition of 0.5 µg Al per minute, corresponding to 15 mg per day, which is an amount that is beyond sufficient to explain the extent of the visible MFs.

## Concluding remarks

A valid aluminum hypothesis cannot consider aluminum alone. To explain the findings mentioned above, the hypothesis must also include inorganic and organic silicon. The AlSiH provides a chemical explanation for the precipitation of Al in the human body after the Al passes through the blood-brain barrier in quantities sufficient to generate plaques, tangles, and other MFs to the extent found in the human neurological system. In this AlSiH, the causative factor is a group of chemical compounds whose consumption depends on the level of urbanization and hygiene of the subject (Buchter, Dunkel, & Li, 2012). The small amounts of freely available data on the production of organic silicon show increases that are similar to the prevalence rates. For instance, the worldwide prevalence rates for AIDs increased by 6 % annually from 1985 to 2015 (Lerner, Jeremias, & Matthias, 2015). The worldwide production of organic silicon increased by 7 % annually from 1991 to 1995 (Chandra, Maxim, & Sawano, 1997). This similarity does not provide proof, but it is an indication of the possible involvement of PDMSs in AIDs that is supported by the fact that PDMS consumption and the occurrence of AIDs began to play a role in the western hemisphere around 1980, with time delays of 20 to 30 years in the eastern hemisphere and in developing countries.

Aside from the AlSiH, none of the other hypotheses proposed thus far can explain the variety of AIDs and their variable prevalence, except for the HH, which is based on the reasoning that a clean environment denies the human body the opportunity to become sufficiently immunized (Okada et al., 2010). This explanation may appear convincing, but it contradicts common medical sense and negates the fact that better hygiene in medicine and in everyday live has reduced the number of deaths and has improved life expectancy. A cleaner environment is also associated with the use of more cleaning products, which harm the human body. Hence, AIDs could be triggered by the excessive usage of chemical substances rather than by the cleanliness of the environment. This reasoning would provide a simpler interpretation of the correlation between hygiene and AIDs, and the HH would fit well with the AlSiH.

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