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Aluminium in allergen-specific subcutaneous immunotherapy – A German perspective

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ABSTRACT

We are living in an "aluminium age" with increasing bioavailability of the metal for approximately 125 years, contributing significantly to the aluminium body burden of humans. Over the course of life, aluminium accumulates and is stored predominantly in the lungs, bones, liver, kidneys and brain. The toxicity of aluminium in humans is briefly summarised, highlighting links and possible causal relationships between a high aluminium body burden and a number of neurological disorders and disease states.

Aluminium salts have been used as depot-adjuvants successfully in essential prophylactic vaccinations for almost 100 years, with a convincing positive benefit-risk assessment which remains unchanged.

However, allergen-specific immunotherapy commonly consists of administering a long-course programme of subcutaneous injections using preparations of relevant allergens. Regulatory authorities currently set aluminium limits for vaccines per dose, rather than per treatment course. Unlike prophylactic vaccinations, numerous injections with higher proportions of aluminium-adjuvant per injection are applied in SCIT and will significantly contribute to a higher cumulative life dose of aluminium. While the human body may cope robustly with a daily aluminium overload from the environment, regulatory cumulative threshold values in immunotherapy need further addressing. Based on the current literature, predisposing an individual to an unusually high level of aluminium, such as through subcutaneous immunotherapy, has the potential to form focal accumulations in the body with the propensity to exert forms of toxicity. Particularly in relation to longer-term health effects, the safety of aluminium adjuvants in immunotherapy remains unchallenged by health authorities. The possibility of providing an effective means of measuring aluminium accumulation in patients undergoing long-term SCIT treatment as well as reducing their aluminium body burden, is discussed.

1. Aluminium exposure

1.1. Aluminium in the environment

Aluminium (Al^{3+}) is the third most abundant element in the Earth's crust [1,2]. In 1825, it was isolated by the Danish physicist Hans Oersted [3]. Most aluminium is stably bound as an ore in clay, minerals, rocks and gemstones. Mobilisation of aluminium in the environment can result from natural processes (acidic precipitation) and through anthropogenic activities. This lightweight, non-magnetic, silvery white-coloured metal can be produced from the aluminium ore—bauxite—by a high energy-consuming mining process; it is this process which provides the world its main source of the metal. As a consequence of this technological progress, aluminium has become increasingly bioavailable for approximately the past 125 years [2]. Toxic mine tailings can leach and seep into aquifers, contaminating local water sources and soils. Most human exposure comes from the environment (the food we eat and the water we drink) [4]; additionally, aluminium is added for the coagulation of contaminants in drinking water. As a raw material, aluminium is used extensively in industry owing to its unique and inherent properties (e.g. as a soft, light weight, resistant, non-corrosive metal). Aluminium and its compounds can be found in drinking water, our food, air, medicines, deodorants (antiperspirants), cosmetics and forms essential components in many household items and equipment, packaging, buildings and in

Abbreviations: SCIT, Subcutaneous Immunotherapy; EFSA, The European Food Safety Authority; TWI, Tolerable Weekly Intake; CHMP, Committee for Medical Products for Human use; EMA, European Medicine Agency; PDCO, The Paediatric Committee.

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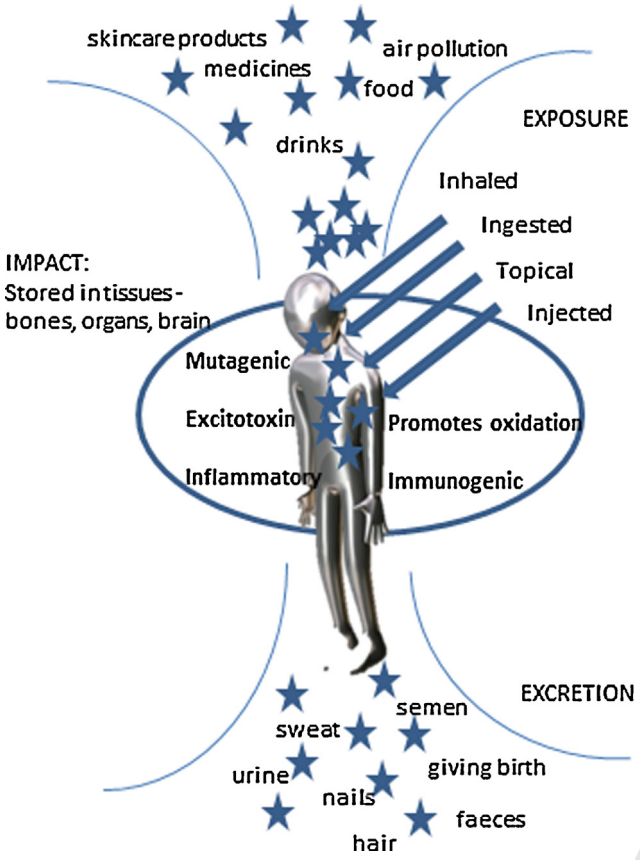

Fig. 1. A representation of human exposure to aluminium and its impact on the body [2].

aerospace engineering. It is the most widely used and distributed metal on the planet. Consequently, the human race is commonly referred to as living in an "aluminium age".

1.2. Human exposure to aluminium

Food, drinking water, air and medicines are considered to be sources of the aluminium load for humans (Fig. 1). With the utilisation of aluminium growing, bioavailability is increasing continuously. In 1950 this dietary aluminium load was thought to be approximately 1 mg per day, it is estimated to be 100 mg in 2050 [2]. Krewski et al. [4] present an overview of aluminium sources from foodstuffs and other products which contribute to this increase in exposure and subsequent load.

Uptake of Al^{3+} via the gastrointestinal tract is low: mostly reported as being between 0.1% and 1% [6], although considerably higher rates are described [7]. Of note, the bioavailability in drinking water is co-dependent on its silicic acid content: large amounts of silica in drinking water reduce the uptake of aluminium and vice versa [6,8]. Furthermore, aluminium interacting with various peptides, (glyco-) proteins and carbohydrates such as [iso-] citrate, malate, oxalate, succinate, tartrate, etc. must be taken into account. Such forms of aluminium significantly increase absorption rates [6,9–11].

Aluminium is excreted primarily via faeces and urine, with skin, hair, nails, sebum, semen, and sweat also having been described as excretion routes [2]. In fact, >95% aluminium is efficiently eliminated through the kidneys which helps explain why we can cope robustly with a daily dietary aluminium overload from the environment, minimising but not completely eliminating the risk of focal accumulations of the metal in other areas of the body. However, dialysis patients have been shown to bear levels of >30 μg/L aluminium in their sera, subsequently being linked with osteomalacia and related disorders [3]. High-risk individuals such as these would be at risk of longer-term health problems linked to aluminium accumulation/toxicity, outlined in Section 2 of this review.

Sweating particularly appears to be an underestimated excretion route for aluminium [12] that has been calling into question the widespread use of antiperspirants, which themselves contribute to the aluminium body burden [13,14].

Recently, the German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung = BfR) calculated the daily systemic absorption of aluminium through the healthy skin to constitute 10.5 μg, which is above the amount considered safe for an adult (8.6 μg per day). Systemic absorption through damaged skin (e.g. after shaving) is much higher. The BfR therefore announced a warning not to apply an aluminium-containing antiperspirant shortly after shaving the armpit because of the significant contribution to the general aluminium body burden [15].

1.3. Aluminium in the body

Aluminium performs no obvious biological function in the human body and there is no evidence to date of aluminium-specific metabolism [16]. However, aluminium will take a number of different routes of absorption and interactions which will now be briefly summarised.

In the blood, >90% aluminium in plasma is associated with transferrin [2], with the approximate concentration of aluminium is believed to be ~1–2 μg/L. The lungs and the bones are considered to be the major deposits in the body. Bone, lung, muscle, liver and brain are described as bearing approximately 60, 25, 10, 3 and 1% of the total body burden of aluminium, respectively [4]. Aluminium concentrations are also thought to increase with age [4]. The monocarboxylate transporter, the transferrin receptor shuttle, aluminium citrate and, recently described, ferritin are considered to be the transport routes of aluminium for crossing the blood–brain barrier [5,7–9,16]. In 2001, Yokel et al. published a half-life of 150 days of aluminium in the brains of rats following a single parenteral application of an ^{26}aluminium isotope [17].

Monitoring aluminium accumulation in humans is challenging. Urine and blood plasma analysis can be performed however neither will provide an accurate indication of the total aluminium body burden of an individual. Exley, 2013 best describes the true body burden of aluminium: "*for an individual is clearly not yet a quantity which is accessible by conventional means, at least not for a living person. While measurements of body burden are available these are actually indirect estimates of the systemic body burden, for example, the aluminium content of urine. These measurements are particularly helpful in comparing relative changes in the body burden of aluminium between individuals or between populations. They are, however, are less informative about where aluminium is found in the body or its potential for systemic toxicity*" [2].

1.4. Human threshold values

EFSA (The European Food Safety Authority) stated in a recent report [18]: "*in view of the cumulative nature of aluminium in the organism after dietary exposure, the Panel considered it more appropriate to establish a tolerable weekly intake (TWI) for aluminium rather than a tolerable daily intake (TDI)...*

...Based on combined evidence... the Panel established a TWI of 1 mg of aluminium/kg bw/week."

Animal studies are the rationale for the definition of this threshold value: "*The available studies have a number of limitations and do not allow any dose-response relationships to be established. The Panel*