National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Human health risk assessment of aluminium

RIVM report 2020-0001

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F. Affourtit (author/editor), RIVM
M.I. Bakker (author/editor), RIVM
M.E.J. Pronk (author/editor), RIVM

With contributions from
B.G.H. Bokkers, RIVM
P.E. Boon, RIVM
E.F.A. Brandon, RIVM (currently Medicines Evaluation Board, CBG)
M.J.B. Mengelers, RIVM
A.G. Oomen, RIVM
B. Tiesjema, RIVM (currently Medicines Evaluation Board, CBG)
B.M. van de Ven, RIVM
M. Weda, RIVM
M.J. Zeilmaker, RIVM

Contact:
Martine Bakker
Centrum voor Veiligheid van Stoffen en Producten
martine.bakker@rivm.nl

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Synopsis

Human health risk assessment of aluminium

People are exposed to aluminium via various sources. Examples are food, personal care products, cleaning agents, soil particles and house dust. Aluminium is also present in some vaccines and medicines, such as certain antacids.

In recent years, there has been public concern that the use of aluminium in personal care products, in particular deodorants, may result in high exposure to aluminium, which can have adverse effects on the nervous system. The Ministry of Health, Welfare and Sport has therefore asked the RIVM to estimate the total exposure to aluminium from all relevant sources for the Dutch population, and to identify whether this exposure is associated with a risk.

Total aluminium exposure from food, soil and consumer products such as personal care products and cleaning agents is estimated to be below the health-based guidance value for aluminium, indicating that there is no health risk. In exceptional cases the exposure from these sources exceeds the guidance value, but only to a slight degree.

Food is the main source of aluminium exposure. In particular infant formula and infant foods sometimes contain relatively high levels of aluminium. It is therefore recommended that the aluminium content in these infant products be kept as low as possible. In some clay-based food supplements the level of aluminium can also be high. Adults are therefore advised not to use such supplements for intestinal cleansing on a long-term or frequent basis, and pregnant women should not use them for reducing morning sickness.

The ingestion of soil is another important source of aluminium in children up to 10 years of age, due to their hand-to-mouth behaviour. On the other hand, skin care products (like deodorants and sunscreen) hardly contribute to the body burden of aluminium in children and adults, as aluminium barely penetrates the skin.

Young children have additional exposure to aluminium via vaccinations, but this exposure is only very small. Moreover, aluminium-adjuvanted vaccines have a long history of safe use. For adults, antacids containing aluminium can be a major source of aluminium exposure. Long-term use of this type of antacids is therefore advised against.

Keywords: aluminium, risk assessment, food, personal care products, cosmetics, anti-perspirant, deodorant, soil, antacids, vaccines

Publiekssamenvatting

Beoordeling van de gezondheidsrisico's van aluminium

Mensen staan via verschillende bronnen bloot aan aluminium. Voorbeelden zijn voedsel, persoonlijke verzorgingsproducten, schoonmaakmiddelen, bodemdeeltjes en huisstof. Aluminium zit ook in sommige vaccins en medicijnen, zoals bepaalde maagzuurremmers.

De laatste jaren bestaan er zorgen in de samenleving dat het gebruik van aluminium in persoonlijke verzorgingsproducten, zoals deodorant, een te hoge blootstelling aan aluminium kan veroorzaken. Te veel aluminium kan schadelijk zijn voor het zenuwstelsel. Het ministerie van VWS heeft het RIVM daarom gevraagd te bepalen aan hoeveel aluminium mensen via alle mogelijke bronnen blootstaan en wat het risico daarvan is.

Volgens het RIVM is de totale blootstelling aan aluminium uit voedsel, consumentenproducten en bodem niet schadelijk voor de gezondheid. Dat komt omdat de totale blootstelling aan deze bronnen over het algemeen ruim beneden de gezondheidskundige grenswaarde ligt. Deze grens wordt alleen bij uitzondering overschreden, en zelfs dan slechts in lichte mate.

Mensen krijgen de meeste aluminium binnen via het voedsel. Omdat zuigelingenvoeding soms relatief hoge gehaltes aluminium kan bevatten, is het raadzaam erop toe te zien dat deze gehaltes zo laag mogelijk zijn. In sommige voedingssupplementen op basis van klei kan ook veel aluminium zitten. Daarom wordt volwassenen afgeraden om vaak of langdurig ontslakkingsklei te gebruiken en zwangeren om zwangerschapsklei in te nemen.

Kinderen tot een jaar of tien kunnen ook vrij veel aluminium binnenkrijgen via bodemdeeltjes die ze via hand-mond-contact inslikken. Aluminium uit huidverzorgingsproducten, zoals deodorant en zonnebrand, dringt nauwelijks door de huid heen. Hierdoor is de blootstelling van het lichaam aan aluminium door gebruik van deze producten heel laag.

Voor jonge kinderen zijn sommige vaccins ook een bron van blootstelling. Ze worden door deze inentingen blootgesteld aan kleine hoeveelheden aluminium. De veiligheid van deze vaccins is bewezen en wordt continu in de gaten gehouden. Voor volwassenen kunnen maagzuurremmers die aluminium bevatten een grote bron van blootstelling zijn. De bijsluiter van dit type maagzuurremmers bevat daarom het advies om ze niet langdurig te gebruiken.

Kernwoorden: aluminium, risicobeoordeling, voedsel, persoonlijke verzorgingsproducten, cosmetica, anti-transpirant, deodorant, bodem, maagzuurremmers, vaccins

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Summary

At the request of the Ministry of Health, Welfare and Sport (VWS), the RIVM has performed a risk assessment of aluminium exposure from all relevant sources for the general population in the Netherlands. The aim of the integrated risk assessment was to identify the major source(s) contributing to the aggregate exposure, and to identify any subpopulation(s) at risk.

Being one of the most abundant elements in the earth's crust, aluminium occurs naturally in air, water and soil. Humans are therefore exposed to aluminium through the inhalation of ambient air and the ingestion of drinking water and food of agricultural origin. Additional sources of aluminium in food are food additives containing aluminium and the migration of aluminium from food contact materials such as packaging materials and kitchenware. Humans can also be exposed to aluminium through the ingestion of soil and house dust, through the use of certain consumer and pharmaceutical products containing aluminium (e.g. some personal care products, antacids and vaccines), and through the ingestion of certain clay-based food supplements.

In the current report, estimates of exposure from food were based on dietary aluminium intakes as calculated from diet studies and reported in the literature. These dietary intake estimates already include aluminium from food additives, packaging materials and kitchenware. Exposure from vaccines was estimated on the basis of the Dutch National Immunisation Programme (NIP). For the estimation of exposure from the other identified sources, use was made of occurrence data found in the literature on aluminium concentrations in the various media and products, in combination with worst case values for daily use amounts or ingestion rates.

The aggregate exposure to aluminium is the summation of the exposures estimated for the individual sources. Since different sources involve different routes of exposure, summation was only possible after converting the estimates into systemic values, taking into account the bioavailability of aluminium via the oral, dermal and inhalation routes. To provide some insight into the exposure variation, the systemic exposure estimates have been given for the average consumer and for the highly exposed consumer, with low- and high-end values indicated for each group of consumers.

From reviews on the oral toxicity of aluminium salts, it appears that aluminium is of moderate to low acute toxicity. Upon repeated administration, aluminium targets various tissues and organs, including the kidneys, liver and, at higher doses, nerve cells and bone. There is no indication of carcinogenicity. Effects on the reproductive system have been observed in male mice, rabbits and dogs, but not in rats. In addition, aluminium compounds may cause embryotoxicity in mice and rats, as well as neurotoxicity in adult mice and rats and their offspring. The provisional tolerable weekly intake (PTWI) of 2 mg/kg bw, as set by JECFA (2012) on the basis of neurodevelopmental effects in rats given

aluminium citrate in drinking water, was used as the health-based guidance value (HBGV) for the current integrated risk assessment of aluminium salts. To allow comparison with the aggregate exposure estimates, the HBGV was converted to a systemic PTWI of 0.012 mg/kg bw/week by adjusting it for the low oral bioavailability of aluminium citrate in rats (0.6%) and assuming similar toxicity following oral, dermal and inhalation exposure to aluminium.

It is to be noted that aluminium exposure due to the use of aluminium-containing pharmaceutical products (i.e. some antacids and some vaccines in the NIP) was estimated but not included in the aggregate exposure and risk assessment. This is because their exposure characteristics are different from the other exposure sources: exposure is not continuous over life but only incidental during childhood (vaccines) or occasionally, for a couple of weeks at a time (antacids), and exposure is expected to be beneficial for health as these products are given for a medical reason.

The aggregate exposure and risk assessment showed that only for a few subpopulations the aggregate exposure might exceed the HBGV, due to exposure from certain specific sources. These are:

- children 0–6 months old and 1–2 years old fed infant formula or diets high in aluminium;
- pregnant women taking clay-based food supplements against morning sickness;
- adults taking clay-based food supplements for intestinal cleansing.

Whereas breast milk contains hardly any aluminium, some infant formula and infant foods have a high aluminium content, in particular soy-based products. Hence, aluminium intake for children of 0–6 months old and 1–2 years old that are regularly fed high-aluminium-content infant products may rise slightly above the internal HBGV (to approximately 0.015-0.018 mg/kg bw/week). Intakes above the HBGV do not directly result in adverse health effects, but initially represent only a reduction of the safety margin. These reductions are relatively small (to 68–79, compared with the standard margin of 100). Furthermore, there are no indications from the literature that aluminium intake levels resulting from the consumption of infant formula and diets are harmful to the health of infants and toddlers. Nevertheless, the aluminium content in marketed infant formula/foods should not be such that the HBGV is exceeded following consumption.
For 0–2-year-olds, soil also appears to be a relatively important contributor to the aggregate exposure (maximally 32–39% of the internal HBGV). The contribution of sunscreen, on the other hand, is virtually negligible.

The use of clay-based food supplements to reduce morning sickness during the first months of pregnancy (mostly by women of Surinam and African origin) may result in aluminium exposure that greatly exceeds the internal HBGV (up to a factor of 32). Given that these supplements may additionally contain dioxins and various other metals that may adversely affect the health of the mother and the unborn child, the use

of such supplements during pregnancy should be strongly advised against.

The use of certain clay-based food supplements for intestinal cleansing by adults may result in aluminium exposure from this source that exceeds the internal HBGV (by a factor of 1.5). This is only the case when clays with the highest aluminium content are used. Whereas the short-term use of clays with a lower aluminium content is likely of no or only limited concern, the long-term or repeated use of intestinal cleansing clays should be advised against.

The risk assessment showed no concern for the aggregate exposure of children 7–12 months old and 3–10 years old, of adolescents 11–17 years old and of adults to aluminium in diet, soil and personal care products. In these age groups, diet is the main contributor to the aggregate exposure, amounting to maximally 37%, 79%, 39% and 56% of the internal HBGV, respectively. Soil is equally important in children aged 7–12 months (maximally 39% of the internal HBGV), and is the second largest contributor in children aged 3–10 years (maximally 13-22% of the internal HBGV).
In adolescents and adults, orally applied personal care products such as whitening toothpastes and lipsticks/lip glosses are a more important contributor (maximally 42% and 11–17% of the internal HBGV, respectively) than soil (maximally 2.5–4% of the internal HBGV). In all likelihood, however, the contribution of toothpastes and lipsticks is smaller than estimated, as aluminium is present in these products as water-insoluble lakes. For exposure estimation, 100% bioaccessibility of aluminium from these lakes was assumed. But as only a small fraction of aluminium will be extractable from these lakes, the exposure estimation for these products is worst case.
The dermal absorption of aluminium from personal care products has recently been shown to be very low (0.00052%), so even though dermally applied personal care products (like antiperspirants, deodorants and sunscreen) form the main external source of exposure to aluminium, their contribution to the total systemic exposure is virtually negligible.
No significant additional exposure (dermal) is to be expected for adults from household products like cleaning agents, in view of the very low dermal absorption of aluminium in humans.

Regarding aluminium exposure from medical uses, the oral use of aluminium-containing antacids can result in aluminium exposure very much higher than that from diet and other sources. Notwithstanding the health benefits of antacid medication, from a toxicological viewpoint such high exposures are not recommendable for prolonged periods. The current advice against the long-term use of antacids is therefore supported. Another option for consumers suffering from heartburn is to choose for aluminium-free antacids.

As to vaccines used in the Dutch NIP, aluminium exposure from aluminium-adjuvanted vaccines is most relevant for children up to 1 year old. A comparison of this exposure with exposure from other sources for this age group is not straightforward, given differences in the frequency (incidental), route of administration (intramuscular

injection) and form of aluminium (aluminium-containing adjuvants are nanoparticles forming micrometre-size agglomerates). Little is known about the kinetic behaviour of these particulates in vaccine formulations, and whether and how this specific form influences the hazard profile of aluminium. However, aluminium exposure from a total of six incidental injections over the first year of life is low. It should be further noted that aluminium-adjuvanted vaccines have a long history of use. Uncertainty as to the pharmacokinetics of the particulates is offset by the many clinical trials and epidemiological studies supporting the safety of these vaccines.

1 Introduction

Aluminium is ubiquitous in the environment, being one of the most abundant elements in the earth's crust. Aluminium and aluminium compounds[1] therefore occur naturally in ambient air and are a natural component of drinking water and many untreated foods such as fruits, vegetables and grains. Aside from its natural presence, aluminium is an environmental contaminant, due to anthropogenic releases associated with industrial processes (e.g. mining, coal combustion and other industrial activities/uses). Consequently, humans are exposed to aluminium by the inhalation of ambient air and the ingestion of food and drinking water. Additional sources of aluminium in food are food additives containing aluminium and the migration of aluminium from food contact materials such as cooking utensils and packaging materials. Certain consumer products (e.g. personal care products[2] and cleaning agents) and pharmaceuticals (e.g. antacids and vaccines) are further sources of aluminium exposure for humans.

Exposure to aluminium has long been considered safe in healthy individuals. In 2011–2014, however, risk assessments by the French Health Products Safety Agency (AFSSAPS, 2011), the Norwegian Scientific Committee for Food Safety (VKM, 2013) and the German Federal Institute for Risk Assessment (BfR, 2014) raised concerns over the use of aluminium in personal care products, in particular antiperspirants and deodorants. Based on the knowledge at that time, the assessments concluded that daily application of antiperspirants/ deodorants under normal conditions of use cannot be considered safe. The Norwegian assessment further showed that these personal care products contribute considerably more than diet to the total systemic exposure to aluminium in individuals using such products.

These assessments resulted in a request from the Ministry of Health, Welfare and Sport (VWS) to the RIVM to carry out an integrated risk assessment of aluminium for the Dutch population, with the following objectives:

- to estimate the aggregate exposure to aluminium from the relevant exposure sources and routes;
- to assess whether there is a risk associated with the aggregate exposure (i.e. is there a risk of exceeding the health-based guidance value (HBGV) for aluminium?);
- to identify the major contributing source(s) to the aggregate exposure; and
- to identify any subpopulation(s) that may be especially at risk.

Given the focus on exposure, the RIVM was not asked to do a full hazard assessment of aluminium, including the derivation of an HBGV. As several international organisations had already thoroughly reviewed the

[1] For readability, in the rest of the report 'aluminium' is short for 'aluminium and its compounds', unless otherwise specified.
[2] Also called cosmetics or cosmetic products. These terms are in use by e.g. the Scientific Committee on Consumer Safety (SCCS).

toxicity of aluminium, the RIVM was to draw on the existing evaluations and HBGVs for the risk assessment.

Regarding aluminium in vaccines and antacids, account was taken of the fact that these sources have exposure characteristics that differ from those of the other exposure sources. First, exposure to these pharmaceuticals is not continuous over life (or major parts thereof). For vaccines it is only incidental, during childhood, and for antacids it is occasional, for a couple of weeks at a time. Second, pharmaceuticals are given/taken for a medical reason; therefore, exposure is expected to be beneficial for health. These differences complicate comparison with the other exposure sources, in which aluminium can be seen as a contaminant, and to which exposure is more continuous in character. Therefore, pharmaceutical use will not be included in the aggregate exposure and risk assessment. Nevertheless, as pharmaceuticals are an exposure source for humans, exposure to aluminium in vaccines and antacids will be estimated so that it can be seen how it compares with exposure from the other sources of aluminium.

An overview of the toxicity of aluminium, including the most relevant HBGVs, is presented in Chapter 2 of this report. Chapters 3 and 4 present an overview of the kinetics of aluminium salts (the form of aluminium in all exposure sources except vaccines) and of aluminium-containing adjuvants, respectively. The latter are applied in several vaccines used in the Dutch National Immunisation Programme (NIP) and are composed of very small primary particles that agglomerate. Their kinetic behaviour potentially differs from that of the aluminium salts present in the other exposure sources. The potential association between exposure to aluminium and adverse effects in humans is discussed in Chapter 5. Chapters 6 to 10 present the exposure estimations for the various exposure sources identified for the Dutch population: diet, food contact materials and food supplements (Chapter 6), consumer products (Chapter 7), ambient air, soil and house dust (Chapter 8), antacids (Chapter 9) and vaccines (Chapter 10). Chapter 11 gives the aggregate exposure from the sources presented in Chapters 6–8, followed by a risk assessment of the aggregate exposure and a discussion of the results. A separate discussion in this chapter is dedicated to antacids and vaccines. Finally, Chapter 12 presents conclusions and recommendations.

2 Toxicity of aluminium

2.1 Introduction

The toxicity of aluminium has been thoroughly reviewed by international organisations like the US Agency for Toxic Substances and Disease Registry (ATSDR; ATSDR, 2008), the European Food Safety Authority (EFSA; EFSA, 2008) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA; JECFA, 2007, 2012), which have also established health-based guidance values (HBGVs) for aluminium. Scientific committees like the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT; COT, 2013), the Scientific Committee on Consumer Safety (SCCS; SCCS, 2014, 2020) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER; SCHEER, 2017) have drawn on these evaluations and HBGVs in their risk assessments of aluminium – particularly on the most recent evaluation, by JECFA (2012). They have also performed additional literature searches to identify relevant papers in the period after 2008, but have concluded that the additional data retrieved did not affect the HBGVs already established.

Given the objective of the current report for an integrated exposure and risk assessment rather than a hazard assessment of aluminium, we also build on the existing evaluations and HBGVs. Sections 2.2.1–2.2.10 below are summaries of these previous evaluations and reports. It is to be noted that these data mostly pertain to soluble aluminium salts, which form the basis for the existing HBGVs described in Section 2.3. Hardly any toxicity data are available on the aluminium salts present in adjuvants (in nanoform) or vaccines (micrometre-size agglomerates of nanoparticles); see Section 2.2.11. In Annex I, more information can be found on the aluminium-containing adjuvants used in vaccines.

2.2 Toxicity of aluminium

2.2.1 Acute toxicity

The acute oral toxicity of those aluminium (Al) compounds for which data are available (bromide, nitrate, chloride and sulfate) is moderate to low, with LD_{50} values ranging from 162 to 750 mg Al/kg bw in rats, and from 164 to 980 mg Al/kg bw in mice, depending on the aluminium compound (EFSA, 2008).

There are no data on acute dermal toxicity. ATSDR (2008) reports that an acute 4-hour exposure to up to 1,000 mg Al/m^3 as aluminium oxide was not lethal to rats.

2.2.2 Irritation / corrosion

Limited information is available on the toxicity of aluminium following dermal exposure. Application of aluminium salts to the skin, such as aluminium chloride in ethanol or potassium aluminium sulfate, may cause rashes in some people. Skin damage has been observed in mice, rabbits and pigs exposed to aluminium chloride or aluminium nitrate, but not following exposure to aluminium sulfate, aluminium hydroxide, aluminium acetate, or aluminium chlorohydrate (ATSDR, 2008). No

studies were located regarding ocular effects in humans or animals following oral, dermal or inhalation exposure to various forms of aluminium (ATSDR, 2008).

2.2.3 *Sensitisation*

The available animal studies do not show the aluminium compounds used in antiperspirants to be skin sensitisers. Although there is limited evidence that aluminium compounds can cause contact allergy in humans, the SCCS considered this to be a rare phenomenon, in view of the widespread use of these compounds (SCCS, 2020).

2.2.4 *Repeated dose toxicity*

The following is extracted from the EFSA (2008) review of oral repeated-dose studies.

After subchronic oral exposure in rats, aluminium compounds (including aluminium nitrate, aluminium sulfate and potassium aluminium sulfate) caused various effects, including decreased body weight gain and mild histopathological changes in spleen, kidney and liver (lowest LOAEL/NOAEL observed 104/52 mg/kg bw/day). The severity of the effects increased with dose, and effects on nerve cells, testes, bone and stomach were also reported at higher doses.

Dietary administration of acidic sodium aluminium phosphate to beagle dogs for 26 weeks produced no toxicologically relevant effects (NOAEL 88–93 mg/kg bw/day). In contrast, 26-week dietary administration of basic sodium aluminium phosphate resulted in decreased food consumption, decreased body and testis weight and histopathological changes in liver and kidney in male beagle dogs (LOAEL 75 mg/kg bw/day, NOAEL 27 mg/kg bw/day) but not in female dogs (NOAEL 80 mg/kg bw/day).

Respiratory effects typically associated with the inhalation of particulates and lung overload were the main effects in animals following repeated inhalation exposure to aluminium chlorohydrate, with an overall NOAEC of 0.061 mg/m^3. No studies were located regarding health effects in animals following intermediate or chronic dermal exposure to various forms of aluminium (ATSDR, 2008).

2.2.5 *Mutagenicity/Genotoxicity*

Aluminium compounds were non-mutagenic in bacterial and mammalian cell systems, but some produced DNA damage and effects on chromosome integrity and segregation *in vitro*. Clastogenic effects were also observed *in vivo* when aluminium sulfate was administered at high doses by gavage or by the intraperitoneal route. Several indirect mechanisms have been proposed to explain the genotoxic effects observed (EFSA, 2008). COT (2013) and SCHEER (2017) concurred with the conclusion of the EFSA Panel that the indirect mechanisms of genotoxicity that occur at relatively high levels of exposure are unlikely to be of relevance to humans exposed to aluminium via diet (EFSA, 2008).

According to SCCS (2020), analysis of the available data, including recent open literature, confirms that:

- soluble aluminium salts (e.g. aluminium chloride, aluminium sulfate, aluminium chloride basic) do not induce gene mutations in bacteria or in mammalian cells;

- it cannot be excluded that the salts may induce chromosomal aberrations *in vitro*;
- the salts may induce increased DNA damage in a comet assay *in vitro*;
- it cannot be excluded that the salts may induce chromosomal aberrations *in vivo*.

The SCCS stressed, however, that the positive results were mostly reported in the open literature, and that generally these studies have some limitations. The SCCS further considered that a threshold mechanism for the genotoxicity of aluminium ions can be assumed, given that the two most commonly reported modes of genotoxic action include induction of oxidative stress and inhibition of proteins involved in mitotic spindle function. Based on all the available evidence, the SCCS concluded that aluminium is not likely to pose a risk of systemic genotoxic effects through dermal exposure from cosmetics use (SCCS, 2020).

2.2.6 Carcinogenicity

The literature on the carcinogenicity of aluminium compounds is limited, with mainly old studies, reporting little experimental detail and generally testing low dose levels of aluminium. However, in the most recent robust study, no indication of any carcinogenic potential was obtained in mice given aluminium potassium sulfate at high levels (850 mg Al/kg bw/day) in the diet (EFSA, 2008). The EFSA Panel further noted the absence of epidemiological evidence of carcinogenicity for aluminium compounds used therapeutically, and that the International Agency for Research on Cancer (IARC) had concluded that aluminium itself is unlikely to be a human carcinogen, despite the observation of an association between inhalation exposure to aluminium dust and aluminium compounds during production/processing and bladder and lung cancer in workers. Overall, the EFSA Panel concluded that aluminium is unlikely to be a human carcinogen at exposures relevant to dietary intake (EFSA, 2008). SCHEER (2017) and SCCS (2014, 2020) took note of this conclusion. The SCCS additionally concluded that aluminium is not considered to have potential carcinogenicity at exposure levels achieved via cosmetic use, and found no support in epidemiological studies for a possible link between dermal aluminium exposure and the development of breast cancer (SCCS, 2014, 2020). This topic is addressed in greater detail in Chapter 5.

2.2.7 Reproductive and developmental toxicity

Studies on reproductive toxicity in male mice (intraperitoneal or subcutaneous administration of aluminium nitrate or chloride) and male rabbits (administration of aluminium chloride by gavage at a level corresponding to 6.4 mg Al/kg bw/day) have demonstrated the ability of aluminium to cause testicular toxicity and decreased sperm quality in mice and rabbits, as well as reduced fertility in mice. No effects on male or female fertility were observed in rats given aluminium nitrate nonahydrate via drinking water (only females treated) or by gavage. In male beagle dogs, dietary administration of basic sodium aluminium phosphate (SALP), at a level corresponding to 75 mg Al/kg bw/day, produced a decrease in testicular weight and degeneration of the germinal epithelium (EFSA, 2008). JECFA (2012) additionally reported that multi-generation reproductive studies in which aluminium sulfate and

aluminium ammonium sulfate were administered to rats in drinking water, showed no evidence of reproductive toxicity. Likewise, no effects on reproduction were observed in rats given aluminium chloride basic (containing 17.0% aluminium oxide, 9.0% aluminium and 19.9% chlorine in aqueous solution) by gavage in a combined repeated-dose toxicity study with reproduction and developmental toxicity screening.

In general, high doses of aluminium compounds (nitrate, chloride or lactate) given by gavage have induced some signs of embryotoxicity in mice and rats – in particular, reduced foetal body weight or pup weight at birth and delayed ossification. The lowest LOAEL was reported for aluminium nitrate at a daily dose corresponding to 13 mg Al/kg bw/day in the rat. After dietary exposure of rats to aluminium chloride and lactate, the lowest NOAEL was 100 mg/kg bw/day for both salts. Gavage administration of aluminium hydroxide at doses providing up to 103 and 264 mg Al/kg bw/day was without embryotoxic effects in mice and rats, respectively (EFSA, 2008). Additionally, no developmental toxicity was observed in rats given aluminium chloride basic by gavage in a combined repeated-dose toxicity study with reproduction and developmental toxicity screening (JECFA, 2012).

2.2.8 Neurotoxicity and developmental neurotoxicity

Aluminium has shown neurotoxicity in patients undergoing dialysis in which insufficiently purified water was used and where the patients were therefore parenterally exposed to high concentrations of aluminium (EFSA, 2008). It has further been suggested that aluminium is implicated in the aetiology of Alzheimer's disease and associated with other neurodegenerative diseases in humans. This subject is discussed in Chapter 5.

Aluminium is a neurotoxicant in experimental animals. It is reported in JECFA (2007) and EFSA (2008) that species variation exists. In susceptible species (rabbits, cats, guinea-pigs, ferrets), toxicity is characterised by progressive encephalopathy resulting in death associated with status epilepticus. Aluminium additionally induced epileptic seizures in all species studied (e.g. primates, rodents and fish). It was, however, noted that the above-mentioned effects were observed after parenteral injection (e.g. intrathecal, intracerebral and subcutaneous). In contrast, behavioural impairment in the absence of overt encephalopathy or neurohistopathology was seen in rats and mice exposed to soluble aluminium salts (e.g. lactate, chloride) in the diet or drinking water generally at doses of 200 mg Al/kg bw/day or higher. Effects involved impairment of passive and conditioned avoidance responses (JECFA, 2007; EFSA, 2008).

The effects of subacute or semichronic exposure to aluminium have been studied in mice and rats. In a study in Swiss Webster mice where aluminium was given in the diet as aluminium lactate for 4, 8 or 13 weeks, no consistent behavioural effects were seen after doses equivalent to 100 mg Al/kg bw/day. In rats of different ages given daily doses of aluminium chloride in their drinking water for periods of 30, 60, or 90 days, a LOAEL of 52 mg Al/kg bw/day and a NOAEL of 30 mg Al/kg bw/day were reported for effects on the vestibulo-ocular reflex (EFSA, 2008).

The effects of oral aluminium exposure (as lactate or chloride) on brain development have been studied in mice. Effects recorded in more than one study in immature animals included impaired performance related to reflexes and simple behaviours. Post-natal mortality and growth were also affected at the higher doses in some of these studies. Adult rats and mice have also been assessed for brain function after developmental exposures. Reduced grip strength and startle responsiveness were found to persist for up to 150 days after birth. There was no effect on reactions to a light avoidance task in rats after gestational or postnatal exposure. In these studies, LOAELs were identified that ranged from maternal doses of 50 to 500 mg Al/kg bw/day (JECFA, 2007; EFSA, 2008).

It was concluded by JECFA (2007) and EFSA (2008) that most animal studies performed on the neurotoxicity and neurodevelopmental toxicity of aluminium had several limitations in their design and conduct. It was further noted that the results reported for aluminium lactate in a series of studies in Swiss Webster mice by one laboratory were inconsistent. For example, in one study a LOAEL of 50 mg Al/kg bw/day was reported for neurodevelopmental effects in offspring (with NOAELs at maternal doses of 10 and 42 mg Al/kg bw/day during pregnancy and lactation, respectively), whereas in another study with administration from conception throughout the whole lifespan, no clear signs of neurotoxicity were observed at 100 mg Al/kg bw/day.

In view of the limitations in the available studies, the JECFA recommended that further studies on developmental toxicity be carried out (JECFA, 2007). In response, a number of new studies were provided that supported previous observations of neurodevelopmental effects in experimental animals. It was, however, concluded that there continued to be a lack of consistency regarding the reported effects, and that there were some limitations to all of the studies (JECFA, 2012). The most robust study was considered to be a 12-month developmental and chronic neurotoxicity study in rats given aluminium citrate in drinking water (Poirier *et al*., 2011), and this study served as the basis for the HBGV (see Section 2.3.2). Starting from gestation day 6, pregnant rats received drinking water at target doses of 30, 100 or 300 mg Al/kg bw/day, based on an expected water intake of 120 ml/kg bw/day. Two control groups received either sodium citrate solution (27.2 g/l), the molar equivalent of the high-dose aluminium citrate, or plain water. The offspring were exposed to aluminium citrate *in utero* and through lactation, and thereafter via drinking water post-weaning. The major treatment-related effects observed were renal damage (hydronephrosis, urethral dilatation, obstruction and/or presence of calculi) and reduced grip strength, but not cognitive impairment, in the pups. Renal damage was not observed in the control group given sodium citrate, so the effect was not due to the citrate ion. The NOAEL and LOAEL for the major effects were at target aluminium doses of 30 and 100 mg/kg bw/day, respectively (Poirier *et al*., 2011, as summarised in JECFA, 2012).

2.2.9 Additional information from relevant recent publications

The most up-to-date literature search for additional relevant publications was performed by SCHEER (2017) and covered the period from 01/01/2008 until 31/01/2017. Although some additional data were

retrieved, it was concluded that these did not affect the HBGVs already established (SCHEER, 2017).

For the current report, we additionally found a series of publications by the same research group investigating the effects of aluminium chloride in rats (Martinez *et al*., 2017a/b/c, 2018), but no full literature search was performed.

In all four studies by Martinez and co-authors, aluminium chloride was administered to male Wistar rats at a low dose in drinking water for 60 days (1.5 and/or 8.3 mg Al/kg bw/day), or at a high dose (100 mg Al/kg bw/day) by gavage for 42 days. In these studies, aluminium at low doses induced vascular dysfunction and (transiently) increased the blood pressure (Martinez *et al*., 2017a), affected the object recognition memory but not the behaviour in open field, plus maze and hot plate tests (Martinez *et al*., 2017b), and impaired spermatogenesis and sperm quality and influenced testis histoarchitecture (Martinez *et al*., 2017c). It further decreased mechanical sensitivity and induced catalepsy, but did not affect thermal sensitivity or spontaneous motor activity (Martinez *et al*., 2018). The degree of effects seen at the low dose was almost the same as that at the high dose. According to the authors, this indicates that the toxicity of aluminium depends on a threshold dose that, once reached, results in almost the same effects.

Although the effective dose level in the above studies is lower than in the studies evaluated in EFSA (2008) and JECFA (2007, 2012), it is unclear at the moment whether and how they would affect the HBGVs already established. Whereas some findings support previous observations at aluminium doses from 50 mg/kg bw/day, this is not the case for all findings. For example, no effects on sperm or testis histopathology were observed in two multi-generation reproductive studies with administration of aluminium sulfate and aluminium ammonium sulfate in drinking water at doses ranging from approximately 2 to 45 mg Al/kg bw/day. In the same studies also no effects were observed on righting reflexes, locomotor activity or learning outcomes (Hirata-Koizumi *et al*., 2011a/b, as also reported in JECFA, 2012). The 12-month developmental and chronic neurotoxicity study in rats given aluminium citrate in drinking water (Poirier *et al*., 2011) also showed no effects on motor activity or on learning and memory at 30 mg Al/kg bw/day. However, behavioural studies in rodents are not easy to conduct or interpret, as many factors (including laboratory conditions) may influence the results. All in all, the findings of the Martinez *et al*. studies need confirmation by other tests, preferably from a different lab and with a different rat strain.

2.2.10 Observations in humans

Human data on the toxicity of aluminium mainly relate to certain patient groups. Neurological and/or skeletal effects have been reported in patients with impaired renal function, in patients receiving parenteral nutrition, and in patients receiving aluminium-containing medications (e.g. phosphate binders). These effects are related to an abnormal accumulation of aluminium, and have limited usefulness in predicting toxicity in the general population. Prematurely born infants also have higher body burdens of aluminium than other infants and may be more

sensitive to the toxicity of aluminium (ATSDR, 2008; EFSA, 2008; JECFA, 2012).

2.2.11 Toxicity studies with aluminium-containing adjuvants

Some studies have investigated the toxicity of aluminium-based nanoparticles, but these are mostly mechanistic in character and do not relate to the route or type of aluminium most relevant for vaccines. Available studies on aluminium adjuvants consist of investigations into behavioural effects in mice (see below). It is noted, though, that in these studies it was not the final vaccine formulation that was administered, but the adjuvants themselves (i.e. without antigen).

Crépeaux *et al*. (2017a) studied the neurotoxicity of Alhydrogel® adjuvant (aluminium oxyhydroxide) in adult (8-week old) female CD-1 mice 180 days after they had received intramuscular injections at doses of 200, 400 or 800 µg Al/kg bw. These doses were divided over 3 injections, given 4 days apart, and represented the mouse equivalent of 2, 4 or 8 human doses of aluminium-containing vaccine. Cognitive and motor performances were assessed by a series of eight behavioural or physical tests, chosen in order to assess locomotor activity in the open field, level of anxiety in the O-maze, short-term memory in the novel object recognition test, muscular strength in the wire mesh hang and the grip strength tests, locomotor coordination in the rotarod test, depression in the tail suspension test, and pain sensitivity in the hot plate test.
Neurobehavioural changes were observed in two of the eight tests (the open field test and the grip strength test), but in an atypical fashion: they were observed only in the low-dose group, not in the mid- and high-dose groups. The changes included decreased activity levels, altered, anxiety-like behaviour and decreased grip strength. Consistent with the neurobehavioural changes, and again restricted to the low-dose group, was an apparent increase in the microglial number in the ventral forebrain and an increase in brain aluminium levels, while muscle granulomas had almost completely disappeared at 6 months. The lack of neurotoxicity in the mid- and high-dose groups was thought to be due to limited translocation of aluminium to the brain, as a consequence of a higher degree of agglomeration in the dosing solution (see also Section 4.3), which complicates transport out of the injected muscle (Crépeaux *et al*., 2017a). It is noted that this study was heavily criticised by Hawkes and Benhamu (2017) with regard to its research ethics, unrealistic dosing, bias and funding – criticism that the study authors subsequently refuted (Crépeaux *et al*., 2017b; Crépeaux and Gherardi, 2018). Regardless of this discussion, the relevance of the observed findings to humans is unclear (see below).

A Canadian research group published a series of papers studying the behavioural effects of Alhydrogel® adjuvant in a CD-1 mouse model. The doses given in these experiments were chosen to mimic adult vaccination with anthrax vaccine (Petrik *et al*., 2007; Shaw and Petrik, 2009) or the US paediatric vaccination schedule (Shaw *et al.*, 2013; Sheth *et al*., 2018). The mice received subcutaneous injections into loose skin behind the neck. In the studies mimicking adult vaccination, the total dose of aluminium given was 100 µg/kg bw in the study by Petrik and co-authors (divided over 2 injections spaced 2 weeks apart)

and 300 µg/kg bw in the study by Shaw and Petrik (divided over 6 injections in a 2-week period). The former study used 3-month-old mice, the latter 9-month-old mice. In the studies mimicking neonatal vaccination (Shaw *et al.*, 2013; Sheth *et al*., 2018), the total dose of aluminium administered was 550 µg/kg bw (divided over 6 injections in a 2-week period). The mice were subjected to various motor, cognitive or social behavioural tests for up to approximately 6 months post-injections. Neonatal mice showed decreased locomotor activity, decreased exploratory behaviour and increased anxiety (Shaw *et al.*, 2013), as well as moderately impaired social behaviour (Sheth *et al*., 2018). Adult mice showed increased anxiety, motor deficits, decreased locomotor activity, memory deficits, and motor neuron loss in the lumbar spinal cord (Petrik *et al*., 2007; Shaw and Petrik, 2009). Not all of the above effects were, however, seen in both sexes of neonatal mice, or in both 3-month- and 9-month-old mice.

Although the above studies seem to indicate neurological/behavioural effects of aluminium-containing adjuvants in some of the tests performed in mice, the relevance to humans is unclear given several shortcomings. One shortcoming is that in the above studies the pure adjuvant was administered and not the adjuvant coupled to an antigen (as is the case in the final vaccine formulation administered to humans). The latter would behave differently. A second flaw is that neonatal mice (as used in Shaw *et al.* (2013) and Sheth *et al*. (2018)) are not a good model to translate findings to humans, given that at birth the central nervous system in mice is less developed than in humans (EMA, 2020). Furthermore, it is not clear how representative the treatment schedule in the Crépeaux *et al*. studies (3 injections over 8 days in adult mice) is for children and adolescents in the Dutch NIP (in total 10 vaccinations with aluminium-containing adjuvants, divided over 6 time points in the first 12/13 years of life; see Section 10.2). The same is true of the four studies by the Canadian research group, which further used subcutaneous rather than intramuscular administration. Another issue is that behavioural studies in rodents are difficult to conduct, as several variables (e.g. observer bias, learning bias, laboratory conditions) cannot always be adequately controlled for. Results can also be variable and inconsistent between studies. For instance, there was no dose–response relation in the two positive tests in the Crépeaux *et al.* (2017a) study and, interestingly, no behavioural changes were seen in another study by Crépeaux and co-authors from 2015. This study used the same treatment protocol and the same series of eight behavioural and motor tests as the 2017 study, but fluorescent aluminium hydroxide nanodiamonds (AluDia) rather than Alhydrogel® were injected and only at the 400 µg Al/kg bw dose (Crépeaux *et al.*, 2015; see also Section 4.3). Finally, both the studies by Crépeaux and co-authors and those by the Canadian research group were (partly) funded by anti-vaccination foundations. Given all this, the findings of the above studies need confirmation by other tests, preferably from different labs and with different mouse (or rat) strains.

2.3 Health-based guidance values (HBGVs)

In the risk assessments previously carried out by national health institutes and scientific committees, the HBGVs for aluminium that were considered most relevant were the ones established by EFSA and JECFA. These are described below.

2.3.1 EFSA

Since the available studies had a number of limitations, the EFSA Panel concluded that they did not allow any dose–response relationships to be established. The Panel therefore based its HBGV on the combined evidence from several studies in mice, rats and dogs that used dietary administration of aluminium compounds, instead of selecting a single study. In these studies the lowest reported LOAELs for effects on neurotoxicity, testes, embryotoxicity and the developing nervous system were 52, 75, 160, and 50 mg Al/kg bw/day, respectively. Similarly, the lowest reported NOAELs for these effects were 30, 27, 100, and 10-42 mg Al/kg bw per day, respectively.

The EFSA Panel used both the lower end of the LOAEL range (50 mg Al/kg bw/day) and the lowest NOAEL (10 mg Al/kg bw/day) as points of departure (PoD) for deriving the Tolerable Daily Intake (TDI). From the LOAEL of 50 mg Al/kg bw/day, a TDI of 0.17 mg Al/kg bw/day was obtained, applying assessment factors of 100 (accounting for inter- and intraspecies variations) and 3 (accounting for using a LOAEL instead of a NOAEL) to the PoD. Alternatively, when the lowest NOAEL of 10 mg Al/kg bw/day was used, a TDI of 0.10 mg Al/kg bw/day was obtained, applying an assessment factor of 100 to allow for inter- and intraspecies variations.

In view of the cumulative nature of aluminium in the organism after dietary exposure, the EFSA Panel considered it more appropriate to establish a Tolerable Weekly Intake (TWI) for aluminium rather than a TDI. Using the LOAEL approach, this resulted in a TWI of 1.2 mg Al/kg bw/week, whereas using the NOAEL approach resulted in a TWI of 0.7 mg Al/kg bw/week. A value of 1 mg Al/kg bw/week, representing a rounded value between the two TWIs, was subsequently selected as the TWI for aluminium (EFSA, 2008).

2.3.2 JECFA

A similar approach was used in 2007 by JECFA. Using the lower end of the range of lowest LOAELs reported for dietary studies in mice, rats and dogs (50–75 mg/kg bw/day), a provisional TWI (PTWI) of 1 mg/kg bw/week was derived for aluminium, using an uncertainty factor of 100 to allow for inter- and intraspecies differences and an additional uncertainty factor of 3 for deficiencies in the database (notably the absence of NOAELs in most studies and the absence of long-term studies) (JECFA, 2007).

Following the arrival of new studies, JECFA re-evaluated the data on aluminium and revised the PTWI (JECFA, 2012). The 12-month developmental neurotoxicity study by Poirier *et al*. (2011) was taken as the key study, with renal damage and reduced grip strength as the main effects (see Section 2.2.8). The NOAEL and LOAEL for these effects were at target aluminium doses of 30 and 100 mg/kg bw/day, respectively.

However, because the aluminium citrate was administered in the drinking water, the actual dose was influenced by the water consumption, which varied in the different stages of the study. Mean doses at the NOAEL were 10–14% below target during gestation, up to 50% above target during lactation, up to about 30% above target in the weaned pups for the first few weeks, but then 15–45% of target for the remainder of the study. At the LOAEL, the mean dosage level was approximately at target during gestation, up to 90% above target during lactation and the first few weeks post-weaning, and then 25–50% of target for the remainder of the study. Hence, if the effects in the pups were mediated *in utero*, 30 mg/kg bw/day as NOAEL would be a slight overestimation (i.e. the actual NOAEL would be slightly lower); conversely, however, if the effects were mediated during lactation or the first few weeks after weaning, 30 mg/kg bw/day as NOAEL would be an underestimation (i.e. the actual NOAEL would be higher). Given that the effect on grip strength was more pronounced in younger animals, exposure *in utero* and/or during lactation was assumed to be more important than exposure during the later stages, when exposure was decreased due to decreased fluid consumption. JECFA concluded that, taking into account the greater bioavailability of aluminium from aluminium citrate than from other aluminium compounds, it was appropriate to assume that the NOAEL was 30 mg/kg bw/day. With application of a safety factor of 100 for inter- and intraspecies differences to this NOAEL, a PTWI of 2 mg/kg bw was established (JECFA, 2012).

2.4 Summary

The oral toxicity of aluminium salts has been thoroughly reviewed by various international organisations. Based on all the available data and evaluations, we support the choice of the rat developmental neurotoxicity study by Poirier *et al*. (2011) as the key study for the HBGV for aluminium, for the time being. In the offspring, urinary tract pathology was evidence of general toxicity, observed most prominently in the high-dose males (300 mg/kg bw/day target), but present also in some high-dose females and some mid-dose males and females (100 mg/kg bw/day target). At the high dose it resulted in increased mortality and significant morbidity, leading to early termination of this group. A dose-related neuromuscular function impairment (decrease in hind-limb and fore-limb grip strength) was observed as neurodevelopmental effect, in both males and females of the mid- and high-dose groups, but not in the low-dose group of 30 mg/kg bw/day. This effect, which was more pronounced in the younger animals, was taken as the critical effect for setting the PTWI of 2 mg/kg bw by JECFA. The COT, SCHEER and SCCS also took the effect on grip strength and its NOAEL (30 mg/kg bw/day) as the critical effect in their assessment of aluminium in infant diet, toys and cosmetic products, respectively (COT, 2013; SCHEER, 2017; SCCS, 2020).

In conclusion, the PTWI of 2 mg/kg bw will be used as the HBGV for the current integrated risk assessment of aluminium salts. This HBGV is a measure of the amount of aluminium that can be ingested on a weekly basis over a lifetime without an appreciable health risk.

3 Kinetics of aluminium salts

3.1 Introduction

Human exposure to aluminium occurs via various sources and various routes. To estimate the potential health effects resulting from the combined exposure to the various sources, the external aluminium exposure estimates given in Chapters 6–10 need to be converted into internal exposure estimates in order to calculate the total systemic aluminium exposure. For that, it is important to know the so-called kinetic behaviour of aluminium, i.e. the extent to which the human body absorbs, distributes and eliminates aluminium.

Most studies on the kinetic behaviour of aluminium salts focus on the oral bioavailability of aluminium from water and/or food. There is limited information available on oral absorption from other media, on absorption through the skin and lungs or on the distribution and excretion of aluminium salts. The available information is described in the sections below.

3.2 Absorption

3.2.1 Absorption from food and drinking water

Aluminium is poorly absorbed after oral intake. In humans, usually only approximately 0.1–0.8% of the aluminium in food and beverages is absorbed (Greger and Baier, 1983; Hohl *et al.*, 1994; Priest *et al.*, 1996; Priest *et al.*, 1998; Stauber *et al.*, 1999) and approximately 0.1–0.4% of the aluminium in drinking water (Priest *et al.*, 1998; Stauber *et al.*, 1999; Steinhausen *et al.*, 2004), as summarised in Table 1. In animals, oral absorption is similarly low. The low oral bioavailability of aluminium results both from the insolubility, at neutral pH, of most naturally occurring aluminium compounds and from the protective barrier that the body's gut wall presents to the uptake of potentially toxic metal ions (Priest, 2004).

The oral absorption of aluminium depends on several factors, including the type of aluminium compound, pH, solubility, complexing ligands (e.g. citrate, lactate, silicate), competing ions (e.g. iron, magnesium, calcium) and co-administration with water or food. Following acid digestion in the stomach a substantial amount of the ingested aluminium compounds is solubilised to Al^{3+} (e.g. hydrated $Al(H_2O)_6)^{3+}$). When the gut content passes from the stomach to the intestine, there is an increase in pH to neutral level that results in the formation of insoluble complexes of aluminium with hydroxide. The majority is then expected to precipitate in the intestine with subsequent faecal excretion, leaving only a minor fraction available for absorption (EFSA, 2008; ATSDR, 2008).

Dietary ligands can either enhance uptake by forming absorbable (usually water-soluble) complexes (e.g. with carboxylic acids such as citric and lactic) or reduce it by forming insoluble compounds (e.g. with phosphate or dissolved silicate). Depending on the type of food and the chemical forms present in the intestine, it is likely that the oral absorption of aluminium from food can vary at least 10-fold (EFSA, 2008; ATSDR, 2008).

Table 1. Summary of oral bioavailability of aluminium from food or drinking water in humans and animals.

Species	Aluminium salt	Matrix	Dose	Fraction absorbed (%)	Reference
Human[1]	lactate	food	~71 µg/kg bw	0.09	Greger and Baier, 1983
	lactate	food	~1786 µg/kg bw	0.78	Greger and Baier, 1983
	mix (naturally present)	water	~2.97–3.33 µg/kg bw	0.39	Stauber *et al*., 1999
		food + tea	~42.9 µg/kg bw	0.28-0.64	
		all three	~45.7 µg/kg bw	0.26–0.29	
	chloride	drinking water	~0.2 µg/kg bw	0.22	Priest *et al.*, 1998
	citrate	water + food	~1429 µg/kg bw	0.52	Priest *et al.*, 1996
	hydroxide	water + food	~1429 µg/kg bw	0.01–0.14[4]	Priest *et al.*, 1996
	chloride	water + food	~1.4 µg/kg bw	0.1–0.24	Hohl *et al.*, 1994
	chloride	solution	~1.44 µg/kg bw	0.13–0.37	Steinhausen *et al.*, 2004
Rat	phosphate	cheese	~55 mg/kg bw/day	0.1	Yokel *et al*., 2008
	phosphate	cheese	~110 mg/kg bw/day	0.3	Yokel *et al.*, 2008
	phosphate	biscuit	~31 mg/kg bw	0.11	Yokel and Florence, 2006
	phosphate	biscuit	~62 mg/kg bw	0.13	Yokel and Florence, 2006
	hydroxide	food	~1079–2688 mg/kg diet	0.01–0.04[4]	Greger and Powers, 1992
	Al^{3+} ion	water	~6.5 mg/kg bw[2]	0.29	Zhou *et al.*, 2008
	citrate	water	~6.5 mg/kg bw[2]	0.61	Zhou *et al.*, 2008
	maltolate	water	~6.5 mg/kg bw[2]	0.50	Zhou *et al.*, 2008
	fluoride	water	~6.5 mg/kg bw[2]	0.35	Zhou *et al.*, 2008
	Al^{3+} ion	water	~2.5 µg/kg bw	0.28	Yokel *et al.*, 2001
	chloride	water	8.1 mg/kg bw	27	Gupta S *et al.*, 1986
	sucralfate	solution	200 mg/kg bw/day	1.7–6.3[3]	Steiner *et al.*, 1982
Rabbit	borate	water	2.7 mg/kg bw	0.27	Yokel and McNamara, 1988
	hydroxide	water	2.7 mg/kg bw	0.45	Yokel and McNamara, 1988
	chloride	water	2.7 mg/kg bw	0.57	Yokel and McNamara, 1988
	nitrate	water	2.7 mg/kg bw	1.16	Yokel and McNamara, 1988
	glycinate	water	2.7 mg/kg bw	0.39	Yokel and McNamara, 1988
	sucralfate	water	2.7 mg/kg bw	0.60	Yokel and McNamara, 1988
	citrate	water	2.7 mg/kg bw	2.18	Yokel and McNamara, 1988
	lactate	water	2.7 mg/kg bw	0.63	Yokel and McNamara, 1988

[1] Based on an average body weight of 70 kg.
[2] Based on an average body weight of 270 g.
[3] The lowest bioavailability is in healthy animals, the highest in animals with gastric ulcers.
[4] In the presence of citrate.

3.2.2 *Absorption from antacids*

There is limited information available on the absorption of aluminium oxide and aluminium hydroxide from antacids. In the Summary of Product Characteristics (SPCs) of two antacids on the Dutch market it is stated that 'magnesium and aluminium are absorbed for about 15-30%' (Regla pH, 2015; Antagel, 2016). It is doubtful whether this is correct, as with reference to several publications ATSDR (2008) reported that when large oral loads of aluminium (1–4 g/day) in the form of (usually aluminium hydroxide) antacids are ingested, only a very small amount of this aluminium is absorbed (<1%, or even ≤0.01%, of the intake amount in healthy individuals). The ATSDR also refers to a study by Weberg and Berstad (1986) in which subjects with normal renal function were given a total of 976 mg aluminium (as aluminium hydroxide in antacid tablets). When the tablets were taken with water, the amount absorbed was calculated as 0.004%, whereas the absorption was 8–50 times higher when the tablets were taken with orange juice (0.03%) or citric acid (0.2%). Based on the available information, the ATSDR concluded that only an extremely small amount of the aluminium found in antacids will be absorbed. In their risk assessment of aluminium, Tietz *et al*. (2019) also presume that, with respect to antacids, the absorption rate in the gastrointestinal tract will be significantly lower with a single administration of high doses of aluminium than with a continuous intake of low doses (as with foods).

3.2.3 *Absorption from soil*

Part of the total aluminium content in soil is inert, so not all aluminium will be available for uptake. How much of the aluminium in ingested soil is available depends on the amount released from the matrix during digestion in the gastrointestinal tract. The pH in the gut and other factors, such as the concentration of reactive surfaces, competing ions and complexing ligands, are important in this process (Groenenberg *et al.*, 2017). The amount released in the gastro-intestinal tract is referred to as the bioaccessible fraction, and this represents the fraction that is considered maximally available for uptake. Only a part of the bioaccessible fraction will be transported across the intestinal epithelium, reach the systemic circulation and be transported throughout the body. This part is the bioavailable fraction.

The bioaccessible fraction of aluminium in soil can be represented by the fraction of the total aluminium that becomes available following a chemical extraction of soil with 0.43 M HNO_3, i.e. the so-called reactive content (Groenenberg *et al.*, 2017). This reactive content thus represents the fraction that is maximally available for uptake, and thus the maximum toxic load (Mol *et al*., 2012). For aluminium, data on both total content and reactive content in five Dutch soils are available from Mol *et al*. (2012), showing that the reactive content of aluminium in these soils is only a small fraction of the total content (0.04–0.16%); see Table 2. As it is not known which part of the bioaccessible aluminium in the gut is taken up in the blood, a worst case would be to assume that 100% of what is potentially available (bioaccessible) is also actually bioavailable. Consequently, the reactive fraction (0.04–0.16%) is a worst case estimate of the absorbed fraction of aluminium from soil.

Table 2. Total and reactive aluminium content in five Dutch soils, based on Mol et al. (2012).

Soil type	Total Al content (g/kg)		Reactive content (mg/kg)		Reactive fraction (%)	
	Median	P95	Median	P95	Median	P95
Peat	34.7	79.4	30.5	73.3	0.09	0.09
Sand	12.4	23.1	19.0	36.4	0.15	0.16
Marine clay	48.2	65.6	17.0	28.0	0.04	0.04
Fluvial clay	52.1	84.7	28.5	58.6	0.06	0.07
Loess	41.8	45.1	16.5	19.6	0.04	0.04

3.2.4 *Absorption from clay-based food supplements*

Information on the oral bioavailability of aluminium from the clays used as food supplements is not available. In its risk assessment of these clays, the NVWA assumed that all aluminium is bioaccessible from the clays, and that the bioavailability of aluminium from the clays is comparable to the bioavailability of aluminium in the toxicological studies used to derive the reference value for aluminium. It was acknowledged that these assumptions may present a worst case situation (NVWA-BuRO, 2009; RIVM-RIKILT, 2009). Indeed, 100% bioaccessibility seems a worst case assumption. Although not directly comparable, these supplements are soil-like in nature. And at least for Dutch soils the bioaccessible part forms only a small fraction of their total aluminium content (0.04–0.16%, see Section 3.2.3).

3.2.5 *Absorption via the skin*

For consumer products such as personal care and cleaning products, dermal contact is the most common exposure pathway. With reference to Cosmetics Europe (2012), the SCCS, in its 2014 opinion on the safety of aluminium in cosmetic products, noted that the majority of cosmetics containing aluminium are applied in formulations where the aluminium is insoluble. This means that very little of the applied aluminium is bioaccessible for skin absorption. Antiperspirants were given as notable exception, as in these the aluminium salts are soluble at the low pH of the formulation. However, once applied to the skin, the aluminium salts form chemically inert complexes with basic components of sweat and skin, limiting the bioaccessibility of aluminium on living skin (SCCS, 2014). The SCCS further noted that the high molecular weight, low octanol/water partition coefficient and high positive charge would limit the potential for skin penetration of aluminium.

Limited human data on the dermal absorption of aluminium from antiperspirants indicated dermal absorption percentages in the range of 0.012 to 10% (Flarend *et al.*, 2001; Guillard *et al*., 2004; Pineau *et al.*, 2012). However, since these studies were performed *in vitro* with skin biopsies (Pineau *et al*., 2012) and/or *in vivo* with a low number (N=1 or 2) of volunteers (Flarend *et al.*, 2001; Guillard *et al.*, 2004), the SCCS considered the data inadequate for estimating the internal dose of aluminium following cosmetic uses and requested a new human exposure study under use conditions (SCCS, 2014).

To that end, an *in vivo* study was performed with a similar technique as used by Flarend *et al.* (2001), now with 12 volunteers and extended exposure scenarios (de Ligt *et al.*, 2018). The authors concluded that

dermal absorption ranged from 0.002% to 0.06%, with a mean of 0.0094%. Nevertheless, after careful analysis of this study the SCCS concluded that it was impossible to use the results to draw a meaningful conclusion for skin absorption, due to the gaps in the mass-balance of ^{26}Al and the lack of information about how missing amounts might be accounted for (SCCS, 2020). For this reason, the SCCS asked the cosmetics industry for a new clinical study and discussed other issues related to study design and residual data gaps, particularly referring to the local fate of aluminium and the ability to determine a fraction absorbed (F_{abs}) value. This new study (by the Netherlands Organisation for applied scientific research (TNO), in 2 parts) was provided to the SCCS in 2019 and evaluated in its opinion (SCCS, 2020), as summarised below.

In the new study, the sensitivity was improved, with a ~25-fold higher level of isotope ^{26}Al in the applied topical dose of antiperspirant, so that very low concentrations of aluminium in urine and blood were measurable and quantifiable at levels above the LOQ. The dermal fraction absorbed was calculated from the ratio of the total fraction excreted in urine (as the most reliable measure) following the topical dose to the total fraction excreted following the intravenous dose. The SCCS considered the resulting mean dermal F_{abs} of 0.00052% an appropriate value for use in risk assessment.

The new study showed that the skin does not act as a 'depot' for aluminium and that aluminium is not absorbed into the skin in any appreciable amount. Tape-stripping data over 24 hours indicated that the vast majority of the applied dose was present in the outer (<10) layers of the stratum corneum and was therefore not dermally absorbed. It was removed from the surface of the skin with time. Between 6 and 24 hours after application, only a very small amount of aluminium could be measured in the tape strips. So, the vast majority of the applied dose remained outside the body and was lost – on experimental equipment, clothing or directly into the environment from the surface of the skin (SCCS, 2020).

The low dermal absorption can be explained by the formation of plugs in the sweat glands. Letzel *et al.* (2020) provided evidence that aluminium salts exert their antiperspirant activity by precipitation of the soluble aluminium salts. This happens rapidly upon contact with biological fluids at physiological pH, forming insoluble gel plugs. Therefore, it may be concluded that aluminium applied in antiperspirant formulations remains almost completely outside the body.

3.2.6 Absorption via the lungs

Inhalation of aluminium is mostly related to occupational exposure, and relatively little to consumer exposure. Nevertheless, a possible source for consumers are aerosols from antiperspirants or other sprays. For absorption via the lungs only small particles with a size <10 µm are considered to be relevant (Rothe *et al.*, 2011). Insoluble larger particles are eliminated from the respiratory tract by macrophage entrapment or via mucociliary clearance and subsequently swallowed. These large particles need to be considered in terms of oral exposure (Rothe *et al.*, 2011).

There is very limited data on the bioavailability of inhaled aluminium, and only from occupational settings. DeVoto and Yokel (1994) and Yokel and McNamara (2001) reported estimates of 3% and 1.5–2%, respectively, for bioavailability in the lung. Yokel and McNamara (2001), however, indicated that it is unknown whether the aluminium is absorbed from the deep lung or from the gastrointestinal tract after mucociliary clearance because experimental studies have not isolated the pulmonary from other absorption routes.

3.3 Distribution

In EFSA (2008) and other reviews on aluminium (e.g. ATSDR, 2008) the following is reported.

After absorption, aluminium binds to the iron-binding protein transferrin, the main carrier of Al^{3+} in plasma (~90%). Most of the remaining 10% is bound to low molecular weight molecules (mainly citrate). Cellular uptake of aluminium in organs and tissues appears relatively slow and most likely occurs from the aluminium bound to transferrin by transferrin-receptor-mediated endocytosis.

In healthy individuals, the total body burden of aluminium is reported to be around 30–50 mg. Aluminium is distributed unequally to all tissues in humans, with approximately 50% of the total body burden in the skeleton and approximately 25% in the lungs (from accumulation of inhaled insoluble aluminium compounds). Most of the aluminium in parts of the body other than the lungs is thought to originate from food intake. Reported normal levels in human tissues are 5–10 mg/kg in bone, around 20 mg/kg wet weight in lungs, 0.25–0.75 mg/kg wet weight in the brain and 1–2 µg/l in plasma. Aluminium has also been found in skin, the lower gastrointestinal tract, lymph nodes, adrenals and parathyroid glands. Soft tissue organs other than lungs contain low levels of aluminium (0.3–0.8 mg/kg wet weight). There is evidence that with increasing age, aluminium concentrations may increase in human plasma, bone and brain tissue.

Similarly in rats, aluminium is not equally distributed throughout the body following oral exposure. Accumulation is typically higher in spleen, liver, bone and kidney than in brain, muscle, heart or lung. Levels of aluminium in a number of tissues and organs (bone, muscle, lung, liver and kidney) of experimental animals have been found to increase with ageing.

Aluminium can enter the brain through the blood–brain barrier and through the blood–cerebrospinal fluid barrier. Aluminium is also able to cross the placental barrier, reaching the foetus, and has been reported to distribute to some extent to breast milk.

Several factors may modulate the distribution of aluminium. Citrate and fluoride may reduce tissue accumulation and increase renal excretion in experimental animals. However, this occurs when the aluminium concentration exceeds the metal binding capacity of transferrin, which seldom happens in humans. In animal experiments, calcium and magnesium deficiency have been shown to contribute to an accumulation

of aluminium in brain and bone. Furthermore, there is a negative correlation between iron status and aluminium accumulation in tissues.

3.4 Excretion

In humans, absorbed aluminium in the blood is eliminated primarily by the kidneys via glomerular filtration (presumably as the citrate) and excreted in the urine. Unabsorbed aluminium is excreted in the faeces. A minor, secondary route is excretion via the bile (EFSA, 2008).

Multiple reported values for the elimination half-life of aluminium (from hours to years) in humans and animals suggest that there is more than one compartment of aluminium storage. This might result from the retention of aluminium in a depot (probably bone) from which it is slowly eliminated. Typically, a longer half-life is observed with increased duration of sampling, and retention times for aluminium appear to be longer in humans than in rodents. Slow aluminium elimination coupled with continued exposure may explain the increasing body burden with age (EFSA, 2008).

The above summary by EFSA of the human data is based mainly on the findings in two studies with human volunteers (Priest *et al.*, 1995; Talbot *et al.*,1995). Given their use in pharmacokinetic modelling (see Section 4.5), the studies are presented in some detail. Healthy volunteers (N=1 in Priest *et al.* (1995) and N=6 in Talbot *et al.* (1995)) received a single intravenous injection of ^{26}Al citrate. In the one subject, more than half of the ^{26}Al had left the blood after 15 min and the decline continued, leaving <1% in the blood after 2 days. The losses occurred both through renal excretion and through uptake by other compartments. Renal excretion up to 13 days was 83%, faecal excretion only 1.8%. At this time point, whole-body retention was 15%, but when the subject was re-examined at 1178 days this had declined to ~4%. Based on this, a half-life of 7 years was calculated (Priest *et al.*, 1995). However, when the same subject was re-examined 10 years after the injection, the calculated half-life had increased to 50 years (Priest, 2004). The study by Talbot *et al.* (1995) showed a similar picture, with a rapid clearance from blood (mean 2% of injection remaining after 1 day), major loss in urine (59% and 72% up to 1 and 5 days, respectively), negligible faecal excretion (~1% up to 5 days) and whole-body retention of 27% at 5 days, but also showed considerable inter-subject variation. These studies show that most of the aluminium entering the blood is rapidly excreted in the urine, but that a small fraction may persist for a very long time in the body.

3.5 Biomonitoring

An alternative way to assess exposure is by biomonitoring, e.g. by measuring aluminium in blood (serum), urine or hair. The big advantage of biomonitoring is that it gives a measure of the total exposure to aluminium (from all sources, via all routes), and it is this measure that is best compared with a biological limit value for aluminium in human blood/tissues/excreta (if such a value exists). However, a disadvantage of biomonitoring is that it does not provide insight into the individual contribution of each source to total exposure, unless a complex and time-consuming inventory is made of all potential sources of aluminium the study subjects have been and are currently exposed to.

In the case of aluminium, some methodological problems in relation to biomonitoring have additionally been identified (see for instance Riihimäki and Aitio (2012); Bertram *et al.* (2015)), such as the very low levels detected in biological specimens (even after high occupational exposure), a high risk of sample contamination, and the need for specialised instrumentation and trained expert personnel. Besides, biomonitoring data on aluminium in the general population are not available, the available data being limited to workers in occupational settings.

3.6 Summary of kinetics of aluminium salts

In humans, the oral bioavailability of aluminium from food and drinking water is low (0.1–0.8%). It varies with, for example, the aluminium compound and available dietary ligands. For the current risk assessment, 0.8% will be taken as the worst case estimate.

The oral bioavailability of aluminium from antacids is also low (<0.01-0.2%). There is no information on the oral bioavailability of aluminium from soil or from clay-based food supplements. As worst case it will be assumed that 100% of the bioaccessible (reactive) fraction (0.04–0.16% for Dutch soils, including clays) is also actually bioavailable.

In humans, dermal absorption of aluminium from antiperspirants is very low (0.00052%). No data are available for other personal care products, but the level of dermal absorption will be taken as similar to that for antiperspirants. This is because most formulations for personal care products include aluminium in insoluble form, so that very little of the applied aluminium will be bioaccessible for skin absorption.

Absorption following inhalation is estimated at 1.5–3% for the respirable fraction, i.e. the fraction that deposits deep in the lungs. This bioavailability is approximately 10-fold higher on average than the gastrointestinal resorption. The latter can be taken for the upper respiratory tract, given mucociliary clearance.

The majority of the aluminium in food, water, antacids and other sources of oral exposure leaves the body quickly in the faeces, in the form of insoluble complexes. Only a minor fraction is available for absorption. Most of what is absorbed quickly leaves the body in the urine. Only a small amount of aluminium is retained in the body.

4 Kinetics of aluminium-containing adjuvants

4.1 Introduction

As noted in Chapter 1, several vaccines used in the Dutch National Immunisation Programme (NIP) contain aluminium-based adjuvants that are composed of nanoparticles. It is generally acknowledged that nanomaterials' properties may alter the ADME (absorption, distribution, metabolism and excretion) and toxicological behaviour of a substance (EFSA, 2018; ECHA, 2017, 2019). The toxicokinetic profile of nanomaterials depends on several physicochemical parameters, e.g. composition, size, shape, surface area, agglomeration/aggregation state, surface properties (including surface charge), hydrophobicity and dissolution. Therefore, nanomaterials may be able to reach parts of the body that are otherwise protected from exposure to larger-sized materials by biological barriers. Due to the differences in physicochemical parameters (e.g. surface chemistry), nanoforms of the same substance may also have different hazard profiles (ECHA, 2017, 2019).

From the above it might be inferred that the kinetic behaviour and toxicity of aluminium-containing adjuvants (nanoparticles) is potentially different from that of (soluble) aluminium salts (non-nano). Whether these adjuvants actually behave as nanoparticles can be questioned. Annex I presents more information on the physicochemical properties of the aluminium-containing adjuvants, from which it appears that it is not the primary nanoparticles that are the functioning units in vaccines, but the aggregates they readily form. These agglomerates have a size in the lower micrometre range and therefore behave differently from the primary nanoparticles.

In the sections below a summary is presented of the available kinetic data that specifically relate to aluminium-containing adjuvants.

4.2 Absorption

In vaccines, the aluminium added is in an insoluble form (e.g. as the phosphate or hydroxide of aluminium). Once injected into muscle, aluminium-containing adjuvants are thought to form an extracellular depot at the injected site (WHO, 1976), from where they are progressively solubilised (by citrate ions in the interstitial fluids of muscle) into blood (Flarend *et al*., 1997; Mitkus *et al*., 2011).

The only available study into the effect of intramuscular injection on the aluminium levels in human body fluids is Movsas *et al*. (2013). This study assessed actual aluminium blood level responses to routine 2-months vaccination in 12 preterm infants, and did not find a significant change in aluminium levels in urine and serum before and 24 h after vaccination.

Flarend *et al*. (1997) showed that in rabbits intramuscularly injected with aluminium hydroxide or aluminium phosphate adjuvant at a dose of 0.85 mg ^{26}Al/animal, dissolution begins upon administration, as ^{26}Al was already found in blood within 1 hr after injection. The blood concentration

of aluminium was fairly steady from days 2 to 28, at which time the terminal phase had not been reached. It was calculated that approximately 17% and 51% of the injected aluminium hydroxide and aluminium phosphate adjuvant dose, respectively, was absorbed into the blood over 28 days (Flarend *et al.*, 1997). It is noted that this study was later criticised by Masson *et al*. (2018), *inter alia* because of the low number of animals (2/adjuvant) and the short duration of the study (28 days), and because the aluminium hydroxide and aluminium phosphate administered (prepared by the study authors by precipitation) differed from the aluminium hydroxide and aluminium phosphate found in vaccines on the market. It is further noted that only the adjuvants were administered and not the adjuvants coupled to an antigen (as is the case in vaccines administered to humans).

Exley *et al*. (2010) presume that only a small proportion of the injected aluminium is present in a rapidly biologically available form (Al^{3+}) that is subsequently transported away from the injection site. The majority of the injected aluminium at the injection site will be (slowly dissociating and dissolving) particulates of the order of 1–20 µm in size (Exley *et al*., 2010). Masson *et al*. (2018) also presume that the time the aluminium particles remain in interstitial fluid is limited as they are rapidly captured by immune cells. This then limits the dissolving effect of the chelating agents present in the interstitial fluid, which is low in any case for aluminium hydroxide: *in vitro* it was practically nil in the presence of a physiological concentration of citrate and remained very low (6%) when the citrate concentration was increased 100-fold (with reference to Seeber *et al.*, 1991).

A significant portion of aluminium remains at the injection site inside the immune cells. The persistence of aluminium-loaded immune cells has been detected at sites of previous injections up to 3–12 months post-injection in studies in monkeys (Verdier *et al*., 2005) and mice (Khan *et al.*, 2013; Eidi *et al.*, 2015) and for up to 8 years in adult patients with macrophagic myofasciitis (MMF) (Gherardi *et al.*, 2001). Clearance of aluminium adjuvants from the vaccine depot in muscle depends upon the chemical form of the adjuvant, aluminium phosphate adjuvant being released faster than aluminium hydroxide adjuvant in rats (Weisser *et al.*, 2019), monkeys (Verdier *et al.*, 2005) and rabbits (Flarend *et al.*, 1997).

Weisser *et al.* (2019) observed that in rats given plain aluminium phosphate adjuvant (i.e. without antigen), approximately 67% of the aluminium dose (1.25 mg/animal) was released from injected muscle over 80 days. For plain aluminium hydroxide adjuvant this was 0%. When rats were given a single human dose of an aluminium phosphate or aluminium hydroxide adjuvanted vaccine (at 0.5 or 0.6 mg/animal, respectively), the release was also faster from the aluminium phosphate adjuvant (85.5% over 80 days) than from the aluminium hydroxide adjuvant (22.3% over 80 days). The profile of the aluminium plasma time courses did not differ much between the groups, all showing a slight positive slope. Total aluminium plasma exposure over 80 days was significantly higher for the plain aluminium phosphate adjuvant group than for the other groups.

4.3 Distribution

The distribution of aluminium adjuvants depends primarily on their behaviour as particulates (Willhite *et al.*, 2014). A few studies have investigated the distribution in rodents, showing that aluminium particles injected by the intramuscular route can reach distant organs.

In the rabbit study by Flarend *et al.* (1997; see also Section 4.2), a similar distribution was found for both adjuvants, with kidney > spleen > liver > heart > lymph node > brain at day 28, but the aluminium concentration in tissues was on average 2.9 times greater for aluminium phosphate than for aluminium hydroxide. It is noted, though, that injection site muscle, draining lymph nodes and bone were not measured for aluminium.

A research group in France published several papers on investigations in mice. Following intramuscular injection of alum (aluminium oxyhydroxide)-containing vaccine and of two types of fluorescent aluminium nanohybrids (exploratory polychromatic fluorescent latex beads (FLBs) and Al-Rho, i.e. rhodamine nanohybrids covalently coated with an $Al(OH)_3$ shell) in C57BL/6 mice, aluminium deposits appeared in spleen and, with a delayed entry, in brain. They were still detected in these tissues one year after injection. The fluorescent material translocated to draining lymph nodes and was thereafter detected in association with phagocytes in blood and spleen. It was stated that the organ aluminium depots could have resulted from either physical translocation of aluminium adjuvant or nanohybrids, or in situ aggregation of soluble aluminium, or both (Khan *et al.*, 2013). Distribution of aluminium particles to draining lymph nodes, spleen and brain was also seen in C57BL/6 mice intramuscularly treated with fluorescent aluminium hydroxide nanodiamonds (AluDia). Aluminium particles were additionally detected in liver (Eidi *et al.*, 2015), an organ not investigated in the Khan *et al.* (2013) study. Using similar fluorescent aluminium hydroxide nanodiamonds, Crépeaux *et al*. (2015) studied the distribution of aluminium after intramuscular administration in another strain of mice (CD1), for a long follow-up period (270 days after injection). The results showed a highly delayed systemic translocation to draining lymph nodes and spleen, the highest number of particles being observed in these tissues at day 270. In contrast with C57BL/6 mice, no translocation of aluminium to brain was observed in CD1 mice during the whole follow-up period of 270 days. Consistent with this finding, the CD1 mice did not display neurobehavioural changes (Crépeaux *et al*., 2015). However, in another study with CD1 mice investigating neurotoxicity (see Section 2.2.11 for details), Crépeaux *et al*. (2017a) did see neurobehavioural changes in two out of eight tests following intramuscular injections of commercially available aluminium hydroxide adjuvant, but in an atypical pattern: only at the low dose, not at the mid and high doses. In the last two dose groups an accumulation of aluminium in immune cells in the injected muscle was seen, but not in the low-dose group. This difference was thought to be due to the agglomerate size in the dosing solution. For the low-dose group the suspension consisted of small agglomerates only (±1750 nm in size), whereas for the mid- and high-dose groups the suspensions consisted of both very large (35,000 nm) and small agglomerates (1500–4800 nm).

The authors concluded that small agglomerates could be transported out of muscle, while this was less so for the large agglomerates (Crépeaux *et al*., 2017a). It is noted that the findings from this study need to be interpreted with care, due to several shortcomings in the study (see Section 2.2.11). It is further noted that the above studies by the French research group were (partly) funded by anti-vaccination foundations.

Weisser *et al.* (2019; see also Section 4.2) found increased aluminium concentrations in bone of rats after intramuscular administration of either plain aluminium adjuvants or vaccines with aluminium adjuvants, with stronger increases for the aluminium phosphate adjuvant groups. Extrapolated amounts in whole skeleton corresponded to 5–12% of the released aluminium dose. In contrast to bone, very low aluminium concentrations (<0.3 µg/g ww, with low inter-individual variation) were observed in brain samples on day 80 post-injection, independent of the adjuvant or vaccine administered (Weisser *et al.*, 2019). The authors noted that their findings for brain differed from those reported in some other publications. It was argued that, since aluminium was determined in a whole brain hemisphere, aluminium clusters due to focal accumulation (as reported by House *et al*. (2012) for human brain tissues) could not have been missed. Whether this is a correct argument is questionable, since measuring aluminium in a whole hemisphere may have diluted the aluminium clusters. It was further argued that the atomic absorption spectrometry method that was used measures both dissolved Al^{3+} ions and insoluble aluminium species, and would thus also capture any aluminium particles transported into the brain by macrophages, as has been postulated by e.g. Gherardi *et al*. (2015), Crépeaux *et al*. (2015) and Shardlow *et al*. (2018). Weisser and co-authors therefore concluded that their results indicate that the contribution of such particulate aluminium to the amount detected in brain, if any, is marginal. Based on dose scaling to human adults they further expect that, after a single vaccination in adults, aluminium levels in bone, and even more so in plasma and brain, will be indistinguishable from baseline levels (Weisser *et al*., 2019).

4.4 Excretion

In the rabbit study by Flarend *et al.* (1997; see also Section 4.2), the cumulative amount of aluminium eliminated in the urine over 28 days was 6% of the aluminium hydroxide adjuvant dose and 22% of the aluminium phosphate adjuvant dose. Aluminium from both adjuvants was still being excreted at a steady rate at day 28.

While this indicates that the body is able to eliminate the aluminium absorbed from the adjuvants, elimination is slow for the aluminium phosphate adjuvant and even slower for the aluminium hydroxide adjuvant. As mentioned in Section 4.3, the amount of adjuvant left at the injection site was not determined; it is therefore unclear whether the un-excreted aluminium is still there, and in what form.

4.5 Pharmacokinetic modelling

The US Food and Drug Administration (FDA) modelled the pharmacokinetics of aluminium for infant dietary and vaccine exposures (updating a similar analysis by the ATSDR (Keith *et al*., 2002)), in an

effort to evaluate the relative contribution to aluminium levels in infants from vaccines and from the diet (Mitkus *et al.*, 2011).
A 3-compartmental (adult) kinetic model was used, with incorporation of infant glomerular filtration rates to compensate for the fact that in children aluminium is cleared more slowly from the blood than in adults. The model further used the aluminium retention function established by Priest (2004) on the basis of a human volunteer intravenously injected with aluminium citrate (see Section 3.4) and aluminium efflux data from the site of injection as found by Flarend *et al*. (1997) in rabbits following intramuscular injection of self-prepared aluminium hydroxide and aluminium phosphate adjuvants (see Section 4.2).
Retention of aluminium following infant dietary exposures from breast milk and/or formula and exposure from vaccines according to the 2011 US recommended childhood vaccination schedule (at maximum 4.225 mg aluminium) were estimated over the first 400 days of life. The body burden of aluminium following maximal exposure to either aluminium hydroxide or aluminium phosphate adjuvants reached approximately 1 mg over the first 400 days of life, the increase in body burden being more gradual for aluminium hydroxide than for aluminium phosphate. The body burden of aluminium from vaccines was not more than 2-fold higher than that received in the diet (Mitkus *et al*., 2011).

It is noted that Masson *et al*. (2018) criticised this pharmacokinetic modelling and the input data from Priest (2004) and Flarend *et al*. (1997). Important criticisms are that soluble aluminium is considered as the only entity of aluminium that can produce adverse effects, that no account is given of the bio-persistence of aluminium in particulate form at the injection site, and that the adjuvant can migrate away from the muscle in its particulate form.

4.6 Biomonitoring

For the reasons given in Section 3.5, biomonitoring is not an option for aluminium. Additionally, blood and urine would give insufficient information in the case of aluminium-containing adjuvants, as a large proportion of the particles remain at the injection site or are translocated to distant organs. Furthermore, the analysis methods normally used measure aluminium as such, and thus do not provide information on the original exposure source of the aluminium (salts or nanoparticles).

4.7 Summary of kinetics of aluminium-containing adjuvants

Aluminium-containing adjuvants are nanoparticles. In vaccines, the nanoparticles readily form lower-micrometre-size agglomerates that are the functioning units in vaccines. Data on the kinetic behaviour of aluminium as present in adjuvants (in nanoform) or vaccines (micrometre-size agglomerates) are limited. From the few data available it appears though that their kinetic behaviour is not identical to that of soluble aluminium forms (as described in Chapter 3).

Only a small proportion of the injected aluminium is thought to be present in a rapidly biologically available form. The majority of the injected aluminium will be in the form of particles, which are rapidly captured by immune cells. A significant portion of these particles will remain at the injection site inside the immune cells. The rest of the

particles may be transported by immune cells to the lymphoid organs, then to the bloodstream and, at a later stage, the particles may reach distant organs like spleen, brain and liver, where they will remain mainly intracellular. The data on excretion suggest a slow dissolution of the aluminium adjuvants and a low elimination rate, which may indicate a potential for accumulation upon repeated injection.

Overall, due to limited information available, there is some uncertainty around the kinetic behaviour of the aluminium present in adjuvants/ vaccines and how that may differ between the various applied nanoforms of aluminium in adjuvants, due to differences in physicochemical parameters.

5 Aluminium and potential association with adverse effects in humans

5.1 Introduction

Vaccinations with aluminium-adjuvanted vaccines have sometimes been associated with side effects. Aluminium exposure has also been related to neurological diseases, such as Alzheimer's disease and autism, to breast cancer and to a very rare muscle disease called macrophagic myofasciitis (MMF). The potential associations of aluminium exposure with side effects and human diseases are discussed in the sections below.

5.2 Side effects following vaccination

Aluminium-adjuvanted vaccines (including those in the Dutch NIP) are medicines that are under strict regulatory oversight, and their safety profile is established prior to registration and continuously monitored thereafter.

Vaccines must undergo clinical trials in order to be registered. To establish the safety of a single vaccine, several thousand people are usually followed for a period of 6–12 months. The aluminium-adjuvanted vaccines on the market have therefore been extensively studied. From these trials, Gupta R *et al.* (1993) and Lindblad (2004) concluded that no serious or severe adverse effects have been detected, only local effects such as erythema, redness and (muscle) pain at the injection site. These signs are indicative of the inflammation induced by the vaccine, necessary for a good immune response.

A number of studies have evaluated the safety of aluminium-adjuvanted vaccines compared with non-adjuvanted vaccines or saline placebo. In a meta-analysis, Jefferson *et al.* (2004), despite the low overall methodological quality of the included studies, were able to conclude that there are no indications that the aluminium present in the diphtheria, tetanus and pertussis vaccines may result in serious or long-term, chronic adverse effects. Neither were vaccine-related serious adverse effects found in the randomised placebo controlled trial of Reisinger *et al.* (2007). These investigators saw a higher proportion of subjects in the aluminium-adjuvanted vaccine group reporting injection-site adverse experiences (redness, swelling and pain) than in the non–aluminium-containing placebo group. On the other hand, they did not detect a difference either between experienced pain (muscle, joints and head) in children exposed to the aluminium adjuvanted vaccine and the placebo, or between the rate of fever in the two groups.

Following licensure, the safety of vaccines is continuously monitored, as they are used in larger and more diverse populations than evaluated in clinical trials. Surveillance of vaccine safety is also necessary to detect rare but serious adverse events that clinical trials are not able to pick up due to their limitations in size. During the post-licensure safety surveillance phase it has been found that aluminium-adjuvanted vaccines sometimes cause persistent nodules or granulomas at the

injection site (Fawcett and Smith, 1984; Frost *et al.*, 1985; Bergfors and Trollfors, 2013). For instance, in the most recent meta-analysis, by Bergfors and Trollfors, these were found in 0.8% of the children (645 out of 76,000 vaccinees). Whilst such nodules generally resolve themselves without medical intervention, the associated persistent itching can cause considerable discomfort lasting several years (Bergfors and Trollfors, 2013). There are no known harmful long-term effects from aluminium granuloma development (Haag, 2019). No other effects associated with aluminium adjuvants in vaccines have been identified upon surveillance.

5.3 Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder that usually starts slowly and gradually worsens over time. The cause of Alzheimer's disease is poorly understood and involves a combination of (epi-)genetic and environmental factors. One such environmental factor implicated as a potential cause is aluminium.

Most epidemiological studies into the potential relation between Alzheimer's disease and aluminium – reviewed by e.g. ATDSR (2008), JECFA (2012), Wang *et al.* (2016) and Principi and Esposito (2018) –have addressed the potential neurotoxicity of aluminium in drinking water or antacids. The results of these studies are controversial: some of the studies on drinking water showed an association between aluminium and dementia or Alzheimer's disease, whereas others reported an absence of neuropsychological effects measured in several ways. None of these studies took into account the ingestion of aluminium in food.
The same controversy is found in relation to neurological effects observed in workers exposed to aluminium dust and fumes. Whereas some studies have observed impaired performance on neurobehavioural tests in workers (ATSDR, 2008), JECFA (2012) and Principi and Esposito (2018) conclude from their respective reviews that occupational exposure to aluminium does not seem to have an impact on cognitive or motor performance or adverse reproductive outcomes in exposed workers.

Walton (2014) applied Hill's causality criteria to reviews relevant to the hypothesis that Alzheimer's disease is a human form of chronic aluminium neurotoxicity. Waltonclaimed that aluminium plays a causative role in the development of Alzheimer's disease. According to Principi and Esposito (2018), Walton's conclusion is debatable, as a correlation was not definitively demonstrated, but even if it had been, this finding could not be considered evidence of causation. Thus, a relationship between aluminium-containing vaccines and Alzheimer's disease was not demonstrated by Walton (Principi and Esposito, 2018).

Besides the controversial findings from the epidemiological studies, an association between chronic aluminium exposure and the development of Alzheimer's disease has been surmised on the basis of findings from *in vitro* and *in vivo* studies (Morris *et al.*, 2017). These experiments demonstrate that aluminium ions accelerate the formation of amyloid plaques and potentiate the development of neurofibrillary tangles (NFTs), both of which are symptoms in brains of patients with Alzheimer's disease (Kawahara, 2005; Exley, 2005 reviewed by Morris

et al., 2017; JECFA, 2012). Nevertheless, studies relating to aluminium concentrations in the brains of patients with Alzheimer's disease have also yielded inconsistent results (Jacobs *et al.*, 1989; Chafi *et al.*, 1991; Landsberg *et al.*, 1992; Lovell *et al.*, 1993; Mirza *et al.*, 2017; Morris *et al.*, 2017; McLachlan *et al.*, 2019). Some of these studies detected higher concentrations in patients' brains (Mirza *et al.*, 2017; McLachlan *et al.*, 2019), whereas others did not (Jacobs *et al.*, 1989; Chafi *et al.*, 1991; Landsberg *et al.*, 1992; Lovell *et al.*, 1993; Morris *et al.*, 2017). Note that some of them did not include age and gender-matched controls (e.g. Chafi *et al.*, 1991; Landsberg *et al.*, 1992; Mirza *et al.*, 2017).

The general conclusion of the current study reviews (up to 2018) is that, although exposure to high doses of aluminium leads to neurotoxicity and developmental toxicity, there is little evidence that aluminium can be associated with Alzheimer's disease in the general population (AFSSA, 2003; EFSA, 2008; JECFA, 2012; BfR, 2014; SCCS, 2014; Willhite *et al.*, 2014; SCHEER, 2017; Principi and Esposito, 2018). Even taking into account the conclusion by Morris *et al*. (2017), who do not rule out a *correlation* between aluminium and Alzheimer's disease, any association between the two does not currently amount to a causal relationship.

Since the publication of the reviews mentioned above, two relevant studies have been published:

Mirza *et al*. (2017) determined concentrations of aluminium in the brain tissue of 12 donors diagnosed with familial Alzheimer's disease[3]. The authors claim that measured concentrations were high, although a control group is lacking in this study. Instead, the authors use previous measurements of the group of professor Exley (N=60, Age=70-103 years) (House *et al.*, 2012) as a 'reference' (Table 3). As they did not have information on the dementia status of the majority of the 60 brain donors, they predicted from the combination of amyloid pathology and the brain burden of aluminium that at least 39 of the 60 donors would have been diagnosed as suffering from dementia (Exley *et al.*, 2012). The mean concentrations of aluminium in each lobe of the brains of this reference group, consisting of a mix of people possibly suffering from sporadic or late onset Alzheimer's disease[1] and people that were not, were lower than those measured in donors diagnosed with familial Alzheimer's disease (see Table 3). Nevertheless, it is highly unlikely that a statistically significant difference exists between the two groups, because the spread in the measurements is very high. This large spread is caused by the large variation both between and within brains, and even between the three parts of one sample (this is not shown in Table 3). Other 'control measurements' are reported by Exley and House in their review of the aluminium content of human brain tissue from 28 publications (Exley and House, 2011). Despite the problems associated with accurate and reproducible measurements of brain aluminium in tissue homogenates, the authors concluded that the normal

[3] Familial Alzheimer's disease (FAD) is a rare form of Alzheimer's that is entirely passed down through genetics, being inherited from a parent. FAD accounts for 2–3% of all cases of Alzheimer's and usually has a much earlier onset than other types of Alzheimer's, with symptoms developing in people in their 30s or 40s. The most common form of Alzheimer's disease is called sporadic or late-onset Alzheimer's disease; this type has no specific family link (www.alzheimers.net; last visited on 18/5/2020).

range is 0.1–4.5 µg/g dry wt, the higher values (>2.00 µg/g dry wt) being measured in brains taken from non-demented elderly (Exley and House, 2011). The values in the brains of people with familial Alzheimer's disease, reported by Mirza *et al*. (2017), are in the same range as the 'normal' range derived in Exley and House (2011).

In a large study, McLachlan *et al*. (2019) report a statistically significant trend for aluminium to be increased in brains from patients with Alzheimer's disease (type of Alzheimer's disease not specified) compared with age- and gender-matched brains from the same anatomical region ($p<0.0001$, ANOVA). The measured aluminium concentrations in Alzheimer's disease patients' brains (N=186) showed a ~6–8-fold increase over the age- and gender-matched controls (N=53) (see Table 3 for details).

McLachlan *et al*. (2019) is the first study verifying the conclusion of Morris *et al.* (2017) that a correlation between aluminium in the brain and Alzheimer's disease seems to exist. Nonetheless, this association does not amount to a causal relationship. For this reason, one can only hypothesise whether aluminium might play a role in the cause or act as a co-factor or that its accumulation is a by-product or symptom of Alzheimer's disease.

Table 3. Aluminium concentration (standard deviation) in µg/g dry wt per lobe of donated human brain tissue.

Group	Occipital (µg/g dry wt)	Frontal (µg/g dry wt)	Temporal (µg/g dry wt)	Parietal (µg/g dry wt)	Overall (µg/g dry wt)	Reference
Control measurements from 28 publications	NA	NA	NA	NA	0.1–4.5	Exley and House, 2011
Reference group of non-AD and sporadic or late-onset AD brain tissues (N=60; 70–103 years)	0.98 (SD not reported)	0.83 (SD not reported)	1.30 (SD not reported)	0.95 (SD not reported)		House *et al.*, 2012[1]
Young control group (N=22; mean age 10.2 years ± SD 6.1)	NA	NA	1.2 (1.19)	NA		McLachlan *et al.*, 2019
Aged control group (N=53; mean age 71.4 years ± SD 9.3)	NA	NA	1.36 (0.28)	NA		McLachlan *et al.*, 2019
Donors diagnosed with familial AD (N=12; 42–86 years)	3.89 (5.86)	3.66 (6.18)	2.03 (2.35)	1.61 (1.90)		Mirza *et al.*, 2017
Donors diagnosed with AD[2] (N=186; mean age 73.1 years ± SD 15.6)	NA	NA	8.08 (2.91)	NA		McLachlan *et al.*, 2019
Donors diagnosed with ASD (N=5; 15–50 years)	3.82 (5.42)	2.30 (2.00)	2.79 (4.05)	3.82 (5.17)		Mold *et al.*, 2018
Donors diagnosed with ASD (N=26, mean age 11.1 years ± SD 6.4)	NA	NA	1.22 (0.2)	NA		McLachlan *et al.*, 2019

AD: Alzheimer's disease; ASD: Autism Spectrum Disorder

[1] SD is not reported, but the raw analysis data are given. High variances were observed for each set of three tissue samples taken from the same lobe, which according to the authors shows that aluminium is not evenly distributed within the brain and supports focal accumulations of aluminium that may have the potential for neurotoxicity.

[2] The type of Alzheimer's disease is not reported.

5.4 Autism

Autism, or autism spectrum disorder (ASD), is a neurological and developmental disorder referring to a broad range of conditions characterized by challenges with social skills, repetitive behaviours, speech, and non-verbal communication. The development of autism is influenced by a combination of genetic, environmental and immunological factors, genetic factors making the largest contributions (Morris *et al.*, 2017). Although aluminium-adjuvanted vaccines have been used for several decades and their safety is carefully studied in clinical trials and monitored post-marketing, some authors hypothesise that autism could result from an immune cascade initiated by an aluminium adjuvant (e.g. Mold *et al.*, 2018; Strunecka *et al.*, 2018). There is, however, no evidence to suggest that autism is a side effect of aluminium-adjuvanted vaccines.

In their evaluations of aluminium, the regulatory and advisory bodies (e.g. ATSDR, 2008; EFSA, 2008; JECFA, 2012; SCHEER, 2017) do not consider autism. Nevertheless, two of them conclude, as with Alzheimer's disease, that the association of aluminium with 'other neurological diseases' remains controversial and there is no evidence to support a causal association (EFSA, 2008; SCHEER, 2017).

A number of studies into the relation of aluminium to ASD have been performed. The results are summarised below.

In an epidemiological study, Tomljenovic and Shaw (2011) hypothesised that vaccines might be a cause of ASD as they found that the administration of vaccines containing aluminium adjuvants had increased in the last 30 years, as had the prevalence of ASD in seven Western countries (Tomljenovic and Shaw, 2011). However, this study was considered 'seriously flawed' by the Global Advisory Committee on Vaccine Safety (GACVS) at the World Health Organization (WHO) in 2012 (WHO, 2012). According to GACVS, the study is based on comparison of aluminium content in vaccines and rates of autism spectrum disorders in several countries, which cannot be used to assert a causal association, since they do not link exposure to outcome in individuals. Other concerns were found in this study that would limit its value for hypothesis generation. These include: incorrect assumptions about known associations of aluminium with neurological disease, uncertainty as to the accuracy of ASD prevalence rates in different countries, and to the accuracy of vaccination schedules and resulting calculations of aluminium doses in different countries (WHO, 2012).

Controversial results have been reported on the potential relation between aluminium concentration in hair and ASD diagnosis. Some studies have found increased levels of metals (e.g. aluminium, mercury, lead and cadmium) in the hair of children diagnosed with ASD (Blaurock-Busch *et al*., 2012; Yasuda and Tsutsui, 2013; Mohamed *et al.*, 2015). On the other hand, elevated levels of aluminium in the hair of children with ASD could not be demonstrated but they were shown for lead, mercury and uranium (Fido and Al-Saad, 2005).

Mold *et al.* (2018) measured aluminium levels in brain tissue from five donors diagnosed with ASD using the same method as Mirza *et al.*

(2017) (see Section 5.2) (Table 3). As in the study of Mirza *et al.*, owing to the lack of a control group, the authors use the measurements of 60 brain tissues from House *et al*. (2012) described above (Section 5.2) as a 'reference' group. The difference between this reference group and the group with autism appears not statistically significant, due to the high variation in the measured concentrations between and within the brains.

McLachlan *et al.* (2019) did not find significant differences between aluminium concentrations in the temporal lobes of patients diagnosed with ASD (N=26, mean age 11 years) and their control group (N=22, mean age 10 years) (Table 3).

5.5 Breast cancer

Aluminium salts used in underarm personal care products (antiperspirants) have been associated with breast cancer development and progression (Exley *et al.*, 2007; Darbe, 2016; Linhart *et al.*, 2017). On the other hand, in animal studies a causal relationship between aluminium exposure and the development of tumours has not been observed (see Section 2.2.6).

The regulatory and advisory bodies ATSDR, EFSA and JECFA did not consider breast cancer in their respective opinions on aluminium, while SCHEER (2017) and the SCCS (2020) are of the opinion that the epidemiological studies do not support the hypothesis that the use of aluminium-containing cosmetics affects the risk of breast cancer.

Epidemiological studies investigating the link between antiperspirant/ deodorant use and breast cancer have led to conflicting results. The reviews by Krewski *et al.* (2007) and Willhite *et al.* (2014) mention two large epidemiology studies, one of which was a population-based case control study that found no relation (Mirick *et al*., 2002), while the other suggested an earlier age for diagnosis of the disease with increasing antiperspirant use (McGrath, 2003). Other, smaller-scale studies (including a review of 59 papers published until 2007), cited by Willhite *et al*. (2014), concluded that underarm antiperspirant use was not associated with an increased risk of breast cancer.

A more recent retrospective study (209 breast cancer cases and 209 healthy controls) revealed an association between self-reported antiperspirant/deodorant use at early ages (<30 years) and breast cancer risk (p=0.0358) after adjusting for age, family history of breast cancer and many other factors (Linhart *et al.*, 2017). The association was triggered by women who reported using antiperspirant/deodorant more than once a day when they were under the age of 30, increasing their risk of contracting breast cancer by an odds ratio of 3.88 (95% CI 1.03–14.66). This study also measured the aluminium concentration of a large sub-sample of breast cancer cases and controls. It was found that self-reported antiperspirant/deodorant use correlates with higher aluminium concentration in the breast. Nevertheless, the subgroup exhibiting a statistically significant association between antiperspirant/ deodorant use and breast cancer risk is small (27 patients) and recall biases may exist in this kind of study. The most pronounced risk factor

for breast cancer from the retrospective study was a positive family history (Linhart *et al.*, 2017).

Although there are various hypotheses on the pathogenicity of aluminium in the development of breast cancer, a causal relationship is not established (Darbre, 2016; Morris *et al.*, 2017; Gorgogietas *et al.*, 2018). It is also currently unclear exactly how aluminium could reach and distribute within the mammary gland after application to the skin, as the dermal absorption of aluminium salts is very low (Mandriota, 2017; see also Section 3.2.5 on dermal absorption).

5.6 Macrophagic myofasciitis (MMF)

Macrophagic myofasciitis (MMF) is a rare muscle disease that is mainly manifested by diffuse muscle pain. In 1999, the WHO's Global Advisory Committee on Vaccine Safety (WHO, 1999) reported that there was evidence of the existence of MMF characterised by 'persistent focal accumulation in the deltoid muscle of densely packed macrophages with crystal inclusions composed of aluminium', and of 'a focal chronic inflammatory reaction'. According to the Committee, evidence suggested that the local lesion which characterised MMF might be caused by intra-muscular injection of aluminium-containing vaccines. The underlying mechanisms triggering the local MMF lesion and its persistence were, however, unclear (WHO, 1999).

The reviews of Krewski *et al.* (2007), Willhite *et al.* (2014), Morris *et al.* (2017) and Principi and Esposito (2018) also reflected on a possible link between aluminium adjuvants and MMF. The hypothesis behind this association is aluminium hydroxide adjuvant from a vaccine remains embedded in the tissue and causes a steady immune reaction leading to MMF (WHO, 1999; Authier *et al.*, 2001; Gherardi and Authier, 2012; Gherardi *et al.*, 2016; Crépeaux *et al*., 2017a). Nevertheless, as Krewski *et al.* (2007) stated, due to the invasiveness of the biopsy procedure, cases of MMF have not been compared with asymptomatic controls (with reference to Netterlid *et al*., 2004) and the mechanisms through which aluminium might induce this disorder are currently unknown (with reference to Authier *et al*., 2001).
A few sporadic paediatric cases have been described, but the association between MMF and central nervous system involvement is unclear in this population (Nevo *et al.*, 2004; Lach and Cupler, 2008; Principi and Exposito, 2018). In their review, Willhite *et al.* (2014) concluded that there was no evidence of a causal relationship with MMF. Principi and Esposito (2018) refine this conclusion by stating that aluminium adjuvant exposure per se does not appear to cause MMF for the vast majority of people. Nevertheless, some predisposed individuals may develop MMF as a result of their inability to clear aluminium from the injected muscle (WHO, 1999; Morris *et al*., 2017; Principi and Esposito, 2018). On the other hand, MMF cases not related to adjuvants have also been described, indicating that other factors unrelated to vaccination can cause this clinical problem (Park *et al.*, 2005; Principi and Esposito 2018).

5.7 Summary of potential association with adverse effects in humans

There is extensive evidence from clinical trials and pharmacovigilance that the only adverse effects associated with aluminium-adjuvanted

vaccines are local reactions at the injection site, such as redness and pain and sometimes nodules or granulomas.

The precise mechanism of Alzheimer's disease is unknown and there is currently no evidence to suggest that aluminium plays a causative role in its development. Supporting the possible mechanisms with experimental studies is difficult, as most measurements of aluminium concentrations in brain tissue show high variations and suffer from a lack of representative controls. Nevertheless, it appears that patients with Alzheimer's disease may have higher concentrations of aluminium in their brains. As there is no evidence for a primary causal role of aluminium in the pathogenesis of Alzheimer's disease, one can only hypothesise whether aluminium might play a role in its cause or act as a co-factor or that its accumulation is a by-product or symptom of Alzheimer's disease.

Concentrations of aluminium measured in the brains of people with autism are not significantly higher than those in the brains of control groups. There is no evidence to suggest an association between aluminium and autism.

Epidemiological studies investigating the link between aluminium and breast cancer have led to conflicting results. Furthermore, it is unclear how aluminium could reach and distribute within the mammary gland after application to the skin, as the dermal absorption of aluminium from anti-transpirants has been shown to be very low (see Section 3.2.5).

Exposure to aluminium adjuvant per se does not appear to cause the muscle disease MMF for the vast majority of patients. A proportion of patients who suffer from MMF may be susceptible to aluminium adjuvants administered by intramuscular injection. For this group, vaccination may have acted as either a cause or a co-factor for MMF.

6 Exposure to aluminium via diet, food contact materials and food supplements

6.1 Introduction

Humans are exposed to aluminium via their diet. Aluminium occurs naturally in food (via uptake from the soil) and drinking water, but may also end up in the diet as a result of industrial food processing or the use of aluminium-containing food additives, packaging materials (food contact materials) or kitchenware used for food preparation and/or serving and/or stocking. Information on the dietary exposure to aluminium by the different subgroups in the population is presented in Sections 6.2 to 6.4. Another source of aluminium is clay-based food supplements (Section 6.5). The exposure data in these sections are for total aluminium; the form of aluminium present (most likely soluble aluminium salts) is not further identified.

6.2 Exposure of infants to aluminium via breast milk and infant formula

Infant formulas are milk-based feeds for infants that have been developed as alternatives to breast milk. Cow's milk is the main ingredient of many infant formulas, but there are also other formulas (for example made from soya) for infants with an intolerance or allergy to cow's milk. Several studies have shown that infant formulas can contain aluminium, the amount of which varies according to their formulation (e.g. Navarro-Blasco and Alvarez-Galindo, 2003; Burrell and Exley, 2010; Chuchu *et al.*, 2013). In general, the aluminium content of formulas prepared from milk powders is higher than that of ready-made milk formulas, soy-based products having higher aluminium content than cow's milk products. Other infant drinks and yoghurts have also been shown to have a higher aluminium content when based on soy rather than on cow's milk (Tietz *et al.*, 2019).

Table 4 summarises the results of studies investigating infant exposure to aluminium.

With reference to JECFA (2007), EFSA (2008) gave estimates of the intake of aluminium in 3-month-old infants weighing 6.1 kg via breast milk and infant formula (see Table 4). Based on the negligible content of aluminium in human and cow milk samples from the USA (<50 µg/l, as reported by Koo *et al*., 1988) and an average daily consumption of 0.7 l, breastfed infants would have an intake of less than 0.035 mg Al/kg bw/week. High consumption (P95; 1 l/day) would lead to an intake of less than 0.07 mg Al/kg bw/week. It is noted that Tietz *et al.* (2019) mention more recent investigations that report rather similar aluminium content in breast milk samples from France (all below the limit of detection (LOD) of 8 µg/l), Spain (7–42 µg/l) and Germany (<LOD–40 µg/l), with somewhat higher levels in breast milk samples from Austria (<10–380 µg/l, median 67 µg/l).

Table 4. Exposure of infants to aluminium in breast milk and infant formula (in mg/kg bw/week).

Type of food	Age (bw)	Exposure		Reference
		Mean	P90	
Breast milk	3 mo (6.1 kg)	<0.035	<0.07 [P95]	EFSA, 2008
Infant formula based on cow's milk	3 mo (6.1 kg)	0.2–0.6	0.3–0.9 [P95]	EFSA, 2008
Infant formula based on soya	3 mo (6.1 kg)	0.75	1.1 [P95]	EFSA, 2008
Milk powder-based formula[1,2]	newborn (3.3 kg)	0.182–2.001	0.202–2.217	BfR, 2012
	4 mo (6.4 kg)	0.131–1.444	0.164–1.805	
	6 mo (7.3 kg)	0.115–1.266	0.144–1.582	
Ready-made liquid formula[3]	newborn (3.3 kg)	0.141–0.937 [median]	0.176–1.172	BfR, 2012
	4 mo (6.4 kg)	0.100–0.665 [median]	0.123–0.816	
	6 mo (7.3 kg)	0.100–0.665 [median]	0.122–0.810	
Milk powder-based formula[4]	newborn (3.3 kg)	0.07–0.19 P + 0.006–0.058 W 0.076–0.248	0.15–0.40 P + 0.011–0.116 W 0.161–0.516	AGES, 2017
	4 mo (6.4 kg)	0.09–0.24 P + 0.009–0.090 W 0.099–0.33	0.11–0.31 P + 0.009–0.090 W 0.119–0.40	
	6 mo (7.3 kg)	0.07–0.19 P + 0.005–0.055 W 0.075–0.245	0.12–0.31 P + 0.009–0.092 W 0.129–0.402	
Infant and weaning foods	0–3 mo	0.10		FSA, 2006 (as reported in EFSA, 2008)
	4–6 mo	0.20		
	7–9 mo	0.43		
	10–12 mo	0.78		

Type of food	Age (bw)	Exposure		Reference
		Mean	P90	
Infant foods (mainly formulas)	1–4 mo	0.21 (LB) 0.22 (UB)[5,6]	0.43 (LB) 0.43 (UB)	ANSES, 2016; Sirot *et al*., 2018
Infant foods (mainly follow-on formulas) + some common foods	5–6 mo	0.32 (LB) 0.32 (UB)	0.52 (LB) 0.52 (UB)	ANSES, 2016; Sirot *et al*., 2018
Infant + common foods	7–12 mo	0.35 (LB) 0.36 (UB)	0.55 (LB) 0.56 (UB)	ANSES, 2016; Sirot *et al*., 2018
Common foods + some infant foods	13–36 mo	0.37 (LB) 0.39 (UB)	0.61 (LB) 0.62 (UB)	ANSES, 2016; Sirot *et al*., 2018

[1] Additional aluminium intake from drinking water (for reconstitution) not included.
[2] At 3 different aluminium content levels in milk powder (1, 5 and 11 mg/kg) and 2 different powder quantities, without specifying what these quantities represent. Results for the lower powder quantity have been presented under mean in the table, for the higher quantity under P90.
[3] At 3 different aluminium content levels (0.130, 0.500, 0.863 mg/l).
[4] At 2 different aluminium content levels (mean and maximum) in milk powder (P: 0.75 and 2.04 mg/kg) and drinking water for reconstitution (W: 0.009 and 0.091 mg/l) and 2 different powder quantities (minimum and maximum of label instructions). Results for the minimum powder quantity have been presented under mean in the table, for the maximum quantity under P90. Total exposure to aluminium is P + W.
[5] LB (lower bound) and UB (upper bound): for aluminium contents below the LOD, the content was taken as 0 (LB) or LOD (UB) in the calculations of the intake; for aluminium contents between the LOD and LOQ the content was taken as LOD (LB) or LOQ (UB).
[6] Reported data (in mg/kg bw/day) multiplied by 7.

Aluminium intake via infant formula was estimated to be higher than that via breast milk: taking the mean aluminium concentrations as found in 8 different types of infant formula available on the Spanish market as a basis (Navarro-Blasco and Alvarez-Galindo, 2003), EFSA calculated an average intake (based on a consumption of 0.7 l/day) of 0.2–0.75 mg/kg bw/week, and a high intake (based on 1 l/day) of 0.3-1.1 mg/kg bw/week. These intakes included aluminium from the water used for reconstitution. EFSA noted that for infants regularly fed certain brands of formula the intake might be higher, given that the highest reported aluminium contents within the types of formula tested were around four times higher than the mean aluminium content taken for intake assessment (EFSA, 2008).

In 2012, the German Federal Institute for Risk Assessment (BfR) estimated the intake of aluminium via infant formula for newborn babies and 4- and 6-month-old infants, based on the aluminium content found in 16 different infant formulas available in the UK (as reported by Burrell and Exley (2010)). The intake was calculated for two types of formula – one based on milk powder (to be mixed with drinking water) and the other ready-made liquid formula – each at three different aluminium content levels (see Table 4). Newborn babies have the highest intake, with a low and high estimate of 0.18–2.0 and 0.20–2.2 mg Al/kg bw/week, respectively, for milk powder-based formulas, and a median (P50) and high (P90) estimate of 0.14–0.94 and 0.18–1.2 mg Al/kg bw/week, respectively, for ready-made liquid foods. It is noted in the report that the estimated intake for milk powder-based formulas does not include any potential aluminium in the drinking water used for preparation, so the intake could be higher (BfR, 2012). This was indeed shown by the Austrian Agency for Health and Food Safety (AGES): for the same age groups as investigated by BfR, the contribution of aluminium via added drinking water to total intake via milk powder-based formula was in the range of 7–10% at average aluminium content and up to 29–38% at maximum aluminium content (AGES, 2017).

In France, a total diet study – 'Infant TDS' (iTDS) – was conducted between 2010 and 2016 to assess the intake of chemicals (including aluminium) in food of non-breastfed children under 3 years (ANSES, 2016; Sirot *et al.*, 2018). This showed that the intake of aluminium increases during the first 36 months of life, the mean intake increasing from approximately 0.2 to 0.4 mg/kg bw/week, the P90 intake from approximately 0.4 to 0.6 mg/kg bw/week (see Table 4). This increase results from the stepwise inclusion of ordinary foods in the daily diet: whereas infant formula is the main source of aluminium intake (85%) until the age of 4 months, thereafter follow-on formulas, ready-to-eat meals for children, and vegetables become an increasingly part of the diet (Sirot *et al.*, 2018). With reference to a survey conducted by the UK Food Standards Agency (FSA, 2006), EFSA (2008) had also reported that aluminium intake from infant formula and weaning foods increases in early life (from 0.10 mg/kg bw/week at 0–3 months to 0.78 mg/kg bw/week at 10–12 months).

6.3 Exposure of children and adults to aluminium via the diet

With reference to Ellen *et al.* (1990), EFSA (2008) reported a mean dietary aluminium intake of 3.1–4.6 mg/day for adults in the Netherlands (corresponding to 0.36–0.54 mg/kg bw/week for a 60 kg adult), based on duplicate diet studies in 1978 and 1984–1985. There are no more recent Dutch duplicate diet studies or total diet studies from which the dietary intake of aluminium can be estimated for adults, nor for children/ adolescents aged 7–18 years. However, for children aged 2–6 years there is a Dutch duplicate diet study from 2014 (Wilson-van den Hooven *et al*., 2015a, 2015b), in which duplicate portions of all the foods and beverages consumed during one day were collected and analysed for energy, macronutrients, vitamins and minerals. In 2016, the samples were also analysed for aluminium (data not published), on the basis of which the aluminium intake was calculated (Wageningen Food Safety Research (WFSR), personal communication). On a weekly basis, the overall mean and P95 aluminium intake for 2–6-year-olds was 0.55 and 1.12 mg/kg bw/week, respectively (see Table 5). Since the foods and drinks analysed included items bought in for example supermarkets and items prepared for meals, exposure to aluminium via food additives and via leaching from kitchenware and/or packaging materials was inherently included in this duplicate diet study. Note that the duplicate portions were collected during just one day. Given the variation in daily food consumption patterns within an individual, the high percentile intake estimates very likely overestimate the true high long-term intake of aluminium in this age group.

In the absence of (recent) Dutch studies for age groups other than 2-6 years, dietary aluminium intake estimates as calculated and reported from total diet studies for France (ANSES, 2011; Arnich *et al*., 2012), Belgium (Fekete *et al.*, 2013), Norway (VKM, 2013), Ireland (FSAI, 2016) and Germany (Tietz *et al*., 2019) are considered instead (Table 5). Given that the intake estimates show a fairly consistent picture across five European countries, it is expected that the intake in the Netherlands is similar and that these estimates can be taken as representative for the Netherlands. In these studies, analytical results for aluminium content in foods were linked to food consumption data as obtained from food consumption surveys. In four of the five studies, the analytical results related to foods bought and subsequently prepared for consumption, so the intake of aluminium via food additives, packaging materials and kitchenware was inherently included. In the Belgian study (Fekete *et al*., 2013), exposure to aluminium leaching from kitchenware (aluminium dishes, ceramicware, aluminium foil, metalware and glassware) was assessed separately from that via food and beverages (which were analysed as bought). At the mean level, it was estimated that aluminium exposure via leaching from kitchenware could be 0.005 mg/kg bw/day, 16.5% of total exposure via foods. At the high end of the exposure distribution (≥P95), aluminium leached from kitchenware could be as high as 30% of aluminium from food. The most important contributor to aluminium exposure through kitchenware was aluminium foil (64%) (Fekete *et al.*, 2013).

Table 5. Exposure of children and adults to aluminium in diet (in mg/kg bw/week) in six European countries.

Country	Age	N	Exposure[1]		Reference
			Mean	P95	
Netherlands	2 yr	26	0.54	0.98	WFSR, personal communication
	3 yr	26	0.51	0.96	
	4 yr	25	0.61	1.17	
	5 yr	23	0.57	1.18	
	6 yr	26	0.52	0.85	
	Overall 2–6 yr	126	0.55	1.12	
Belgium[2,3,4]	≥15 yr	3083	0.25	0.72	Fekete *et al.*, 2013
France[3,4]	3–6 yr	1444	0.64	1.02	ANSES, 2011; Arnich *et al.*, 2012
	7–10 yr		0.49	0.82	
	11–14 yr		0.34	0.58	
	15–17 yr		0.26	0.46	
	18–45[5] yr	1918	0.29	0.51	
	65–79 yr		0.27	0.49	
Norway[4]	1 yr	1635	0.89	1.9	VKM, 2013
	2 yr	1674	0.88	1.7	
	4 yr	391	0.53	0.90	
	9 yr	310	0.35	0.66	
	13 yr	1005	0.22	0.49	
	18–70 yr	1787	0.29	0.67	
Ireland[6]	5–12 yr	594	0.36 (LB) 0.37 (UB)	0.74 (LB) 0.75 (UB) [P97.5]	FSAI, 2016
	≥18 yr	1500	0.35 (LB) 0.35 (UB)	0.83 (LB) 0.84 (UB) [P97.5]	
Germany[7,8]	14–80 yr	13926	0.18 (LB) 0.21 (UB)	0.42 (LB) 0.44 (UB)	Tietz *et al.*, 2019

[1] Intake based on foods purchased and then prepared for consumption before analysis.
[2] Intake is sum of intake through foods analysed as purchased and intake through kitchenware.
[3] Reported data (in mg/kg bw/day) multiplied by 7.
[4] Intake reported as MB (middle bound) values: for foods with aluminium content below the LOD, the content was taken as 0.5*LOD, whereas for aluminium content between the LOD and LOQ the content was taken as 0.5*LOQ.
[5] Women of childbearing age.
[6] Intake reported as LB (lower bound) and UB (upper bound) values: for foods with aluminium content below the LOD, the content was taken as 0 (LB) or LOD (UB) in the calculations of the intake.
[7] Intake reported as LB (lower bound) and UB (upper bound) values: for foods with aluminium content below the LOQ, the content was taken as 0 (LB) or LOQ (UB) in the calculations of the intake.
[8] No significant differences between age and gender groups were observed.

6.4 Exposure to aluminium via packaging material and kitchenware

Materials and articles that are used for production, packaging, cooking, eating and storage of food can release aluminium into the food – see for instance the Belgian total diet study (Fekete *et al*., 2013) described in Section 6.3. The recent study by Ertl and Goessler (2018) also presents evidence that baking or storing food in aluminium foil moderately increases its aluminium concentration, especially in food with high acidic and salt contents, and that storage on a stainless steel serving plate in combination with an aluminium foil covering leads to much higher increases in aluminium concentration.

A preliminary investigation by the BfR further points to the release of aluminium from uncoated aluminium trays into acidic foods during the Cook & Chill process and subsequent keeping warm phase (BfR, 2017). This process is widely used in e.g. daycare centres, schools, companies, retirement homes and out-of-home catering. The test results show that in particular the keeping warm phase (for 2 hours at ≥65 °C) results in a considerable release of aluminium ions from the food compartment trays (to above the Specific Release Limit (SRL) of 5 mg/kg food for aluminium) and transfer into the food. Despite the limited number of samples examined, the exploratory results indicate that, when it occurs on a daily basis, this may contribute considerably to the overall exposure of consumers to aluminium.

Aluminium drinking bottles (in particular uncoated ones) and moka pots, as well as aluminium dishes and pans used for grilling or cooking and aluminium camping utensils (pots and pans), have also been shown to release aluminium into water, coffee, tea, acidic drinks and marinated foods (Stahl *et al.*, 2017a/b). It is, however, concluded by the authors that for water and coffee there is little additional aluminium exposure to be expected when properly using drinking bottles and moka pots.

Given these and other investigations, Tietz *et al.* (2019) have concluded that significant transition of aluminium into food is to be expected above all when uncoated aluminium articles are used in connection with acidic, alkaline or salty foodstuffs, but also that ceramics, paper or board used as food contact materials may be sources of aluminium exposure.

6.5 Exposure to aluminium via clay-based food supplements

Some clay-based food supplements contain aluminium and may therefore contribute to the exposure of consumers to aluminium. There are in general two reasons that clay-based food supplements are taken: for intestinal cleansing and for reducing morning sickness (nausea) during the first months of pregnancy (‘pregnancy clays’). In 2009, the Netherlands Food and Consumer Product Safety Authority (NVWA-BuRO, 2009; RIVM-RIKILT, 2009) detected aluminium in five out of nine ‘pregnancy clays’ tested (at levels ranging from 78 to 120 g/kg) and in four out of seven intestinal cleansing clays (6.9–24 g/kg). Using the levels found in ‘pregnancy clays’, and assuming all aluminium to be bioaccessible from the clays, the NVWA estimated an oral exposure of 353-543 mg Al/kg bw/week for pregnant women, assuming a daily consumption of 42 g clay (based on limited public literature). Oral exposure to aluminium for adults and children using intestinal cleansing clays was estimated at 3.9–24.8 and

9.2–107.5 mg/kg bw/week for adults (bw 65 kg) and children (bw 15 kg), respectively, based on consumption rates as recommended on the labels for these products. Whereas the NVWA expected the intestinal cleansing clays to be mainly used by adults, they could not exclude use by children. However, we consider it very unlikely that children will be subjected to intestinal cleansing, and will therefore not take the exposure estimate for children forward in this report.

Regarding the exposure estimates for pregnant women and adults, these can only be taken as crude estimates given the limited information available. Although the estimates indicate that exposure from clay-based food supplements can be high, it also needs to be borne in mind that not all clays contain aluminium (as was shown for four out of the nine 'pregnancy clays' and three out of seven intestinal cleansing clays tested), that not all aluminium in the clays will be bioaccessible (cf. the findings for soil, see Section 3.2.3), that intestinal cleansing clays will not be used continuously (usually for a couple of weeks only) or with a high frequency, and that in the Netherlands 'pregnancy clays' are generally used only by some women of foreign (in particular Surinam and African) origin.

6.6 Summary of exposure via diet, food contact materials and food supplements

Table 6 provides a summary of aluminium intake via diet, food contact materials and food supplements for the 'averagely' and 'highly' exposed consumer within different age groups. Although for the major part not based on Dutch data, the dietary intakes presented in Tables 4 and 5 can be taken as representative for the Netherlands, given the fairly consistent picture across a number of European countries. As it is not known to which intake the Dutch intake would be most similar, the low and high ends of the mean and high (P90/P95/P97.5) intake values as given for the particular age groups in Tables 4 and 5 are shown in Table 6, for the averagely and highly exposed consumer. For the clay-based food supplements, the lower ends of the intake ranges are taken for the average consumer, the higher ends for the highly exposed consumer.

For infants, aluminium intake via breast milk is significantly lower than aluminium intake via infant formula. The intake via infant formula might be higher for infants regularly fed the same brand of (high-aluminium-content) formula. It might also be higher for infants with an intolerance or allergy to cow's milk, due to the higher aluminium content of soy-based infant products than cow's milk products.

Table 6. Summary of oral exposure (external) of averagely and highly exposed infants, children and adults to aluminium via diet[1] and food supplements (in mg/kg bw/week).

Age	Source	Exposure			
		Average		High	
		low end	high end	low end	high end
0–6 mo	Breast milk	<0.035		<0.07	
	Infant formula	0.075	2.001	0.119	2.217
7–12 mo	Infant formula/foods	0.35	0.78	0.55	0.56
1–2 yr	Diet	0.37	0.89	0.61	1.9
3–6 yr	Diet	0.51	0.64	0.85	1.18
7–10 yr	Diet	0.35	0.49	0.66	0.82
11–14 yr	Diet	0.22	0.34	0.49	0.58
15–17 yr	Diet	0.26		0.46	
≥18[2] yr	Diet	0.18	0.35	0.42	0.84
	Intestinal cleansing clay	3.9		24.8	
	'Pregnancy clay'	353		543	

[1] Intake values presented for diet include contribution from food additives, packaging materials and cook-/kitchenware.
[2] Including women of childbearing age.

As can be seen from Table 6, aluminium intake is highest during the first 6 years of life; thereafter it decreases. It is clear from several investigations that food contact materials and kitchenware used for preparing, cooking, serving and storing food can contribute to dietary aluminium intake, especially from foods and drinks with high acidic and salt contents. It is noted, however, that the dietary intakes shown in Table 6 already include these contributions.

Whereas for clay-based food supplements the intake of aluminium appears high, the estimates can only be taken as crude estimates given the limited data available. Most probably they are overestimations, given that 100% bioaccessibility of aluminium from the clays is not likely (see Section 3.2.4) and it has been shown that not all clays contain aluminium. It is also a source that not all adults or pregnant women are exposed to, and not on a continuous or frequent basis either.

7 Exposure to aluminium via consumer products

7.1 Introduction

Aluminium may be present in all kinds of consumer products, e.g. household and personal care products. The following databases were searched for information on concentrations of aluminium in consumer products:

- Consumer Product Information Database[4] (CPID; formerly known as US Household Products Database);
- Substances in Preparations In the Nordic countries (SPIN) database[5];
- Danish EPA Database on Chemicals in consumer products[6];
- SkinDeep database[7] (Environmental Working Group's database on personal care products); and
- CosIng database[8] (European Commission's database on cosmetic substances and ingredients).

Data on aluminium concentrations are available only for certain personal care products, so the exposure assessment is limited to these types of products. Consumer products other than personal care products will be briefly addressed in Section 7.3.

Aluminium is present in a wide range of personal care products, such as deodorants and antiperspirants, shaving products, foundations, make-up for eyes, lips, nails and skin, make-up removers, hair dyes and products for dental, oral, skin and sun care (AFSSAPS, 2011; BHGR, 2015; SkinDeep). In these products aluminium is present in a variety of aluminium compounds including simple inorganic and organic salts, chlorohydrates, minerals, glasses and clays, aluminium lakes, carbohydrates and fatty acids salts (AFSSAPS, 2011; SCCS, 2014; SkinDeep; CosIng). Aluminium compounds are applied as an abrasive, absorbent, moisturiser, antiperspirant, astringent, colorant, coating agent, soothing agent, viscosity agent, bulking agent, opacifying agent, anticaking agent, or a combination thereof. See Annex II for more detailed information on the use of aluminium in personal care products.
The general population will be exposed to aluminium in personal care products via dermal and oral contact and/or, in the case of antiperspirant sprays, via inhalation.

7.2 Exposure of children and adults to aluminium via personal care products

7.2.1 Aluminium concentration in personal care products

There are limited data on aluminium concentrations in personal care products such as lipstick, lip gloss, antiperspirant/deodorant, (whitening) toothpaste, and sunscreen/sunblock. These concentrations are presented in Table 7. A few data on aluminium in personal care products based on Dead Sea mud are also available. Some of these products contain relatively high

[4] https://www.whatsinproducts.com/
[5] http://spin2000.net/
[6] https://vidensbank.mst.dk/V2/default.aspx?eng=y
[7] https://www.ewg.org/skindeep/
[8] https://ec.europa.eu/growth/sectors/cosmetics/cosing_en

aluminium concentrations (up to 8.5 mg/kg, in facial creams and muds), while others (soap, hand cream, body lotion, shampoo, moisturiser and shaving soap) contain very little aluminium (0.002 to 0.65 mg/g) (Abdel-Fattah and Pingitore, 2009). As these mud-based products are not used by a large part of the general population and their aluminium content is generally lower than that in the more widely used products listed in Table 7, they will not be addressed further.

7.2.2 *Exposure estimation – oral and dermal*

In various risk assessments of aluminium in personal care products (e.g. VKM, 2013; BfR, 2014; Tietz *et al*., 2019; SCCS, 2020), (external) exposure to aluminium resulting from the use of these products was estimated using the default values for daily use amounts and retention factors from the SCCS Notes of Guidance (SCCS, 2018). According to these Notes, the defaults for daily use amounts are conservative (P90) values that can be used to assess exposure in a first tier. For the current estimation of exposure from antiperspirant, lipstick/lip gloss, sunscreen and toothpaste use, the respective SCCS defaults were taken, in combination with the highest mean and maximum aluminium concentrations reported for these products (see Table 7). The SCCS defaults are for adults, but the use amounts of antiperspirant, toothpaste and lipstick were also applied to children for those age groups where we assumed a regular/daily use of these products (see the paragraph below). The exposure is expressed on a body weight basis, default values for body weight for the different age groups being taken from Te Biesebeek *et al.* (2014).

It is assumed that antiperspirants and lipstick/lip gloss will not be used on a regular/daily basis by children under 11 years of age, even though from some publications it appears that they might be used by this age group. Ficheux and co-authors, for instance, have reported that the fraction of boys and girls from 4 to 14 years of age using antiperspirants on a daily basis is 36% and 51%, respectively. They further reported that 24% of 0–15-year-old girls use lipstick with a frequency of 0.47 times per day (Ficheux *et al.*, 2015). Garcia-Hidalgo and co-authors found daily use of antiperspirants by 15% of 0–15-year-old children and another 15% having a use frequency of 2–3 times per week (Garcia-Hidalgo *et al*., 2017). However, the specific use of these products in the younger age categories included in the current report (e.g. 3–6 years, 7–10 years) is not given in these publications. We assume that these products will primarily be used by the older children and not be used on a regular/daily basis by children under 11 years of age. Toothpaste will also not be considered further for this age group, given that for children up to 12 years of age there is special toothpaste (low in fluoride). Besides, it seems that the vast majority of toothpastes contain sodium fluoride rather than aluminium fluoride (Storehagen *et al.*, 2003). For exposure assessment, only the use of whitening toothpastes may be relevant, as these may contain aluminium oxide or hydroxide as abrasives, although hydrated silica is more commonly used as an abrasive (Storehagen *et al.*, 2003). It is assumed that only adults will use whitening toothpaste. It is noted, however, that, since only a few whitening toothpastes contain aluminium, not all adults using whitening toothpaste will be exposed to aluminium on a daily basis.

Table 7. Aluminium concentrations (mg/g) in a number of personal care products. Values in bold are taken as worst case values for exposure estimation.

Personal care product	Minimum	Mean/Median	Maximum	Reference
Antiperspirant (N=25)	2	28/NR	58	AGES, 2017
Antiperspirant/deodorant (N=8)	28	**45**/41	**71**	VKM, 2013
Antiperspirant – roll-on/stick (N=11)	21	28/NR	34	RIKILT, 2015
Non-spray antiperspirant (N=NR)			62.5[1]	SCCS, 2020
Spray antiperspirant[2] (N=10)	30	**63**/NR	94	RIKILT, 2015
Spray antiperspirant[2] (N=4)	68		94	Schwarz *et al.*, 2018
Spray antiperspirant[2] (N=NR)			**106**[1]	SCCS, 2020
Lipstick/lip gloss (N=22)		**10**/NR	19	AGES, 2017
Lipstick/lip gloss (N=11)	<0.00035	8.7/7.7	**28**	VKM, 2013
Lipstick/lip gloss (N=32)	0.0004	5.2/4.4	27	Liu *et al.*, 2013
Toothpast (N=15)		**9**/<0.2	39	AGES, 2017
Whitening toothpaste (N=NR)			**45**[3]	VKM, 2013
Toothpaste (N=NR)			26.5[1]	SCCS, 2020
Sunscreen (N=14)	<LOQ (5/14)	**1**/NR (of 9/14)	**8** (9/14)	AGES, 2017
Sunscreen/block (N=7)	0.001		>1[4]	Nicholson *et al.*, 2007

NR = not reported

[1] Maximum level of aluminium, according to a survey by Cosmetics Europe of its members in 2013 (no further details available).

[2] Aluminium in non-volatile fraction.

[3] Personal communication Norwegian Food Safety Authority.

[4] The aluminium content of this product was in excess of what could be reliably measured using Graphite Furnace Atomic Absorption Spectrometry (GFAAS).

For lipsticks/lip gloss only oral exposure is estimated. It is assumed that the whole amount applied to the lips is swallowed (0.057 g/day; SCCS, 2018) as a conservative estimation, covering also potential dermal exposure.

For sunscreen, a daily application of 18 g is assumed on 25 days/year, leading to an estimated daily amount applied of 1233 mg/day (18,000 mg * 25/365 days) (SCCS, 2018). For the dermal exposure of infants and children (<11 years) to sunscreen the SCCS considered the Skin Surface Area over Body Weight ratio (SSA/BW) to be 2.3, 1.8, 1.6, 1.5 and 1.3 times higher for newborns, 6-month-old and 1-, 5- and 10-year-old children, respectively, than for adults (and, presumably, children ≥11 years) (SCCS, 2018). Hence, for these age groups the exposure estimates were calculated as 2.3, 1.8, 1.6, 1.5 and 1.3 times the exposure estimated for adults, respectively, whereas for children aged 11–17 years the exposure estimate was taken to be identical to that of adults.

Table 8. Dermal and oral exposure of children and adults to aluminium in personal care products (in mg/kg bw/week).

Personal care product	Daily amount applied[1] (g/day)	Age	Bw[2] (kg)	Exposure Mean	Exposure High
DERMAL					
Non-spray deo/ anti-perspirant	1.5	11-14 yr	44.8	10.5	16.6
		15-17 yr	59.3	7.97	12.6
		≥18 yr	68.8	6.87	10.8
Spray deo/ antiperspirant	0.69[3]	11–14 yr	44.8	6.79	11.4
		15–17 yr	59.3	5.13	8.63
		≥18 yr	68.8	4.42	7.44
Sunscreen[4]		0		0.29	2.31
		6 mo		0.23	1.81
		1 yr		0.20	1.61
		5 yr		0.19	1.51
		10 yr		0.16	1.30
		11–14 yr		0.13	1.00
		15–17 yr		0.13	1.00
	1.233	≥18 yr		0.13	1.00
ORAL					
Lipstick/ lip gloss	0.057	11–14 yr	44.8	0.09	0.25
		15–17 yr	59.3	0.07	0.19
		≥18 yr	68.8	0.06	0.16
Whitening toothpaste	0.138	≥18 yr	68.8	0.13	0.63

[1] Defaults taken from SCCS (2018).
[2] Default body weights for the different ages taken from Te Biesebeek *et al*. (2014).
[3] For non-ethanol based sprays.
[4] Exposure for newborns, 6-month-olds and 1-, 5-, 10-, 11-14- and 15-17-year-olds estimated at 2.3, 1.8, 1.6, 1.5, 1.3, 1 and 1 times the adult exposure estimates, respectively, based on differences in Skin Surface Area over Body Weight ratio (SSA/BW) (SCCS, 2018).

The calculated mean and high dermal and oral exposure estimates are presented in Table 8. These are all external values and can be considered worst case estimates, as the defaults taken for daily amount applied are conservative and per product type the highest reported mean and maximum aluminium concentrations have been used in the calculations. On the other hand, the concentration data available relate to only a limited number of products per product type.

7.2.3 *Exposure estimation – inhalation*

Where an aluminium-containing antiperspirant in the form of a spray is used, the possibility of inhalation must be taken into account in addition to dermal exposure. The quantities of aluminium inhaled are *inter alia* related to product parameters such as formulation, nozzle geometry, type of propellant gas and pressure. Aerosols can consist of a wide spectrum of particle sizes. Exposure to larger particles (>10 µm) is limited to the upper respiratory tract and tracheobronchial tree, whereas respirable particles (<10 µm) can reach deep lung regions. The particle/droplet size distribution is complex and depends on the product formulation and the technical details of the applicator.

In its 2020 opinion, the SCCS reported only systemic, not external, exposure estimates for the inhalation route following the use of antiperspirant sprays. Aside from a reference to Schwarz *et al.* (2018) for the methodology, no further details are presented as to how the estimates were derived (SCCS, 2020).

Schwarz *et al*. (2018) modelled the deposition of aluminium in the respiratory tract following the use of antiperspirant sprays. Four typical products (containing 0.5–1.5% aluminium in the total product, but 6.6-9.4% aluminium when considering the non-volatile fraction only (excluding the propellant) were sprayed for 2 seconds onto a skin surrogate in defined rooms. For the determination of the respiratory tract deposition, only the 'overspray' fraction (i.e. the part not deposited on the skin surrogate) was taken into account. Per spray application this resulted in mean deposited doses of 4.52 (range over 4 sprays 1.25-6.54), 10.89 (range 2.40–17.4) and 37.42 µg (range 8.23–58.91) in the pulmonary, tracheo-bronchial and extra-thoracic compartment of the respiratory tract, respectively. Assuming for antiperspirant sprays 2 applications per day, 7 days per week (SCCS, 2018), the highest deposited doses per region have been recalculated into (worst case) inhalation exposure estimates in mg/kg bw/week. Body weight defaults for the different age groups were taken from Te Biesebeek *et al.* (2014). The results are presented in Table 9.

Table 9. Inhalation exposure of children and adults to aluminium in spray antiperspirants (in mg/kg bw/week), based on Schwarz et al. (2018).

Age	Bw[1] (kg)	Exposure			
		Pulmonary	Tracheo-bronchial	Extra-thoracic	Total
11-14 yr	44.8	0.0020	0.0054	0.0184	0.0258
15-17 yr	59.3	0.0015	0.0040	0.0139	0.0195
≥18 yr	68.8	0.0013	0.0035	0.0120	0.0168

[1] Default body weights for the different ages taken from Te Biesebeek *et al*. (2014).

7.3 Consumer products other than personal care products

The CPID and SPIN databases indicate the presence of aluminium in cleaning agents such as all-purpose cleaners, toilet cleaners, oven cleaners, dishwashing agents, laundry detergents, metal polishes and furniture oils. However, little to no information on the concentration of aluminium in these kinds of household products is available. For this reason, the exposure resulting from use of these products cannot be estimated.

The CPID and the Danish EPA database point to other consumer products that may contain aluminium, e.g. paints, coatings, printer ink, mortar, filler, cement, concrete, cat litter, plant fertiliser, sex toys, tattoo ink and bicycle helmets. However, again information on aluminium concentrations in and/or migration from these products is limited or not available. Hence, the exposure resulting from these products cannot be estimated, either. It can be assumed, however, that exposure resulting from use of these products is less than from cleaning agents and personal care products, given that consumers in general will not use them on a frequent/daily basis and that aluminium may not easily migrate from these products.

Children's toys including slimy toys may also contain aluminium (Danish EPA database), but due to the lack of representative information on the aluminium content in toys, exposure from this source cannot be estimated. It is noted that aluminium in toys is regulated by the Toy Safety Directive 2009/48/EC, which sets maximum migration limits for aluminium from 'dry, brittle, powder-like or pliable' (2250 mg/kg), 'liquid or sticky' (560 mg/kg), and 'scraped-off' (28,130 mg/kg) toy materials.

7.4 Summary of exposure via consumer products

Table 10 presents a summary of aluminium exposure via personal care products for the 'averagely' and 'highly' exposed consumer within different age groups.

As noted in Section 7.2.2, these are worst case estimates for personal care product use, given the conservative nature of the defaults for daily use amounts and the fact that the highest reported mean and maximum aluminium concentrations have been taken from the limited data available per product type. Additionally, the assumption that the personal care products used will always contain aluminium is an overestimation, as for each product type there are alternatives without aluminium available. Furthermore, it may be assumed that the bioaccessibility of aluminium from most personal care products is limited, given the presence of water-insoluble lakes in e.g. lipsticks, toothpastes and sunscreen, or the formation of insoluble gel plugs by aluminium in antiperspirants (see Section 3.2.5 and Annex II).

Table 10. Summary of dermal, oral and inhalation exposure (external) of averagely and highly exposed children and adults to aluminium via personal care products (in mg/kg bw/week).

Age	Source	Route	Exposure	
			Average	High
0	Sunscreen	Dermal	0.29	2.31
6 mo	Sunscreen	Dermal	0.23	1.81
1 yr	Sunscreen	Dermal	0.20	1.61
5 yr	Sunscreen	Dermal	0.19	1.51
10 yr	Sunscreen	Dermal	0.16	1.30
11–14 yr	Sunscreen	Dermal	0.13	1.00
	Non-spray	Dermal	10.5	16.6
	Spray deo/antiperspirant	Dermal	6.79	11.4
		Inhalation	0.026	
	Lipstick/lip gloss	Oral	0.09	0.25
15–17 yr	Sunscreen	Dermal	0.13	1.00
	Non-spray	Dermal	7.97	12.6
	Spray deo/antiperspirant	Dermal	5.13	8.63
		Inhalation	0.020	
	Lipstick/lip gloss	Oral	0.07	0.19
≥18 yr	Sunscreen	Dermal	0.13	1.00
	Non-spray	Dermal	6.87	10.8
	Spray deo/antiperspirant	Dermal	4.42	7.44
		Inhalation	0.017	
	Lipstick/lip gloss	Oral	0.06	0.16
	Whitening toothpaste	Oral	0.13	0.63

Antiperspirants are the largest contributor to the external aluminium exposure of consumers via personal care products. This exposure is mainly dermal; the inhalation route hardly contributes.

Compared with antiperspirants, external exposure via the other personal care products for which data are available is much smaller, the contribution of sunscreen being slightly larger than that of toothpaste and lipstick/lip gloss. For small children the exposure via sunscreen may be overestimated, as small children's skin should not be exposed to direct sunshine but should be largely covered by clothing, so that sunscreen needs only be applied to a few uncovered skin parts.

Even though worst case, it is to be noted that the estimates presented in Table 10 are limited to a few personal care products and do not include exposure to household products like cleaning agents, for which exposure estimation was not possible due to lack of data. If and how substantially the use of cleaning agents might add to the worst case estimates shown in Table 10 is therefore unknown. On the other hand, in view of their main exposure route (dermal) and the very low fraction of aluminium that will be dermally absorbed, they are not expected to add considerably to the aggregate (internal) exposure.

8 Exposure to aluminium via ambient air, soil and house dust

8.1 Introduction

Since aluminium is ubiquitous in the environment, it is present in ambient air, soil and house dust. The background concentrations of aluminium in the atmosphere are, however, low, so for the general population the inhalation of ambient air is not an important pathway for aluminium exposure. Even though in some urban and industrial environments the air may contain above-average levels of aluminium, no significant inhalation exposure from air is expected for the general population (ATSDR, 2008; SCHEER, 2017). Therefore, exposure via ambient air will not be addressed further in the current report.

Exposure to aluminium via ingestion of and dermal contact with soil is intuitively very unlikely. However, aluminium is naturally common in Dutch soils, and soil particles can be ingested inadvertently, especially by young children due to their hand-to-mouth behaviour. Soil can therefore be a source of oral exposure to aluminium. House dust may be an additional source of aluminium exposure. Like soil, house dust can be inadvertently ingested via contact between the hand or an object and the mouth, particularly by young children. Humans can also inhale dust particles with air, so this route may in principle also contribute to the exposure. However, Oomen *et al*. (2008) found that the amount of inhaled suspended dust particles is negligible compared with the amount of ingested dust. Hence, for house dust, only the oral route is considered relevant. It is also considered likely that aluminium in house dust originates mainly from tracked-in soil rather than from indoor sources. Hence, house dust other than tracked-in soil is not further addressed in the current report.

8.2 Exposure of children and adults to aluminium via soil

8.2.1 Aluminium concentration in soil

Sandy soils and marine clay form the main soil types in the Netherlands (together ~75%, as roughly estimated from figure 1 in Mol *et al.*, 2012); fluvial clay and (especially) peat and loess are only minor soil types. Concentrations of aluminium in these soil types vary greatly. Aluminium is mostly present in soil as Al_2O_3 and $Al(OH)_3$ and these minerals are mainly associated with clay silicates in Dutch soil. Hence, aluminium concentration is highest in fluvial and marine clay soils; for Dutch top soils (0–20 cm) median values of 9.84 and 9.10 wt-% Al_2O_3 (corresponding to 52.1 and 48.2 g Al/kg soil)[9] are reported, respectively. Peat and loess are also rich in aluminium (median for top soil 6.55 and 7.90 wt-% Al_2O_3, respectively, corresponding to 34.7 and 41.8 g Al/kg), whereas sandy soils contain relatively low concentrations (median 2.34 wt-%, corresponding to 12.4 g Al/kg) (Mol *et al.*, 2012). The P95 values are 16.0, 12.4, 15.0, 8.51 and 4.37 wt-% Al_2O_3 (corresponding to 84.7, 65.6, 79.4, 45.1 and 23.1 g Al/kg) for fluvial clay, marine clay, peat, loess and sand, respectively (Mol *et al.*, 2012).

[9] 1 weight% Al_2O_3 (molecular weight 102 g/mol) corresponds to ~5.3 g/kg Al (molecular weight 27 g/mol).

For the exposure estimation, the highest median and P95 values reported (52.1 and 84.7 g Al/kg, respectively, for fluvial clay) are taken as the basis. This is considered a worst case approach, since fluvial clay represents only a minor soil type in the Netherlands, and its median and P95 values are 1.1–4.2 times higher than those for soil types present in approximately three-quarters of the country.

8.2.2 Soil ingestion rates

Reliable determination of ingestion rates of soil is difficult, due to the paucity of data on age-related time activity patterns, transfer factors and intrinsic differences in children's behaviour. Based on limited data, Otte *et al*. (2001) have suggested soil ingestion rates of 100 mg/day for children 1–6 years old (P95 200 mg/day) and 50 mg/day for children ≥7 years old and adults. These values are presently used by the RIVM as default values for soil ingestion in risk assessments of contaminated soil. It is to be noted that, using a similar database, the US Environmental Protection Agency (US EPA) derived 50 mg/day as the central tendency for soil ingestion for 1–21-year-olds (with 200 mg/day as upper percentile for 3–6 year olds), whereas for adults they derived 20 mg/day as the central tendency (US EPA, 2011). These estimates were used until 2017, when US EPA adjusted these estimates downwards (see Table 11) as a result of new information becoming available (US EPA, 2017). These adjusted estimates are considered more up-to-date and are therefore used for the current exposure estimation.

Table 11. Soil ingestion rates for adults and children (in mg/day), based on US EPA (2017).

Age group	Soil ingestion rate	
	CT[1]	UP[2]
<6 mo	20	50
6–<12 mo	30	90
1–<2 yr	40	90
2–<6 yr	30	90
6–<12 yr	30	90
12 yr to adult	10	50

CT = central tendency; UP = upper percentile

[1] The average of the central tendency values from the various studies.

[2] The average of the 95th percentile values from the various studies.

8.2.3 Exposure estimation

Table 12 presents the exposure estimates for averagely and highly exposed children and adults to aluminium via the ingestion of soil. For averagely and highly exposed consumers, these estimates are based on the worst case median and P95 aluminium soil content values (for fluvial clay), respectively, in combination with either the central tendency (low end value) or upper percentile (high end value) for soil ingestion rate as given in Table 11. For body weight, default values for the different age groups are taken from Te Biesebeek *et al*. (2014).

Table 12. Exposure (external) of averagely and highly exposed children and adults to aluminium via ingestion of soil (in mg/kg bw/week).

Age[1] (bw)	Exposure			
	Average		High	
	low end	high end	low end	high end
<6 mo (4.5 kg[2])	1.62	4.05	2.64	6.59
6–12 mo (8.0 kg)	1.37	4.10	2.22	6.67
1–2 yr (9.8 kg)	1.49	3.35	2.42	5.45
2–6 yr (14.3 kg)	0.77	2.30	1.24	3.73
6–11 yr (24.3 kg)	0.45	1.35	0.73	2.20
12–16 yr (44.8 kg)	0.08	0.41	0.13	0.66
16–18 yr (59.3 kg)	0.06	0.31	0.10	0.50
Adults (68.8 kg)	0.05	0.27	0.09	0.43

[1] Based on the categories in Te Biesebeek *et al*. (2014).
[2] For 1–3-month-olds.

8.3 Summary of exposure via soil, house dust and ambient air

Oral exposure to aluminium via the unintended ingestion of soil particles is relatively high in all age groups. It is highest for very young children, with average and high estimates of 1.62–4.05 and 2.64-6.59 mg Al/kg bw/week, respectively. Relative to body weight, the exposure via this route becomes less substantial with increasing age of children and adolescents into adulthood. It is to be noted that the estimates are of low reliability and should be considered as worst case estimates, since the highest median and P95 value reported for five different soil types in the Netherlands have been used for the exposure calculations. Moreover, from Section 3.2.3 it is clear that almost all of the aluminium in soil is inert and thus not bioaccessible. Additional exposure via inhalation of ambient air or soil/dust particles is considered negligible.

9 Exposure to aluminium via antacids

9.1 Introduction

Aluminium salts are present in some over-the-counter (OTC) medicinal antacids. Antacids are taken orally to quickly relieve occasional heartburn, indigestion or stomach upset. Treatment with antacids alone is symptomatic and only justified for minor symptoms. The active ingredients in antacids include magnesium carbonate, magnesium hydroxide, aluminium hydroxide, aluminium oxide, calcium carbonate and sodium bicarbonate. These substances are bases, and can help by increasing the pH level to neutralise the stomach acidity that causes the discomfort.

Since antacids are available on the Dutch market as OTC products (no prescription needed), it is not possible to obtain a complete and reliable picture regarding the use of antacids.

9.2 Exposure of adults to aluminium via antacids

Antacids are available as suspensions, powders for suspension, tablets and chewable tablets. Examples of freely available antacids on the Dutch market containing aluminium as the active substance are shown in Table 13. In the Summary of Product Characteristics (SPC) of these antacids advice is given on the dosing and method of administration. The exposure of adults to aluminium via antacids is based on this advice (Table 13). A calculation for children was not made, as we assume that the use of antacids by children is negligible.

For the different brands of antacids, the estimated minimum recommended daily dose ranges between 423.5 mg Al^{3+} (4 x 1 tablet x 200 mg Al_2O_3, Gastilox/Maalox, or 4 x 2 tablets x 100 mg Al_2O_3, Gastilox/Maalox Plus Dimeticon)[10] and 1906 mg Al^{3+} (4 x 10 ml x 90 mg Al_2O_3/ml, Gastilox Forte suspension)[10]. Depending on the product, the estimated maximum recommended daily doses are 1.5-2 times higher, and range from 847 to 3812 mg Al/day. Divided by a body weight of 68.8 kg (default taken from Te Biesebeek *et al*., 2014) and multiplied by 7, this leads to an exposure of 43–194 (minimum) or 86–388 (maximum) mg Al/kg bw/week. As can be seen from Table 13, antacids in suspension form result in higher aluminium exposure than antacids in chewable tablet form. It is noted that in none of the SPCs is a maximum duration of treatment specified. According to the Informatorium Medicamentorum[11], long-term use of antacids should be avoided. In regulatory terms, this means that for continued intake after a few weeks of use a critical reassessment of the need for these products is necessary.

[10] Calculated by dividing the amount of Al_2O_3 by the molecular weight of Al_2O_3 (102 g/mol) and then multiplying the molecular weight of elemental Al (27 g/mol) by 2. For Regla pH, which contains $Al(OH)_3$ instead of Al_2O_3 ,the dose is calculated by dividing the amount of $Al(OH)_3$ by the molecular weight of $Al(OH)_3$ (78 g/mol) and then multiplying by the molecular weight of elemental Al (27 g/mol).

[11] https://www.knmp.nl/producten/knmp-kennisbank/module-farmacotherapie-in-de-knmp-kennisbank/informatorium-medicamentorum-im-in-de-knmp-kennisbank, accessed 3/4/2020.

Table 13. Exposure of adults to aluminium in antacids (in mg/kg bw/week).

Product	Active ingredient(s)	Aluminium content[1]	Prescribed dose[1]	Exposure
Antagel (suspension)	aluminium oxide (as algeldrate); magnesium hydroxide	40 mg Al_2O_3 per ml	10-15 ml after every meal and before sleeping (If necessary 10–15 ml every 2 hours in between)	86–129
Gastilox Forte suspension	aluminium oxide (as algeldrate); magnesium hydroxide	90 mg Al_2O_3 per ml	10–20 ml after every meal and before sleeping	194–388
Gastilox and Maalox chewable tablets	aluminium oxide (as algeldrate); magnesium hydroxide	200 mg Al_2O_3 per tablet	1–2 tablets after every meal and before sleeping	43–86
Gastilox and Maalox Plus Dimeticon chewable tablets	aluminium oxide (as algeldrate); magnesium hydroxide	100 mg Al_2O_3 per tablet	2–4 tablets after every meal and before sleeping	43–86
Regla pH chewable tablets	aluminium hydroxide; magnesium carbonate	450 mg $Al(OH)_3 \cdot MgCO_3$ coprecipitate per tablet[2]	1–2 tablets after every meal and before sleeping (If necessary 1–2 tablets every 2 hours in between)	48–95

[1] According to the Summary of Product Characteristics (Antagel, 2016; Gastilox Forte/Gastilox, 2019; Gastilox Plus Dimeticon, 2019; Maalox, 2018; Maalox Plus Dimeticon, 2020; Regla pH, 2015), specifying no contra-indication for use during pregnancy; www.cbg-meb.nl

[2] Ratio between 2 active ingredients not specified in SPC. Ratio 3:1 is assumed, given that on SPC it is mentioned that 'in proper ratio of the combination aluminium and magnesium (3: 1) no problems such as constipation and laxation are to be expected'.

9.3 Antacids and pregnancy

Pregnant women often suffer from heartburn. As guidance for general practitioners, the Dutch standard on pregnancy recommends antacids as the first choice treatment in cases of gastric hyperacidity during pregnancy (NHG-Standaard Zwangerschap en kraamperiode, 2012). It prescribes the use of a suspension of algeldrate (Al_2O_3) and magnesium hydroxide, at up to 4 times 15 ml per day. This is similar to e.g. the Antagel dosage. If the antacid use does not give sufficient relief, the use of a histamine type 2 receptor antagonist (e.g. ranitidine) is indicated; if neither medication works, omeprazole is prescribed. Ranitidine and omeprazole do not contain aluminium.

Currently, the use of aluminium-containing antacids during pregnancy is not contra-indicated. It is noted that in 2004, the safety of aluminium-containing antacids used during pregnancy was debated in the Netherlands. Based on a case of an extremely high dose of antacid used in pregnancy and on studies in animals and dialysis patients, it was considered inadvisable to use aluminium-containing antacids during pregnancy (Frankhuisen *et al.*, 2004). Others, however, argued that at normal therapeutic doses no toxic effects in human foetus or embryo were observed, and that no increased levels of aluminium were seen in umbilical cord blood or in serum of the mother when the last dose of antacid was taken just before delivery (Verduijn *et al.*, 2004). The only case report on toxic effects concerned a mother having taken 75 antacid tablets per day (containing 200 mg of aluminium hydroxide per tablet, corresponding to 36,350 mg aluminium/week, i.e. 606 mg/kg bw/week for a 60 kg woman) during her entire pregnancy, giving birth to a baby with neurodegenerative disorders. In the end, the Dutch standard on pregnancy remained as was (and still is), considering the short-term use of aluminium-containing antacids during pregnancy (a couple of weeks) at therapeutic doses to be no cause for concern. The Netherlands Pharmacovigilance Centre, Lareb[12], has also indicated that antacids can be used throughout pregnancy in normal doses but advises against the long-term use of antacids and high doses of antacids.

In the Netherlands, there is a pregnancy drug register with information on medicines used by pregnant women (pREGnant[13]), based on self-reporting. It includes information on the use of OTC antacids by this subpopulation. In May 2016, for 751 pregnant women data on medicinal product use were available, covering the entire pregnancy. Of these women, about 5% reported the use of aluminium-containing antacids. The reported period of use ranged from 2 days to 7 months. Frequency of use ranged from once a month to four times a day.

9.4 Summary of exposure via aluminium-containing antacids

Adults, including pregnant women, may be exposed to aluminium through the use of aluminium-containing antacids. When taken at normal doses for a couple of weeks (as long term-use is advised against), the oral exposure of the averagely and highly exposed consumer can be roughly estimated at 45 (low end)–200 (high end) and 85 (low end)–390 (high end) mg Al/kg bw/week, respectively.

[12] https://www.lareb.nl/ (last visited on 21/11/2019).
[13] https://www.pregnant.nl/

10 Exposure to aluminium via adjuvants in vaccines

10.1 Introduction

Aluminium-containing adjuvants are present in a number of vaccines to enhance, accelerate and prolong the immune response to vaccine antigens. These adjuvants are applied in several vaccines used in the Dutch National Immunisation Programme (NIP), in two different forms: aluminium phosphate and aluminium hydroxide. More information on the physicochemical properties of aluminium-containing adjuvants and their relation to immunopotentiation can be found in Annex I of this report. Notably, the aluminium-containing adjuvants are composed of very small particles (nanometre dimension); these nanoparticles form aggregates that are the functioning units in vaccines. The fact that they are nanoparticles makes the aluminium-containing adjuvants different from the sources described in the previous chapters, in which aluminium is mostly present as soluble salts. The exposure route is also different, as vaccines are injected intramuscularly (into the thigh or upper arm).

10.2 Exposure of children to aluminium via adjuvants in vaccines under the Dutch National Immunisation Programme

In the Netherlands, children between the ages of 3 months and 14 years receive various vaccines against a number of diseases according to a specific vaccination schedule (see Figure 1).

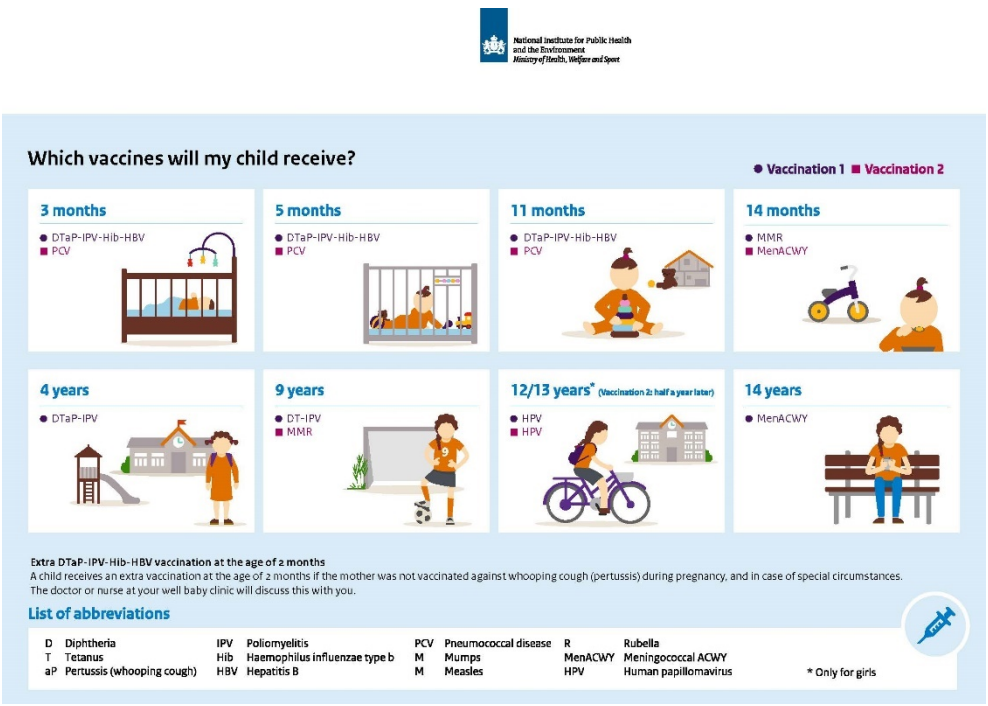

Figure 1. The Dutch National Immunisation Programme.
Source: https://www.rivm.nl/en/national-immunisation-programme, consulted 25/2/2020.

When adhering to the NIP, total exposure to aluminium ranges from 1.35 to 3.99 mg for a child in its first year of life, depending on the brand of vaccines used (see Table 14). Since early 2020, pregnant women are offered a vaccination against whooping cough (pertussis) in week 22, to protect their 0–3-month-old baby against pertussis. This vaccination will not result in a relevant exposure of the unborn child. If a mother does not take up the offer, her baby receives an extra vaccination at 2 months of age.

Children receive additional aluminium-containing vaccines at the ages of 4, 9 and 12/13 years. The last – for HPV – is currently for girls only. From 2021 onwards, the HPV vaccine will also become available for boys. Both boys and girls will then receive the HPV vaccine when they are 9 years old.

Table 14. Exposure of children to aluminium via adjuvants in vaccines of the 2020 Dutch National Immunisation Programme.

Age (bw[1])	Vaccine 1 (mg Al/injection)	Vaccine 2 (mg Al/ injection)	Total Al exposure (mg)	Total Al exposure (mg/kg bw)
2 mo[2] (4.5 kg)	DTaP-IPV + Hib + HBV (0.32-0.83)		0.32–0.83	0.07–0.18
3 mo (6.1 kg)	DTaP-IPV + Hib + HBV (0.32-0.83)	PCV (0.125-0.5)	0.45–1.33	0.07–0.22
5 mo (6.1 kg)	DTaP-IPV + Hib + HBV (0.32-0.83)	PCV (0.125-0.5)	0.45–1.33	0.07–0.22
11 mo (8.0 kg)	DTaP-IPV + Hib + HBV (0.32-0.83)	PCV (0.125-0.5)	0.45–1.33	0.06–0.17
14 mo (9.8 kg)	MMR (no Al)	MenACWY (no Al)	0	0
4 yr (15.7 kg)	DTaP-IPV (0.33-0.5)		0.33–0.5	0.02–0.03
9 yr (24.3 kg)	DT-IPV (0.33-0.35)	MMR (no Al)	0.33–035	0.01–0.01
12/13 yr[3] (44.8 kg)	2x HPV (2x 0.23-0.5)		0.46–1.0	0.01–0.02
14 yr (44.8 kg)	MenACWY (no Al)		0	0

HBV=hepatitis B; D=diphtheria; aP=pertussis, T=tetanus; IPV=poliomyelitis; HiB=haemophilus influenza type b; PCV=pneumococcal disease; MMR=mumps, measles and rubella; MenACWY=meningococcal ACWY; HPV=human papillomavirus.
[1] Default body weights for the different ages taken from Te Biesebeek *et al*. (2014).
[2] Only if the mother was not vaccinated against pertussis during pregnancy.
[3] Only for girls, with the second HPV vaccination 6 months after the first.

10.3 Vaccines outside the Dutch National Immunisation Programme

Outside the NIP, other vaccines are available to protect children and adults against infectious diseases such as influenza, shingles, chickenpox and rotavirus infection. In addition, for travel to some countries vaccination against e.g. hepatitis A, typhoid and yellow fever is recommended. Furthermore, in certain professions vaccines against influenza or hepatitis B are recommended. Some of these vaccines contain aluminium adjuvants.
Products used for allergen immunotherapy – a medical treatment for environmental allergens and asthma – can also contain aluminium

adjuvants. Adjuvants in products used for immunotherapy are both approved and regulated by the US FDA and the European Medicines Agency (EMA).

In the current report exposure to aluminium from vaccines outside the NIP is not addressed in more detail, given that they are mostly intended only for groups at risk or upon medical indication. Use is therefore incidental.

10.4 Summary of exposure via adjuvants in vaccines

Table 15 presents a summary of external aluminium exposure via vaccines in the NIP, for children of different age groups.

Table 15. Summary of intramuscular exposure of infants and children to aluminium via vaccines (in mg/kg bw).

Age	Exposure
0–6 mo	0.14–0.44 (in 2 injection rounds)[1]
7–12 mo	0.06–0.17 (1 injection round)
1–2 yr	0 (1 injection round)
3–6 yr	0.02–0.03 (1 injection round)
7–10 yr	0.01 (1 injection round)
11–14 yr	0.01–0.02 (girls; in 3 injection rounds) 0 (boys; 1 injection round)

[1] Or 0.21–0.62 (in 3 injection rounds), if the mother did not take up the offer of a pertussis vaccination during pregnancy.

11 Aggregate exposure and risk assessment of aluminium, including discussion

11.1 Introduction

In the previous chapters the relevant sources of aluminium exposure for children and adults were identified. An overview of these exposure sources and their corresponding external exposure estimates is compiled in Table 16. In order to estimate the potential health effects resulting from the combined exposure to the various sources, the total systemic aluminium exposure must be calculated. For this, the external aluminium exposure estimates as given in Table 16 must be converted into internal (i.e. systemic) exposure estimates. For that conversion, the following absorption values are used (see Section 3.6):

- 0.8% for oral exposure via diet and personal care products, and for the inhalation dose from spray antiperspirants that is deposited in the upper respiratory tract;
- 0.07% for oral exposure via soil and clay-based food supplements, based on the reactive fraction for the soil type that was used for exposure estimation (fluvial clay);
- 0.00052% for dermal exposure via personal care products;
- 3% for the inhalation dose from spray antiperspirants that is deposited deep in the lungs.

As noted and explained in Chapter 1, the exposures to aluminium from antacids and vaccines are not included in the aggregate exposure and risk assessment. Nevertheless, their exposure estimates are presented in Table 16 for comparison purposes, and a discussion follows in Sections 11.5 (antacids) and 11.6 (vaccines).

For all other exposure sources, the aggregate exposure and risk assessment is presented and discussed separately for children aged 0-2 years (Section 11.2), for children and adolescents aged 2–17 years (Section 11.3) and for adults, including pregnant women (Section 11.4). For the aggregate exposure assessment, the systemic exposure estimates are given for the average consumer and for the highly exposed consumer, with low- and high-end values indicated for both groups of consumers (see Section 6.6 for an explanation). For risk assessment, the total systemic exposure estimates are to be compared with the internal HBGV for aluminium, assuming similar toxicity following oral, dermal and inhalation exposure to aluminium. The HBGV is 2 mg/kg bw/week (see Section 2.4), based on a 12-month developmental neurotoxicity study in rats given aluminium citrate in drinking water. After adjusting this HBGV by the rat oral bioavailability of aluminium citrate from drinking water (0.6%, see Table 1), the systemic exposure at the HBGV is estimated to be 0.012 mg/kg bw/week.

Please note that the systemic exposure estimates are given to 4 decimal points. This is not to be taken as a sign of precision, but allows a better comparison with the internal HBGV, which is shown to 3 decimal points.

Table 16. Summary of external exposure (oral, dermal, inhalatory, intramuscular) of averagely and highly exposed infants, children and adults to aluminium via all relevant sources (in mg/kg bw/week for oral, dermal and inhalation, in mg/kg bw for intramuscular route).

Age	Source	Oral exposure				Dermal exposure		Inhalation exposure	Intramuscular exposure
		Average		High		Average	High		low–high end
		low end	high end	low end	high end				
0–6 mo	Breast milk	<0.035		<0.07					
	Infant formula	0.075	2.001	0.119	2.217				
	Soil	1.62	4.05	2.64	6.59				
	Sunscreen					0.29	2.31		
	Vaccine								0.14–0.44[1]
7–12 mo	Infant formula/foods	0.35	0.78	0.55	0.56				
	Soil	1.37	4.1	2.22	6.67				
	Sunscreen					0.23	1.81		
	Vaccine								0.06–0.17
1–2 yr	Diet	0.37	0.89	0.61	1.9				
	Soil	1.49	3.35	2.42	5.45				
	Sunscreen					0.2	1.61		
3–6 yr	Diet	0.51	0.64	0.85	1.18				
	Soil	0.77	2.3	1.24	3.73				
	Sunscreen					0.19	1.51		
	Vaccine								0.02–0.03
7–10 yr	Diet	0.35	0.49	0.66	0.82				
	Soil	0.45	1.35	0.73	2.2				
	Sunscreen					0.16	1.3		
	Vaccine								0.01
11–14 yr	Diet	0.22	0.34	0.49	0.58				
	Soil	0.08	0.41	0.13	0.66				
	Lipstick/lip gloss	0.09		0.25					

Age	Source	Oral exposure				Dermal exposure		Inhalation exposure	Intramuscular exposure
		Average		High		Average	High		low–high end
		low end	high end	low end	high end				
	Deo – Spray					6.79	11.4	0.0258	
	Deo – Non-spray					10.5	16.6		
	Sunscreen					0.13	1		
	Vaccine								0.01–0.02[2]
15–17 yr	Diet		0.26		0.46				
	Soil	0.06	0.31	0.1	0.5				
	Lipstick/lip gloss		0.07		0.19				
	Deo – Spray					5.13	8.63	0.0195	
	Deo – Non-spray					7.97	12.6		
	Sunscreen					0.13	1		
≥18 yr	Diet	0.18	0.35	0.42	0.84				
	Soil	0.05	0.27	0.09	0.43				
	Lipstick/lip gloss		0.06		0.16				
	Whitening toothpaste		0.13		0.63				
	Antacids	45	200	85	390				
	Intestinal clays		3.9		24.8				
	'Pregnancy clays'		353		543				
	Deo – Spray					4.42	7.44	0.0168	
	Deo – Non-spray					6.87	10.8		
	Sunscreen					0.13	1		

[1] Or 0.21–0.62 if the mother did not take up the offer of a pertussis vaccination during pregnancy.
[2] Girls only.

11.2 Aggregate exposure and risk assessment for children aged 0-2 years

Table 17 presents the aggregate systemic exposure of children aged 0-2 years to aluminium, for the averagely and highly exposed groups separately. Values matching or exceeding the internal HBGV of 0.012 mg Al/kg bw/week are marked in red.

Table 17. Aggregate systemic aluminium exposure of averagely and highly exposed children aged 0–2 years (in mg/kg bw/week). Values matching or exceeding the internal HBGV of 0.012 mg/kg bw/week are marked in red.

Age	Source	Systemic exposure			
		Average		High	
		low end	high end	low end	high end
0–6 mo	Breast milk	0.0003	0.0003	0.0006	0.0006
	Infant formula	0.0006	0.0160	0.0010	0.0177
	Soil	0.0011	0.0028	0.0018	0.0046
	Sunscreen	1.5E-06	1.5E-06	1.2E-05	1.2E-05
	Total breastfed	**0.0014**	**0.0031**	**0.0024**	**0.0052**
	Total formula-fed	**0.0017**	**0.0188**	**0.0028**	**0.0224**
7–12 mo	Infant formula/foods	0.0028	0.0062	0.0044	0.0045
	Soil	0.0010	0.0029	0.0016	0.0047
	Sunscreen	1.2E-06	1.2E-06	9.4E-06	9.4E-06
	Total	**0.0038**	**0.0091**	**0.0060**	**0.0092**
1–2 yr	Diet	0.0030	0.0071	0.0049	0.0152
	Soil	0.0010	0.0023	0.0017	0.0038
	Sunscreen	1E-06	1E-06	8.4E-06	8.4E-06
	Total	**0.0040**	**0.0095**	**0.0066**	**0.0190**

For breastfed infants, the aggregate exposure from breast milk and soil ingestion is well below the internal HBGV. For non-breastfed infants, however, slight exceedances of the internal HBGV may occur, but only for 0–6-month-old infants, not for 7–12-month-olds. This is due not so much to soil ingestion, but mostly to the feeding of infant formula, depending on the aluminium content present in the milk powder (and in the water used for reconstitution) or in the ready-made formulas. It is noted that for infants given soy-based formula, the systemic exposure may be underestimated, as soy-based infant products contain more aluminium than cow's milk products. The contribution of sunscreen to the aggregate exposure of 0–6 and 7–12-month-old children is almost negligible.

For 1–2 year-old children, a slight exceedance of the internal HBGV is observed only for the high end of the highly exposed toddlers, where the intake from diet (which includes the contribution from food contact materials and kitchenware) is already sufficient for the exceedance. No exceedance of the internal HBGV is observed for the other toddlers. The contribution of sunscreen to the aggregate exposure of toddlers is almost negligible, that from soil ingestion only small – and likely to be even smaller than shown, given that the exposure estimates for soil ingestion are worst case, *inter alia* because it was assumed in the

calculation that 100% of the bioaccessible fraction is also bioavailable, which is almost certainly an overestimation.

From the above it can be concluded that small exceedances of the HBGV are possible for 0–6-month-old and 1–2-year-old children fed infant formula or diets with a high aluminium content, in particular soy-based products. This was previously also concluded by e.g. EFSA (2008), JECFA (2012), and BfR (2012). Notably, however, these committees/institutes took values of 0.1 or 0.3% for oral absorption. When doing the same here (instead of taking 0.8%), all exceedances would disappear. It is further noted that if small children have additional exposure from personal care products (other than sunscreen), this will not add considerably to the aggregate exposure, given that these products are mostly applied dermally and the uptake of aluminium via the skin is very low. Likewise, if small children have additional exposure from ingested toy material, this will add little to the aggregate exposure. As remarked in Section 7.3, the presence of aluminium in toys is regulated by the Toy Safety Directive 2009/48/EC, which sets maximum migration limits for aluminium in toys. These limits have last been revised in 2019, in view of new toxicity data resulting in a lower TDI (0.3 mg/kg bw/day, based on the NOAEL of 30 mg/kg bw/day in the Poirier *et al*. (2011) study) (SCHEER, 2017). In setting migration limits, a maximum of 10% of the HGBV is allocated to exposure from toys. Due to a lack of data the actual aluminium exposure from toys is not known. Nevertheless, even if the migration limits were reached, toys would add maximally 10% of the (external) HBGV to the aggregate exposure. Whereas in itself this is a relatively small contribution, the SCHEER's recommendation to minimise additional exposure from toys can nevertheless be supported, given that dietary exposure (especially from soy-based infant formulas/foods) may already exceed the HBGV.

Exceeding the HBGV does not directly result in adverse health effects, as the HBGV is a measure of the amount of a substance that can be ingested daily (TDI)/weekly ((P)TWI) over a lifetime without an appreciable health risk. An exceedance will initially represent only a reduction of the safety margin. For the children 0–6 months old and 1–2 years old fed high-aluminium-content infant formula/diets, the safety margins are reduced to 68–75 and 79, respectively, compared with the standard safety margin of 100. These reductions are relatively small. Furthermore, there are no indications from the literature that aluminium intake levels resulting from the consumption of infant formula and diets are harmful to the health of infants and toddlers. Nevertheless, exceeding the HBGV for prolonged periods is not desirable from a toxicological viewpoint, and in view of the fact that infants constitute an especially vulnerable group, it is to be preferred that the aluminium content in marketed infant formula/foods should not be such that the HBGV is exceeded following consumption.

11.3 Aggregate exposure and risk assessment for children and adolescents aged 3–17 years

Table 18 presents the aggregate systemic exposure to aluminium of children and adolescents aged 3–17 years, for the averagely and highly

exposed groups separately. Values matching or exceeding the internal HBGV of 0.012 mg Al/kg bw/week are marked in red.

Table 18. Aggregate systemic aluminium exposure of averagely and highly exposed children and adolescents aged 3–17 years (in mg/kg bw/week). Values matching or exceeding the internal HBGV of 0.012 mg/kg bw/week are marked in red.

Age	Source	Systemic exposure			
		Average		High	
		low end	high end	low end	high end
3–6 yr	Diet	0.0041	0.0051	0.0068	0.0094
	Soil	0.0005	0.0016	0.0009	0.0026
	Sunscreen	9.9E-07	9.9E-07	7.9E-06	7.9E-06
	Total	**0.0046**	**0.0067**	**0.0077**	**0.0121**
7–10 yr	Diet	0.0028	0.0039	0.0053	0.0066
	Soil	0.0003	0.0009	0.0005	0.0015
	Sunscreen	8.3E-07	8.3E-07	6.8E-06	6.8E-06
	Total	**0.0031**	**0.0049**	**0.0058**	**0.0081**
11–14 yr	Diet	0.0018	0.0027	0.0039	0.0046
	Soil	0.0001	0.0003	0.0001	0.0005
	Lipstick/lip gloss	0.0007	0.0007	0.0020	0.0020
	Deo – Spray	3.5E-05	3.5E-05	5.9E-05	5.9E-05
	Deo – Spray (inhalation)	0.0003	0.0003	0.0003	0.0003
	Deo – Non-spray	5.5E-05	5.5E-05	8.6E-05	8.6E-05
	Sunscreen	6.8E-07	6.8E-07	5.2E-06	5.2E-06
	Total D/S/Ps[1]	**0.0028**	**0.0040**	**0.0063**	**0.0074**
	Total D/S/Pns[2]	**0.0026**	**0.0038**	**0.0061**	**0.0072**
15–17 yr	Diet	0.0021	0.0021	0.0037	0.0037
	Soil	0.0000	0.0002	0.0001	0.0004
	Lipstick/lip gloss	0.0006	0.0006	0.0015	0.0015
	Deo – Spray	2.7E-05	2.7E-05	4.5E-05	4.5E-05
	Deo – Spray (inhalation)	0.0002	0.0002	0.0002	0.0002
	Deo – Non-spray	4.1E-05	4.1E-05	6.6E-05	6.6E-05
	Sunscreen	6.8E-07	6.8E-07	5.2E-06	5.2E-06
	Total D/S/Ps[1]	**0.0029**	**0.0031**	**0.0055**	**0.0058**
	Total D/S/Pns[2]	**0.0027**	**0.0029**	**0.0053**	**0.0056**

[1] Total diet, soil and personal care products (including spray deodorant but not non-spray deodorant).
[2] Total diet, soil and personal care products (including non-spray deodorant but not spray deodorant).

No exceedance of the internal HBGV is observed for children aged 3-10 years, with the exception of the high end of the highly exposed 3-6-year-old group. For this group, the individual sources are all (well) below the internal HBGV, but their total equals the internal HBGV. For children aged 3–10 years, aluminium in the diet (including contributions from food contact materials and kitchenware) contributes the most to

the aggregate exposure. Sunscreen hardly contributes at all, and the contribution from soil ingestion is at the most one-third of that from diet. The latter contribution is likely to be even lower, given that the exposure estimates for soil ingestion are worst case – first because they are based on the highest median and P95 soil content values reported for fluvial clay, only a minor soil type in the Netherlands, and second because, in the absence of data on bioavailability in the gastro-intestinal tract, it was as a worst case assumed that 100% of the aluminium in the bioaccessible (reactive) fraction of soil is also actually bioavailable. Taking this into account, the aggregate exposures will in all likelihood be lower than shown in Table 18 for all groups of 3–10-year-olds, resulting in exposures well below the internal HBGV. Hence, no risk is identified for the aggregate exposure to aluminium of children aged 3–10 years. This conclusion is not expected to change in the event that these children are found to use personal care products other than just sunscreen, in view of the fact that most such products are applied dermally and dermal absorption of aluminium is very low.

Just as for children aged 3–10 years, no risk is identified for adolescents aged 11–17 years. The internal HBGV is not exceeded or even nearly reached in any group, despite adolescents having exposure from additional personal care products like lipstick/lip gloss and deodorants/ antiperspirants. This is in contrast with findings in earlier risk assessments by AFSSAPS (2011), VKM (2013) and BfR (2014), which all concluded that personal care products (in particular deodorants/antiperspirants) under normal use conditions may increase the risk of adverse health effects. These risk assessments did, however, use much higher dermal absorption fractions than we did, acknowledging the scientific uncertainty in the effective skin penetration rate from the limited data available at that time. This scientific uncertainty was the reason the SCCS requested new data in 2014, which were subsequently provided and showed a very low dermal absorption of aluminium from antiperspirants (0.00052%, see Section 3.2.5). This low percentage was used by the SCCS in its assessment of aluminium in cosmetic products.[14] In the light of the new data provided, the SCCS considered the use of cosmetic products, including spray and non-spray antiperspirants at aluminium concentrations up to 10.6% and 6.25%, respectively, safe (SCCS, 2020). This conclusion is supported by the current risk assessment: where on an external level personal care products, in particular deodorants/ antiperspirants, contribute considerably more than diet to the total aluminium exposure in adolescents, this is no longer the case systemically because of the very low fraction dermally absorbed (0.00052%, compared with 0.8% orally). In fact, for spray-deodorants/ antiperspirants there is now a larger contribution from inhalation than from dermal exposure. Given the very low absorption, the picture of an overall low contribution for personal care products would not change if adolescents used deodorants/antiperspirants even more frequently or in larger amounts than assumed. So, as with the age group 3–10 years, diet is the main source of aluminium for 11–17-year-olds. Lipstick/lip gloss is also a relatively large contributor, but it is noted that the systemic

[14] It is noted that the SCCS additionally used a value of 0.00192% for dermal bioavailability in the risk assessment, following comments received during the commenting period on the SCCS preliminary opinion. Use of this value (based on cumulative recovery from urine and faeces) did not alter the safety assessment vis-à-vis the value of 0.00052% (based on cumulative recovery from urine and considered by the SCCS as the appropriate value for use in risk assessment). The same is true for the current risk assessment.

exposure estimates for lipstick/lip gloss are worst case estimates – not only because of the conservative nature of the defaults for daily use amounts and the fact that the highest reported mean and maximum aluminium concentrations have been taken from the limited data available for lipstick/lip gloss, but also because we did not take into consideration the low bioaccessibility of aluminium from lipstick/lip gloss. In lipsticks, as in e.g. toothpastes and sun-care products, aluminium is present as salts and as aluminium colloidal colorant 'lakes' (see Annex II). These water-insoluble lakes are complex molecular structures with high molecular weights, and the extractable (bioaccessible) part will represent only a fraction of the aluminium present in the lakes. It is noted that the SCCS in its risk assessment assumed a bioaccessibility of only 7% for lipstick (SCCS, 2020). It is further noted that, should adolescents use more personal care products than the few for which concentration data are available, this would not be expected to add considerably to the aggregate exposure nor to result in a risk. This is because most personal care products are applied dermally, and only a very small fraction of aluminium will be absorbed via the skin. Furthermore, even for highly exposed 11–17-year-olds, the internal HBGV is not even reached.

11.4 Aggregate exposure and risk assessment for adults, including pregnant women

Table 19 presents the aggregate systemic exposure of adults (including pregnant women) to aluminium, for the averagely and highly exposed groups separately. Values matching or exceeding the internal HBGV of 0.012 mg Al/kg bw/week are marked in red.

Adults can be exposed to aluminium via multiple sources and multiple routes. Among these, diet and personal care products are the most common sources, whereas it is expected that clay-based food supplements (for intestinal cleansing and/or for reducing morning sickness during the first months of pregnancy) will be used by only a (small) part of the adult population.

Regarding the aggregate exposure via diet, soil and personal care products, no exceedance of the internal HBGV is observed for adults, except for the high end of the highly exposed consumer group, where the total is slightly higher than the systemic exposure at the HBGV. It is, however, very unlikely that a particular consumer is a high-end consumer for all individual sources, the exposure to which is individually (well) below the internal HBGV. Of the individual sources, diet and whitening toothpaste, and to a lesser extent lipstick/lip gloss, appear relatively important exposure sources for the adults in this group. However, account needs to be given to the worst-case nature of the systemic exposure estimates for both whitening toothpaste and lipstick/lip gloss, for the same reasons as already specified for lipstick/lip gloss in Section 11.3. So, in all likelihood the exposure from whitening toothpaste and lipstick/lip gloss will be lower than estimated, resulting in an aggregate exposure below the internal HBGV for the high end of the highly exposed consumers as well. This is even to be expected in cases where adults use other personal care products than the few for which there are concentration data available, in view of the fact that most of these products are applied dermally and dermal absorption of aluminium

is very low. Soil, sunscreen and deodorants/antiperspirants contribute little to the aggregate exposure of adults. As with adolescents and already discussed in Section 11.3, deodorants/antiperspirants are systemically no longer the main source of aluminium for adults, whereas they are externally.

Table 19: Aggregate systemic aluminium exposure of averagely and highly exposed adults, including pregnant women (in mg/kg bw/week). Values matching or exceeding the internal HBGV of 0.012 mg/kg bw/week are marked in red.

Age	Source	Systemic exposure			
		Average		High	
		low end	high end	low end	high end
≥18 yr	Diet	0.0014	0.0028	0.0034	0.0067
	Soil	0.0000	0.0002	0.0001	0.0003
	Lipstick/lip gloss	0.0005	0.0005	0.0013	0.0013
	Whitening toothpaste	0.0010	0.0010	0.0050	0.0050
	Deo – Spray	2.3E-05	2.3E-05	3.9E-05	3.9E-05
	Deo – Spray (inhalation)	0.0002	0.0002	0.0002	0.0002
	Deo – Non-spray	3.6E-05	3.6E-05	5.6E-05	5.6E-05
	Sunscreen	6.8E-07	6.8E-07	5.2E-06	5.2E-06
	Total D/S/Ps[1]	**0.0032**	**0.0047**	**0.0099**	**0.0135**
	Total D/S/Pns[2]	**0.0030**	**0.0045**	**0.0098**	**0.0134**
	Intestinal cleansing clays	0.0027	0.0027	0.0174	0.0174
	'Pregnancy clays'	0.2471	0.2471	0.3801	0.3801

[1] Total diet, soil and personal care products (including spray deodorant but not non-spray deodorant).
[2] Total diet, soil and personal care products (including non-spray deodorant but not spray deodorant).

Due to a lack of data, an exposure estimation was not possible for household products such as cleaning agents, for which the dermal exposure route will be the most relevant route. Whereas these may add to the aggregate exposure of adults, they are not expected to add considerably, in view of the very low dermal absorption of aluminium in humans. Note that the lack of concentration data on aluminium in cleaning products and several personal care products is also the reason for not applying the Probabilistic Aggregate Consumer Exposure Model (PACEM; Delmaar *et al.*, 2015; Dudzina *et al.*, 2015), which can otherwise yield more realistic exposure estimations, as it combines data on the use of these product groups (frequency and amount) with distributions of data on the occurrence of the relevant substance in the products.

Overall, no risk is identified for the aggregate exposure of adults to aluminium in diet, soil and personal care products.

It is clear from Table 19 that the use of clay-based food supplements may in themselves already result in an exceedance of the internal HBGV, in particular for pregnant women taking such supplements to reduce morning sickness (exceedance up to a factor of 32; see Table

19). It is recognised that the systemic exposure estimates are worst case, as it is assumed in the calculation that 100% of the bioaccessible fraction (taken as 0.07%, as for soil) is also bioavailable, which is almost certainly an overestimation. It is further recognised that not all clays have been shown to contain aluminium. Whereas clays do not present a problem on a population basis, they are sources that can result in very high aluminium exposures for the people taking them, in particular for pregnant women, where the safety margin is reduced to less than zero. So, the use of 'pregnancy clays' should be advised against. It is noted that the NVWA in fact strongly advised against the use of 'pregnancy clays' in 2009, given that the dioxins and metals (including aluminium) in all or some of these clays may adversely affect the health of the mother and the unborn child. A series of measures was proposed to reduce the consumption of 'pregnancy clays', which is mainly by women of Surinam and African origin (NVWA-BuRO, 2009). Whether or not after 2009 the measures were indeed taken and have resulted in reduced consumption of 'pregnancy clays' is not known.
For intestinal cleansing clays the exceedance of the HBGV (by a factor of 1.5) is less dramatic, and is observed only in the group of highly exposed consumers, i.e. adults using clays with the highest aluminium content. For these consumers the exceedance of the internal HBGV means a reduction of the safety margin to 69, compared with the standard safety margin of 100. In 2009, the NVWA advised against the long-term or repeated use of intestinal cleansing clays because of the presence of dioxins and various metals, but concluded that short-term use of clays with a lower aluminium content possibly poses no or only a limited health risk (NVWA-BuRO, 2009). The current risk assessment seems to support that.

11.5 Aluminium in antacids

Aluminium-containing antacids, a medication for heartburn, are very high in aluminium. For those taking such antacids, the aluminium exposure is in fact higher than for any other source, with the exception of 'pregnancy clays' (see Table 16). As previously explained, the medical use of aluminium is not included in the integrated risk assessment. However, if we were to compare (on an external level) the oral exposure estimates for antacid use with the HBGV established for oral exposure (if possible and valid), the HBGV would be greatly exceeded (by a factor of 22.5–195). Even though it has been reported that when large oral loads of aluminium in the form of antacids are ingested, only an extremely small amount of this excess aluminium will be absorbed, on an internal level such large loads may still exceed the HBGV (even with an absorption as low as 0.01%). Whereas exceeding the HBGV does not directly result in adverse health effects, this should not occur for prolonged periods. Hence, the current advice against the long-term use of antacids is supported. Given that there are also (OTC) antacids available without aluminium, these seem preferable to aluminium-containing antacids.

11.6 Aluminium in vaccines

In Tables 15 and 16 aluminium exposure from vaccines is presented for the different age categories, based on the Dutch NIP. This exposure is most relevant for infants up to one year, as they receive in total up to 3.99 mg Al, spread over 3x2 vaccinations. From one year on, children receive an additional 6 (boys) to 8 (girls) injections, but over a period of 13 years (ages 1–14), and with either no aluminium present in the vaccine or low concentrations of aluminium.

The exposure from vaccines for 0–1-year-olds cannot easily be compared with the exposure from the other exposure sources, as the frequency and route of administration are different (six injections over a period of 1 year, intramuscularly), and also the form of aluminium in vaccines is different (aluminium-containing adjuvants are nanoparticles forming micrometre-size agglomerates). Comparison is further complicated by the fact that there is limited information available on the kinetic behaviour of the aluminium adjuvants in vaccine formulations.

In an attempt to assess the relative contribution to aluminium levels in infants from vaccines and from the diet over the first 400 days of life, the US FDA modelled the pharmacokinetics of aluminium for infant dietary and vaccine exposures (Mitkus *et al.*, 2011; see Section 4.5). It was found that the body burden following maximal exposure to either aluminium hydroxide or aluminium phosphate adjuvants in vaccines used in the USA (at maximum 4.225 mg aluminium) was less than 50% of the oral safe level at all times during the first 400 days of life. The body burden of aluminium from vaccines was not more than 2-fold higher than that received via the diet. It was therefore concluded that episodic exposures to vaccines that contain aluminium adjuvant represent an extremely low risk to infants and that the benefits of using these vaccines outweigh any theoretical concerns (Mitkus *et al*., 2011). In 2012, the WHO Global Advisory Committee on Vaccine Safety reviewed this work by the US FDA and concluded that the comprehensive risk assessment further supports the clinical trial and epidemiological evidence of the safety of aluminium in vaccines (WHO, 2012).

Another attempt to compare the aluminium exposure from vaccines and diet in children was made by the Paul Ehrlich Institute (PEI) in Germany (Weisser *et al*., 2015). The cumulative intake of aluminium from all aluminium-containing vaccines recommended in Germany in the first two years of life (2–5.8 mg) was calculated to be in the range of the systemic exposure allowed for dietary aluminium, taking the HBGV derived by JECFA (2 mg/kg bw/week) as the starting point and adjusting it for 0.3% oral absorption. It was further estimated that the body burden resulting from vaccination (0.5 mg; assuming 20 vaccinations with a maximum of 1.25 mg aluminium each and an aluminium retention of 1–2%) contributes only very little to the total body burden of approximately 35 (5–60) mg built up over life. Compared with other aluminium sources and in the light of the health benefits of vaccination this was seen as acceptable, and it was concluded that exposure to aluminium from vaccines does not pose a health risk to children (Weisser *et al*., 2015).

In the above risk assessments by the US FDA and PEI it is acknowledged that intramuscular injection of aluminium in insoluble form is different from intravenous injection of soluble aluminium citrate or continuous oral intake via diet. But in view of muscle tissue being a storage depot for aluminium adjuvant following intramuscular vaccination, it is assumed that the insoluble aluminium hydroxide or aluminium phosphate particles are solubilised by citrate ions in the interstitial fluids of muscle. It is further assumed that after solubilisation the uptake and distribution kinetics of aluminium will be similar to the kinetics after intravenous and oral administration, although the absorption into blood will not be as instantaneous (nor complete, when followed one month after injection) (Mitkus *et al*., 2011).

The assumption of soluble aluminium being the only entity of aluminium able to produce adverse effects has been criticised by some research groups (e.g. Crépeaux *et al.*, Exley *et al.*, Shaw *et al.*). These groups consider that only a small part of the aluminium injected with vaccinations will be present in a rapidly biologically available form (Al^{3+}), and that the rest of the aluminium will remain in particulate form, part of which will stay at the injection site, and part of which will over time translocate to draining lymph nodes and distant organs like spleen, brain and liver (see Sections 4.2 and 4.3). It is this behaviour that is thought to be related to some neurological/behavioural effects that they observed in mice (see Section 2.2.11).
Interestingly, Weisser *et al*. (2019) found no significant contribution of such particles in the brain of rats. In this study, described in Sections 4.2 and 4.3, an atomic absorption spectrometry method was used to study the kinetics of aluminium-containing adjuvants following a single intramuscular injection in (adult) rats. This method measures dissolved Al^{3+} ions as well as insoluble Al species, and would thus also capture any Al particles in blood and transported via the blood to the tissues studied (bone and brain), or remaining in the injection site muscle. The study revealed systemically available Al from both aluminium phosphate and aluminium hydroxide adjuvants and adjuvanted vaccines through increased Al levels mainly in bone (but not in brain), corroborated by significant correlations with total Al release from the injection site. Different rates of absorption were noted, with markedly higher systemic availability from aluminium phosphate than from aluminium hydroxide-adjuvanted vaccines. From the very low Al levels found in brain the authors concluded that the contribution of particulate Al amounts in the brain, if there is any, is marginal. Based on dose scaling to human adults they further expected that after a single vaccination in adults, Al levels in bone, and even more so in plasma and brain, would be indistinguishable from baseline levels (Weisser *et al*., 2019).

Given all of the above, it is clear that a comparison between the aluminium exposure from vaccines and the aluminium exposure from other exposure sources is not straightforward, as little is known about the kinetic behaviour of the aluminium adjuvants in vaccine formulations, and whether and how that influences the hazard profile of aluminium. What can be seen is that the incidental exposure to aluminium from vaccinations is low for 0–1-year-old infants (0.06–0.22 mg/kg bw, see Table 14). So, whatever the magnitude of the part of the injected aluminium in readily bioavailable Al^{3+} form, this part will in all

likelihood not add significantly to the aggregate exposure to aluminium from other sources, given also the incidental character of the vaccinations (six in total over the first year of life). Whether or not the part of the injected aluminium that is in particulate form is potentially of concern cannot be predicted from the available kinetic and toxicity data.

However, aluminium-adjuvanted vaccines are medicines that are under strict regulatory oversight, and their safety profile is established prior to registration as well as continuously monitored thereafter. This has resulted in extensive evidence from clinical trials and pharmacovigilance (see Section 5.2) that the only adverse effects associated with these vaccines are local reactions at the injection site, including redness and pain and, sometimes, nodules or granulomas. In addition, from epidemiological studies there are no indications of causal relations between aluminium and diseases or disorders in humans (see Chapter 5). So, all in all, the known safety profile of aluminium-containing vaccines and the benefits of vaccination for both the individual and the population as a whole outweigh the uncertainties around the kinetic behaviour of aluminium particulates following vaccination.

12 Conclusions and recommendations

In this study we estimated the aggregate exposure of the Dutch population to aluminium from the most relevant exposure sources and routes, identified as:

- the ingestion of food, drinking water, certain food supplements and soil;
- skin contact through the use of personal care products and household products; and
- the inhalation of ambient air or aerosols from personal care products (sprays).

In the subsequent risk assessment, the total of the internal (i.e. systemic) exposure estimates for the above-mentioned sources was compared with the internal HBGV for aluminium (0.012 mg/kg bw/week), assuming similar toxicity following oral, dermal and inhalation exposure to aluminium. Table A1 in Annex III shows for each age group in the population the maximal contribution of the individual exposure sources to the aggregate exposure on the one hand, and to the internal HBGV on the other hand.

For two additional sources of aluminium, i.e. the ingestion of antacids and the intramuscular injection of vaccines containing aluminium-based adjuvants, the exposure was estimated but not included in the aggregate exposure and risk assessment. This is because their characteristics are different from those of the other exposure sources in that, first, exposure is not continuous over life but only incidental during childhood (vaccines) or occasionally, for a couple of weeks at a time (antacids), and, second, exposure is expected to be beneficial to health as these products are given for a medical reason.

The aggregate exposure and risk assessment showed that only for a few subpopulations might the aggregate exposure exceed the HBGV, due to certain specific exposure sources. These subpopulations are:

- children 0–6 months old and 1–2 years old fed infant formula or diets high in aluminium;
- pregnant women taking clay-based food supplements against morning sickness;
- adults taking clay-based food supplements for intestinal cleansing.

No exceedance of the HBGV was identified for the aggregate exposure of children 7–12 months old and 3–10 years old, of adolescents 11–17 years old and of adults to aluminium in diet, soil and personal care products.

Subpopulations for which the aggregate exposure is below the HBGV

As noted above, the risk assessment showed no concern for the aggregate exposure of children 7–12 months old and 3–10 years old, of adolescents 11–17 years old and of adults to aluminium in diet, soil and personal care products.

In these age groups, diet is the main contributor to the aggregate exposure, amounting to maximally 37%, 79%, 39% and 56% of the internal HBGV for the high end of the highly exposed consumer groups, respectively. In the 7–12-month-old group, soil is equally important (39%). Part of the dietary exposure to aluminium is unavoidable, as unprocessed foods inherently contain aluminium, due to its being one of the most abundant elements in the earth's crust. For the additional sources of aluminium in foods, i.e. food additives in certain foods and the release from food contact materials, regulation is in place in the EU[15] to limit the overall aluminium exposure of consumers. It is to be noted that the dietary intake estimates in our assessment were based on foods as bought and subsequently prepared for consumption, so no additional intake of aluminium via food additives, packaging materials and kitchenware needs to be considered. Nevertheless, consumers can avoid unnecessary aluminium intake from the improper use of e.g. aluminium foil, aluminium grill trays and uncoated aluminium food compartment trays, as significant transition of aluminium from uncoated aluminium articles into food and drinks can be expected, especially those with higher acidic and salt contents.

There is also regulation in place in the EU on the use of aluminium in cosmetic products.[16] From the risk assessment it appears that for all human subpopulations, the contribution of personal care products to the aggregate exposure is relatively small. This is particularly true of dermally applied products, given that only a very small fraction of aluminium is absorbed via the skin. For products applied orally, such as whitening toothpaste and lipsticks/lip gloss, exposure is somewhat higher. It is to be noted, though, that in these products aluminium is present in water-insoluble lakes, from which only a small fraction of aluminium will be bioaccessible. As no data were available to assess this fraction, 100% bioaccessibility was assumed in the exposure estimation, which is worst case. The assumption that all personal care products contain aluminium is also worst case, as for each product type there are aluminium-free alternatives on the market.

No significant additional (dermal) exposure is to be expected for adults from household products such as cleaning agents, in view of the very low dermal absorption of aluminium in humans.

Subpopulations for which the aggregate exposure may exceed the HBGV

Children aged 0–6 months and 1–2 years

In contrast to breastfed infants, small exceedances of the internal HBGV are possible for children aged 0–6 months and 1–2 years fed infant formula or infant foods/diet, particularly those regularly given infant formula/foods with a high aluminium content. In general, the aluminium content of formulas prepared from milk powders is higher than that of ready-made milk formulas. Milk powders require water for reconstitution, which may contain additional aluminium. It is further noted that soy-based infant formula/foods have higher aluminium content than cow's

[15] Regulation (EC) No 1333/2008 on food additives; Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food; Resolution CM/Res(2013)9 on metals and alloys used in food contact materials and articles.

[16] Regulation (EC) No 1223/2009 on cosmetic products.

milk products, so infants and toddlers with an intolerance or allergy to cow's milk may have higher exposure to aluminium. Although the literature provides no indication that aluminium intake levels resulting from the consumption of infant formula and diets are harmful to the health of infants and toddlers, it is to be preferred that the aluminium content in marketed infant formula/foods should not be such that the HBGV is exceeded following consumption.
Given that dietary exposure (especially from soy-based infant formulas/foods) may already exceed the HBGV in these age groups, it seems advisable to minimise additional exposure from ingested toy material, even though in itself this source is only allowed to contribute a maximum of 10% of the HBGV.

Pregnant women taking clay-based food supplements against morning sickness.
The use of clay-based food supplements against morning sickness during the first months of pregnancy in itself may already result in a large exceedance of the internal HBGV. It is recognised, however, that the systemic exposure estimates are worst case, that 'pregnancy clays' are used only by a small proportion of the pregnant women in the Netherlands (mainly women of Surinam and African origin) and that use is not on a lifetime basis. Nevertheless, they result in such high aluminium exposures that the use of 'pregnancy clays' should be advised against, as was recommended in 2009 by the NVWA because of the presence of dioxins and various metals in these clays (NVWA-BuRO, 2009).

Adults taking clay-based food supplements for intestinal cleansing
As with 'pregnancy clays', the use of intestinal cleansing clays may also result in exceedance of the internal HBGV, albeit less dramatically and only for people using the most contaminated clays (i.e. highly exposed consumers). Short-term use of less contaminated clays is possibly of no or only limited concern, but the long-term or repeated use of intestinal cleansing clays should be advised against, as was in fact recommended in 2009 by the NVWA (NVWA-BuRO, 2009).

Exposure from medical uses
Adults taking antacids
Regarding aluminium exposure from medical uses, it is clear that the oral use of aluminium-containing antacids in particular can result in aluminium exposures very much higher than those from diet and other sources. Notwithstanding the health benefits of antacid medication, from a toxicological viewpoint such high exposures are not recommendable for prolonged periods. The current advice against long-term use of antacids is therefore supported. It is further noted that there are antacids on the Dutch market that do not contain aluminium. These seem a preferred option for consumers suffering from heartburn.

Children receiving vaccinations in the Dutch NIP
As to vaccines used in the Dutch NIP, aluminium exposure from aluminium-adjuvanted vaccines is most relevant for infants up to 1 year. A comparison of this exposure with the other exposure sources for infants is, however, not straightforward, given differences in the frequency and route of administration, as well as the form of aluminium

in vaccines. Besides, little is known about the kinetic behaviour of the aluminium-containing adjuvants in vaccine formulations. Nevertheless, from the incidental character of the vaccinations and the fact that the aluminium exposure from a total of six injections is low, it is expected that the part of the injected aluminium that is in the readily bioavailable Al^{3+} form will not add significantly to the aggregate exposure from all other sources of 0–1-year-old infants. There is some uncertainty around the kinetic behaviour of the part of the injected aluminium that is in particulate form, and whether and how this form influences the hazard profile of aluminium. However, aluminium-adjuvanted vaccines have a long history of use, and the uncertainty on the pharmacokinetics is offset by the many clinical trials and epidemiological studies supporting the safety of these vaccines.

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Annex I Physicochemical properties of aluminium adjuvants

Aluminium-containing adjuvants contribute to the efficacy of many vaccines by potentiating the immune response. The physicochemical properties of aluminium-containing adjuvants and their relation to immunopotentiation has been reviewed by Hem and HogenEsch (2007). The following is mainly taken from that review.

Structure of aluminium-containing adjuvants

There are two main forms of aluminium-containing adjuvants licensed for use in humans: aluminium hydroxide and aluminium phosphate. The chemically correct term for aluminium hydroxide adjuvant is crystalline aluminium oxyhydroxide, AlO(OH). The chemically correct term for aluminium phosphate adjuvant is amorphous aluminium hydroxyphosphate, $Al(OH)_x(PO_4)_y$. This is aluminium hydroxide in which phosphate has been substituted for some hydroxyls. The degree of phosphate substitution depends on the reactants and method of preparation.

Sometimes the term 'alum' is used in relation to adjuvant. Alum is, however, not an adjuvant but a reagent used to prepare aluminium-containing adjuvants. Alum is chemically aluminium potassium sulfate ($AlK(SO_4)_2$), a water-soluble compound to which a solution of antigen in phosphate buffer is added, followed by precipitation through addition of a basic solution such as NaOH. In alum-precipitated vaccines, the adjuvant is an amorphous aluminium hydroxide in which some hydroxyls are replaced by sulfate anions (the resulting adjuvant being amorphous aluminium hydroxysulfate) and other anions that may be present in the reaction mixture such as phosphate (the resulting adjuvant being amorphous aluminium hydroxyphosphate sulfate). Alum may also be used as a reagent for the production of aluminium hydroxide adjuvant.

Surface groups

All of the surface groups in aluminium hydroxide adjuvant are hydroxyls that are coordinated to aluminium. The surface groups of aluminium phosphate adjuvant are a mixture of hydroxyls and phosphates. When a hydroxyl is coordinated to a metal, such as aluminium, a metallic hydroxide is formed. Metallic hydroxyls can accept a proton and exhibit a positive charge, or donate a proton and exhibit a negative charge. Hence, the material has an isoelectric point (IEP). With an IEP of 11.4, aluminium hydroxide adjuvant is positively charged at the pH of interstitial fluid (pH 7.4). The IEP of aluminium hydroxide adjuvant can be modified to as low as 4.0 through the use of a phosphate buffer in the vaccine formulation or by pre-treatment of the adjuvant with a phosphate solution. The IEP for aluminium phosphate adjuvant depends on the degree of phosphate substitution for hydroxyl: it approaches 4.0 at the highest levels of phosphate substitution and 9.6 at the other end. Commercial aluminium phosphate adjuvants have an IEP of approximately 5.0, yielding a negative surface charge at neutral pH.

Morphology
All these aluminium-containing adjuvants are composed of very small particles (nanometre dimension). However, these primary nanoparticles form aggregates that are the functioning units in vaccines. The aggregates readily deaggregate during mixing and fragments then reaggregate to uniformly distribute adsorbed antigen throughout the aluminium-containing vaccine.
Aluminium hydroxide adjuvant has a crystalline structure (known as boehmite) and a fibrous morphology with average dimensions of 4.5x2.2x10 nm. The specific surface area is about 500 m^2/g. The primary, fibre-like particles readily form irregularly shaped porous agglomerates with a diameter of 1–20 µm. The primary particles of aluminium phosphate adjuvant are plate-like structures with a diameter of about 50 nm (no specific surface area reported), forming porous agglomerates in a range from 1 to 20 µm in size.

Functionality of aluminium-containing adjuvants
The morphology of aluminium-containing adjuvants facilitates uniform distribution of antigen in vaccines. The aggregates readily deaggregate during mixing and fragments then reaggregate to uniformly distribute adsorbed antigen throughout the aluminium-containing vaccine.
Adsorption of the antigen to aluminium-containing adjuvants is necessary for immunopotentiation. Antigens may adsorb to the aluminium particles via electrostatic attraction, hydrogen bonding, hydrophobic interaction, ligand exchange and van der Waals forces (or a combination thereof), ligand binding being the strongest adsorption force. The strength of adsorption by ligand exchange can be controlled by modifying the number of phosphate groups on the antigen or by pretreating the adjuvant with phosphate to reduce the number of surface hydroxyls available for ligand exchange.

Antigen stability
Adsorbed antigens may degrade by pH-dependent reactions. These reactions occur at a rate associated with the pH of the double layer surrounding the particle rather than the bulk pH. It is of note that for surface-charged particles like aluminium-containing adjuvants, the pH of the microenvironment surrounding the charged particle may be different from the bulk pH. For the positively charged aluminium hydroxide adjuvant the microenvironment pH may be approximately two units higher than the bulk pH.

Adjuvant stability
Aluminium-containing adjuvants age in time and lose their adsorptive capacity. Furthermore, freezing induces irreversible coagulation and loss of adjuvant potency. Repeated autoclaving should also be avoided.

Solubility and dissolution of aluminium-containing adjuvants
The solubility of aluminium hydroxide and aluminium phosphate adjuvants is pH-dependent; it has its lowest solubility at between pH 5 and 7. Amorphous aluminium phosphate adjuvant is more soluble than crystalline aluminium hydroxide adjuvant. Interstitial fluid contains at least three α-hydroxycarboxylic acids (citric, lactic and malic acid) that are good chelators of metal ions. They facilitate dissolution of the aluminium-containing adjuvants when exposed to interstitial fluid

following intramuscular or subcutaneous administration, the solubilisation of aluminium phosphate adjuvant being greater than that of aluminium hydroxide adjuvant.

Annex II Functions of aluminium-containing substances in personal care products

Aluminium-containing substances have various functions in different categories of personal care products. The function of aluminium in personal care products ranges from a mild abrasive action in toothpaste, a shiny effect in lipstick, an antibacterial effect in deodorant and a sweat-reducing effect in antiperspirant products.

The functions of aluminium-containing substances are:

- Abrasive
  E.g. aluminium oxide (alumina) and aluminium silicate are used in toothpaste mainly to act as a mild abrasive and to provide shine/gloss through polishing of the enamel (SCCS, 2020).
- Absorbent, moisturiser, astringent, soothing agent
  Several aluminium-containing substances (e.g. aluminium starch octenylsuccinate, magnesium aluminium silicate, aluminium sulfate potassium / sodium / ammonium alum, aluminium zirconium chlorohydrex glycine, aluminium oxide, aluminium silicate) are thought to have a beneficial effect on the skin and are therefore used in various skin care products.
  Astringents, also referred as toners, are chemical compounds that contract the tissues. In skin care, astringents are used to tone the skin and make it firm by constricting the pores. Astringents create a protective layer between the underlying layers of the skin and the external elements. They are said to contain antioxidants that fight bacteria on the skin and help it to look clean and fresh.
- Antiperspirant
  Aluminium salts in antiperspirants, such as aluminium (zirconium) chlorohydrates, form insoluble aluminium hydroxide polymer gel plugs within sweat ducts to temporarily prevent sweat reaching the surface of the skin (SCCS, 2020). These substances are soluble at very low pH in the formulation; however, once applied on the skin they form chemically inert complexes with the basic components of sweat and skin. The relatively high molecular weight of the compounds and their low 'Log P' and high positive charge limit the potential for skin penetration through the stratum corneum. Moreover, absorption across the skin is further minimised by the formation of protein complexes in the outermost layers of the stratum corneum. These chemical properties limit the systemic delivery of aluminium via the skin (SCCS, 2020).
- Colorant, opacifying agent
  Aluminium salts (white) and aluminium colloidal colorants 'lakes' (blue, red, yellow) are used in various personal care products such as make-up (e.g. blush, nail polish, lipsticks, eye shadow), toothpaste and creams (e.g. sunscreen, shampoo). Colloidal colorants are prepared under aqueous conditions by reacting aluminium oxide with the pigments in order to make them insoluble (EFSA, 2008). Aluminium oxide is usually freshly

prepared by reacting aluminium sulfate or aluminium chloride with sodium carbonate or sodium bicarbonate or aqueous ammonia. Due to the complex molecular structures and high molecular weights of organic lakes, the aluminium represents only a small part of the weight of the raw material of which the extractable part will represent only a fraction. Aluminium content in the lakes usually ranges from 0.01 to 10%, but a lake with 18% aluminium is also found on the market (SCCS, 2020).

- Coating agent
  Aluminium hydroxide is used to coat titanium oxide in sunscreens. In sunscreen lotion formulations, titanium dioxide ($nTiO_2$) nanoparticles are coated with an $Al(OH)_3$ layer to shield skin from the harmful effects of hydroxyl radicals (•OH), superoxide anion radicals (O^{2-}•), and other reactive oxygen species (ROS) (e.g. H_2O_2) generated when TiO_2 nanoparticles are exposed to UV radiation (Virkutyte *et al*., 2012).
- Viscosity agent, anti-caking agent
  Various aluminium-containing substances (e.g. aluminium starch octenylsuccinate, aluminium stearate, magnesium aluminium silicate, alumina) are used to improve viscosity and prevent caking in make-up, skin-care and sun-care products.
- Bulking agent
  Bulking agents or thickeners are used to control phase separation, prevent syneresis, extend shelf life, add volume, slow down or eliminate crystal growth, help suspend particulate materials, form gels and have a positive effect on product application, for example spreadability and delivery.
  Substances like calcium aluminium borosilicate, aluminium oxide and aluminium calcium sodium silicate are used as bulking agents in make-up.

Annex III Maximal contributions of individual exposure sources

Table A1. Summary of the maximal contributions of the individual exposure sources to (1) the total (aggregate) exposure and (2) the internal HBGV (0.012 mg/kg bw/week), based on the exposure estimates for the high end of the highly exposed consumer group within each age group, as presented in Tables 17–19 in Chapter 11.

Age	Source	Systemic exposure (mg/kg bw/week)	Contribution to total exposure (%)		Contribution to internal HBGV (%)	
0–6 mo	Breast milk	0.0006	10.8		4.7	
	Infant formula	0.0177		79.3		147.8
	Soil	0.0046	89.0	20.6	38.4	38.4
	Sunscreen	1.2E-05	0.2	0.1	0.1	0.1
	Total breastfed	**0.0052**			**43.2**	
	Total formula-fed	**0.0224**				**186.3**
7–12 mo	Infant formula/foods	0.0045	48.9		37.3	
	Soil	0.0047	51.0		38.9	
	Sunscreen	9.4E-06	0.1		0.1	
	Total	**0.0092**			**76.3**	
1–2 yr	Diet	0.0152	79.9		126.7	
	Soil	0.0038	20.1		31.8	
	Sunscreen	8.4E-06	0.0		0.1	
	Total	**0.0190**			**158.5**	
3–6 yr	Diet	0.0094	78.3		78.7	
	Soil	0.0026	21.7		21.8	
	Sunscreen	7.9E-06	0.1		0.1	
	Total	**0.0121**			**100.5**	
7–10 yr	Diet	0.0066	80.9		54.7	
	Soil	0.0015	19.0		12.8	
	Sunscreen	6.8E-06	0.1		0.1	
	Total	**0.0081**			**67.6**	

Age	Source	Systemic exposure (mg/kg bw/week)	Contribution to total exposure (%)	Contribution to internal HBGV (%)
11–14 yr	Diet	0.0046	62.6	38.7
	Soil	0.0005	6.2	3.9
	Lipstick/lip gloss	0.0020	27.0	16.7
	Deo – Spray[1]	0.0003	4.2	2.6
	Sunscreen	5.2E-06	0.1	0.0
	Total	**0.0074**		**61.8**
15–17 yr	Diet	0.0037	63.6	30.7
	Soil	0.0004	6.0	2.9
	Lipstick/lip gloss	0.0015	26.3	12.7
	Deo – Spray[1]	0.0002	4.0	1.9
	Sunscreen	5.2E-06	0.1	0.0
	Total	**0.0058**		**48.2**
≥18 yr	Diet	0.0067	49.6	56.0
	Soil	0.0003	2.2	2.5
	Lipstick/lip gloss	0.0013	9.4	10.7
	Whitening toothpaste	0.0050	37.2	42.0
	Deo – Spray[1]	0.0002	1.5	1.7
	Sunscreen	5.2E-06	0.0	0.0
	Total	**0.0135**		**112.9**

[1] Only result for spray deodorant given, as for spray deodorant exposure (dermal + inhalation route) is higher than for non-spray deodorant (dermal route onl

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