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New studies on antiperspirants containing aluminium: impairments to health unlikely as a result of aluminium uptake via the skin

BfR Opinion No 030/2020 issued 20 July 2020

In 2014, the German Federal Institute for Risk Assessment (BfR) prepared an assessment of the health risks posed by antiperspirants containing aluminium. Available data were inconsistent at this time. Accordingly, the Institute highlighted the need for further research on the topic. Recently, two clinical studies were published, which make it necessary to reassess the safety of aluminium in antiperspirants.

Aluminium salts are important active substances in antiperspirants: by temporarily blocking sweat pores, they prevent underarm perspiration. Since they also have an antibacterial effect, the bacteria that normally break down sweat have no opportunity to propagate, which reduces body odour. Aluminium chlorohydrate (ACH) is the primary salt used in antiperspirants.

Together with the new studies from 2016 and 2019, three studies in human volunteers are now available on the dermal bioavailability of aluminium from antiperspirants containing ACH (Flarend et al. 2001; TNO 2016; 2019). The studies are based on measuring the concentration of aluminium in blood and/or urine. BfR has compared the study designs and the results of these three human studies, and used this to prepare a risk assessment. One difficulty in determining the dermal bioavailability of aluminium is that a distinction must be made between the portion of aluminium taken up via the skin and the portion of aluminium in the body that can be ascribed to the uptake from other sources (such as food). Accordingly, all three studies utilised formulations containing ACH that had been labelled with the extremely rare radionuclide aluminium-26 (^{26}Al).

The three studies in humans yield very different results. The most reliable value for bioavailability is provided by the 2019 study, which BfR consulted in its original form. For the uptake of aluminium via the skin, this study determined a bioavailability of 0.00192% of the amount applied. This is the value that BfR used as the basis for its risk assessment, applying a model calculation to derive the amount taken up via the skin.

Result: According to the current state of scientific knowledge, adverse health effects resulting from the day-to-day use of antiperspirants containing ACH are unlikely. In assessing the health risks posed by aluminium, however, it is of paramount importance to consider total uptake via the various uptake paths and sources such as food or products containing aluminium that come into contact with food. Nevertheless, the contribution made by antiperspirants containing aluminium to the total body burden of aluminium is much lower than previously assumed.

BfR risk profile:
Aluminium in antiperspirants (Opinion no. 030/2020)

A	Affected persons	General population				
B	Likelihood of an impairment to health from the daily use of anti-perspirants	Practically impossible	**Unlikely**	Possible	Probable	Certain
C	Severity of an impairment to health from the daily use of antiperspirants	**No impairment**	Mild impairment [reversible/irreversible]	Moderate impairment [reversible/irreversible]	Severe impairment [reversible/irreversible]	
D	Validity of available data	**High: The most important data are available and are internally consistent**	Medium: Some important data are missing or inconsistent	Low: A large volume of important data is missing or inconsistent		
E	Controllability by the consumer	**Control not necessary**	Controllable with precautionary measures	Controllable by avoidance	Not controllable	

Fields with a dark blue background indicate the properties of the risk assessed in this opinion (for more details, see the text of Opinion no. 030/2020 from the BfR dated 20 July 2020).

Explanations

The risk profile is intended to visualise the risk outlined in the BfR Opinion. The profile is not intended to be used to compare risks. The risk profile should only be read in conjunction with the corresponding Opinion.

GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT (BfR)

1 Subject of the assessment

BfR prepared a safety assessment of the dermal uptake of aluminium via antiperspirants containing aluminium chlorohydrate (ACH) for the first time in 2014. Since then, further human studies have been published, which have necessitated a reassessment of the potential health risks of antiperspirants containing ACH.

In 2014, the available data were inconsistent. In its risk assessment of aluminium in antiperspirants, BfR based its work on a study published by Flarend et al. (2001): this is the only study in humans known to the BfR at that time that has investigated the dermal uptake of aluminium from a formulation containing aluminium chlorohydrate, the most common perspiration inhibitor in antiperspirants.

In 2015, Cosmetics Europe, the European trade association for the cosmetics and personal care industry, commissioned a comprehensive study of the uptake of aluminium via the skin under use conditions. The results of this study were communicated to the EU Commission in October 2016, and forwarded for assessment to the Scientific Committee on Consumer Safety (SCCS). In relation to this study, the EU Commission asked SCCS in a mandate dated 7 March 2017 (EC 2017) to update the statement that it had published in March 2014 by taking into account the new data. While the EU Commission had originally set a deadline for this update in October 2017, this deadline was then moved to June 2019 (EC 2017), since the SCCS had requested additional data that were to be submitted until November 2018 (SCCS 2017). In the meantime, excerpts of data from the first study have been published by de Ligt et al. (2018).

BfR considers the newly published clinical studies to be relevant for obtaining a realistic estimate of dermal exposure to aluminium from antiperspirants containing ACH. Accordingly, BfR has prepared a risk assessment based on these new studies in humans.

2 Results

On the strength of the new human data concerning the absorption of aluminium through the skin under realistic conditions of use, the BfR concludes that the uptake of aluminium by consumers is considerably less than the amount originally estimated (in the BfR risk assessment published in 2014). In order for cosmetic substances to be considered harmless to human health, a margin of safety (MoS) of at least 100 is required. Given the lower uptake via the skin for aluminium, the MoS in this case is at least 3000. According to the current state of scientific knowledge, adverse health effects resulting from the day-to-day use of antiperspirants containing ACH are unlikely.

3 Rationale

3.1 Risk assessment

3.1.1 Hazard identification

Owing to its specific properties, aluminium is today used in so many products and technical processes that it is the second most common metallic material used after steel. In 2019, around 64 million tonnes of aluminium were produced worldwide (IAI 2020).

Food is an important route of exposure to aluminium for humans. Aluminium is a natural constituent of many human foods, especially those of plant origin (EFSA 2008; Kolbaum et al. 2019). This presence of aluminium in food can be traced back to a wide range of different sources. Alongside this naturally occurring prevalence, food may also be enriched with additives that contain aluminium. Aluminium may also migrate into food from food contact materials that contain aluminium, such as cookware, kitchen appliances and packaging materials. Aluminium is also found in drinking water, certain kinds of medicinal products and consumer products such as cosmetics. While many aluminium compounds are not soluble in water at neutral pH, this solubility increases as pH becomes basic or acidic.

The EU Inventory of Cosmetic Ingredients (CosIng[1]) currently lists 170 compounds that contain aluminium (search term used ‘alumin*’), which might be used in cosmetics on account of their abrasive, deodorising, astringent or other properties (date of search 26 March 2020).

Aluminium salts are used in antiperspirants as an active ingredient to regulate perspiration. Aluminium salts inhibit perspiration because they cause sweat gland ducts to contract (an astringent effect). In addition, these salts also form gel-like complexes with the body’s own proteins, which also act to temporarily block the ducts of sweat glands (Bretagne et al. 2017). As a result, less sweat reaches the body surface. Aluminium salts also have antibacterial properties, which kill off or slow the growth of the bacteria who feed off perspiration, helping to prevent body odour (Blank and Dawes 1960). Most antiperspirants are based on the use of aluminium chlorohydrate (ACH, CAS no. 12042-91-0) since the early 1960s. According to the EU Cosmetics Regulation (EC) No. 1223/2009, ACH is currently not subjected to any use restrictions.

[1] Database of ingredients used in cosmetics

3.1.2 Hazard characterisation

Aluminium is a nephrotoxin (impairs renal function by promoting the formation of kidney stones or causing hydronephrosis), is toxic to bone and testes, and is also a neurotoxin (causes cognitive impairment) (Dekant 2019; Klotz et al. 2017; Krewski et al. 2007). The most sensitive toxicological endpoint for aluminium is considered to be (developmental) neurotoxicity. No reliable data are available that support a causal link between aluminium and Alzheimer's or breast cancer, however (Drexler 2018; Klotz et al. 2017).

Long-term animal study on aluminium toxicity

In a 12-month study in Sprague Dawley rats, Poirier et al. (2011) investigated the neurodevelopmental toxicity of aluminium. This GLP[2]-compliant study was carried out based on OECD Test Guideline No. 426. Aluminium was administered as aluminium citrate in drinking water. Based on an assumed consumption of drinking water of 120 ml/kg body weight (bw) per day (d), target doses were aimed at 30, 100 and 300 mg aluminium/kg bw/d. The control substances in this experiment were either sodium citrate or water. The study design envisaged exposing the five treatment groups (30, 100, 300 mg/kg bw/d and 2 control groups), each initially consisting of 20 pregnant rats, from the 6th day of gestation. From the generation of rat pups then born (F1 generation), four male and four female animals were selected from each dam, and also exposed to aluminium citrate or the control substances over a period of up to 364 days. At specific time points (PND[3] 23, 64, 120, 364) various tests, such as neurological/neuromotor tests and histopathological investigations, were conducted on/with the rat offspring.

At a dose of 300 mg/kg bw/d, signs of renal toxicity were observed, including hydronephrosis, ureteral dilation, kidney obstruction and/or kidney stones. In the male animals, this led to a high mortality in this dose group as well as a lower mortality in the dose group receiving 100 mg/kg bw/d. Since these adverse effects were not observed in the animals given sodium citrate, they were therefore considered to have been caused by exposure to aluminium. No influence from aluminium exposure on the cognitive performance of the offspring could be identified. All other neuropathological investigations were also unremarkable when compared to the control cohorts.

The functional neuromuscular tests were an exception, however. Both female and male animals in the dose group 100 mg/kg bw/d exhibited a (relevant) reduction in forelimb and hindlimb grip strength, which had not been observed at a dose of 30 mg/kg bw/d. This adverse effect was used to derive a NOAEL (*no observed adverse effect level*) of 30 mg/kg bw/d.

Over the course of the study, the administration of aluminium citrate and sodium citrate led to deviations in fluid consumption, and therefore to a dose of aluminium that deviated from the target dose. An analysis of the dose actually ingested revealed that in the lowest dose group, the exposure to aluminium for pregnant animals during gestation was 10–14% below the target dose of 30 mg/kg bw/d. During lactation, however, the animals were exposed to higher aluminium doses than intended, namely of 40 mg/kg bw/d. The same applied to the rat pups in the first few weeks after weaning. During this phase, the average exposure to aluminium

[2] Good laboratory practice
[3] Postnatal day

for the rat pups was 40.2 mg/kg bw/d for the females and 43.5 mg/kg bw/d for the males. Under-dosing occurred during all later phases of the study, with some doses administered being only 50% of the nominal dose (SCHEER 2017).

The observed reduction in grip strength in the front and hind legs, especially in younger animals, would implicate a critical window at an earlier point in time in the study—such as *in utero* and/or during the lactation phase—than later stages of development. Accordingly, the NOAEL of 30 mg/kg bw/d is justified.

For the subsequent calculation of the margin of safety (MoS), the external NOAEL of 30 mg/kg bw/d from the study by Poirier et al. (2011) was converted into a systemic NOAEL. In a study determining the oral bioavailability of aluminium in rats, 0.6% of the administered aluminium citrate became systemically available (Zhou et al. 2008). An adjustment of the NOAEL for oral bioavailability in rats results in 180 µg/kg bw/d as a PODsys (point of departure) for calculating the MoS.

In pharmaco-/toxicokinetics the experimental set-up used in the oral bioavailability study published by Zhou et al. (2008) is considered the gold standard. The authors utilised a study design in which ^{26}Al-labelled aluminium citrate was administered in water via gavage at a dose relevant for drinking water, whilst a solution containing ^{27}Al was simultaneously administered via infusion as a reference. (Preparatory phase of the experiment: feed containing 10% protein, daily between 8 a.m. and 4 p.m. for 7 days; the animals consumed no feed or water 14 h prior to/4 h after oral administration.) This study determined a bioavailability for aluminium citrate of 0.61%. This value is considered relevant for determining the bioavailability because, as in the key study for the derivation of the NOAEL (Poirier *et al.,* 2011), this study also administered aluminium citrate via drinking water.

A comparable bioavailability of 0.50% was also observed with aluminium maltolate in the study by Zhou et al. (2008); this argues in favour of the improved uptake of aluminium compounds featuring complexation of the aluminium ion by carboxyl groups of organic acids rather than free dissolved aluminium ions. By way of comparison: in the reference group that received aluminium in drinking water without complexing agents, bioavailability was 0.29%.

On the other hand, the increased bioavailability in the aluminium citrate/aluminium maltolate group did not differ significantly from the bioavailability determined for the reference group. For the effect size observed, the group size (5 animals per group) was too small to reach statistically significance. An evaluation in terms of the pharmacokinetic principle of bioequivalence – which envisages an acceptance range of 80–125% for a new pharmaceutical product compared with a reference product – showed that the bioavailability of aluminium citrate and aluminium maltolate cannot be viewed as bioequivalent to the bioavailability of aluminium in the absence of citrate or maltolate. It is important to note here that the bioavailability of 0.29% determined for the reference group is in line with data obtained from an earlier study by the same research group (Yokel et al. 2001). In that study, the bioavailability of aluminium in soft water was 0.23% (on an empty stomach) and 0.21% (with food in the stomach).

The data on aluminium citrate from the two toxicokinetic studies (Yokel et al. 2001; Zhou et al. 2008) are interpreted by the BfR to imply that the actual figure for the bioavailability of aluminium citrate is likely to be closer to 0.6% than 0.3%. The figure of 0.3% is conventionally taken to represent bioavailability from drinking water (EFSA 2008). Accordingly, a calculation of the MoS using 0.6% would lead to a slight underestimation of the risk. In contrast, the use

of 0.3% would represent a conservative approach. The BfR has calculated the corresponding MoS for both values.

3.1.3 Exposure

The relevant route for the uptake of ACH into the body from antiperspirants is the skin. Additionally, in the case of antiperspirant sprays, the uptake of aluminium could also occur by inhalation.

Three studies in humans are available on the dermal bioavailability of aluminium from antiperspirants (Flarend et al. 2001; TNO 2016; 2019). The studies use standard toxicokinetic approaches that are based on measuring the concentrations of aluminium in blood and/or urine. A general description of these approaches will be provided below, before the specific details of each study are then examined in more detail.

Bioavailability describes how much of a dose and how quickly that portion reaches the systemic circulation. The standard approach for determining dermal bioavailability consists of administering the test substance once dermally (derm) and once intravenously (IV), and then taking blood samples at separate points in time in order to reconstruct the blood concentration-time curve for the test substance. Assuming that the clearance (the blood volume fully 'cleared' of the substance per unit of time) is the same for a dose given dermally and intravenously, the area under the curve (AUC) for the blood concentration-time curve from the time $t = 0$ to infinity as well as the dose used (D) can be used to calculate the bioavailable fraction (F) as follows:

$$F = \frac{AUC_{\mathrm{derm}}}{AUC_{\mathrm{IV}}} \cdot \frac{D_{\mathrm{IV}}}{D_{\mathrm{derm}}}$$

Alternatively, dermal bioavailability can be determined from the cumulative urinary excretion of the substance for a dose given dermally and intravenously:

$$F = \frac{A_{\mathrm{derm}}}{A_{\mathrm{IV}}} \cdot \frac{D_{\mathrm{IV}}}{D_{\mathrm{derm}}}$$

where A_{derm} and A_{IV} are the quantities of substance excreted from $t = 0$ to infinity, respectively. This approach assumes that the proportion of renal clearance to total body clearance is the same for dermal/intravenous administration.

When determining the bioavailability of aluminium from antiperspirants, the quantity absorbed dermally must be distinguished from background levels of aluminium that are taken up from other sources (e.g. ingested with food). To do so, all three studies labelled the formulation containing ACH with the radionuclide ^{26}Al. Owing to its lower mass compared with the naturally occurring isotope ^{27}Al, the concentrations of ^{26}Al in blood and urine can be determined analytically using the highly sensitive method of accelerated mass spectrometry (AMS).

Table 1 presents an overview of the study designs used in the three studies in humans.

Flarend et al. (2001)

In this study, two subjects received a single application of a ^{26}Al-labelled aqueous ACH solution to one armpit each. The applied quantity of 0.246 g and 0.230 g of the 21% ACH solution (corresponding to 13.3 mg and 12.4 mg of ^{27}Al, respectively) had an activity measured at 5.6 Bq and 6.0 Bq, which corresponds to a ^{26}Al dose of 7.75 ng and 8.31 ng. In the 3 weeks prior to application, the subjects were not allowed to use any cosmetic products on the underarm region to be exposed and also shaved this area two days before application. After application, the exposed skin area was allowed to dry naturally before being covered with an adhesive bandage (described as *a large occlusive-type bandage with adhesive on the edge of the bandage*). In the first 6 days following application, the bandage was removed every morning, and the residual ACH as well as the top dead layer of skin was removed using a 'tape stripping' method, which was performed twice. The armpit was then gently washed with pre-wetted towelettes, allowed to dry naturally and then covered once more with a bandage.

Over a period of 53 days following application, samples of blood and urine were collected at specific points in time (Table 1). Although concentrations of ^{26}Al in most of the blood samples were too low to be quantified, it was possible to measure ^{26}Al in the urine over a period of several weeks following application. The time course of cumulative urinary excretion showed that the daily excretion of ^{26}Al remained largely constant during the first two weeks and was subsequently decreasing. Over the entire test period, 0.0082% and 0.016% (average: 0.012%) of the quantity of the substance applied was excreted in urine.

Since the substance was not given intravenously in this study, and data on residual quantities in the body following an IV dose were therefore unavailable, the authors consulted information from the literature. The proportion remaining in the body was estimated from a human study examining the intravenous injection of ^{26}Al-labelled aluminium citrate in one volunteer, for whom 80% of the dose and 90% of the dose was eliminated renally in the first 7 and 40 days after injection, respectively (Priest et al. 1995). Flarend et al. used this to derive a correction factor of 0.85, which was applied to the excreted proportion of 0.012% to derive an average value of 0.014% of the dermally applied amount that was systemically bioavailable.

An analysis of the bandages, tape strips, wash solution and urine samples revealed a recovery rate of 48% for the male subject and 31% for the female subject. The authors attributed the low recovery rate to environmental losses (the bandages had become detached from the skin a number of times during the experiment) as well as to residues retained as precipitated plugs in the sweat gland ducts.

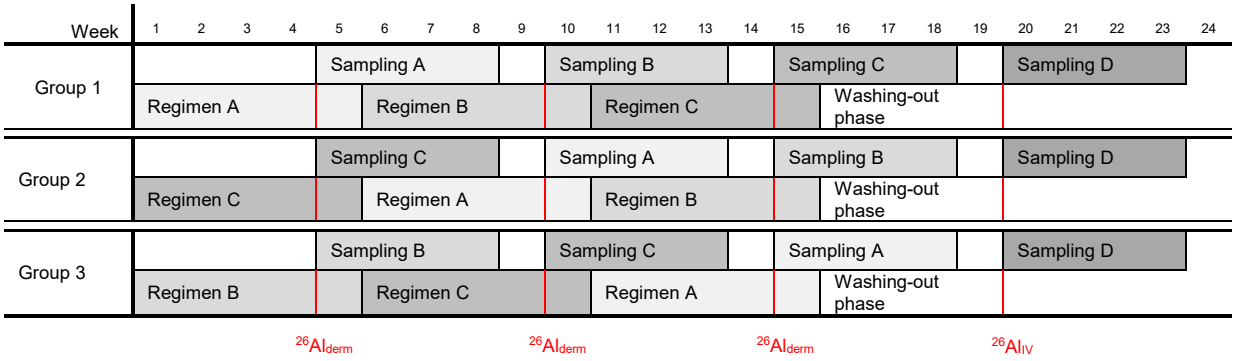
<u>TNO 2016</u>

In this study, a ^{26}Al-labelled formulation containing ACH was used, which was then thickened with hydroxyethylcellulose in the same way as for commercial antiperspirants, to achieve the viscosity typical for such roll-on products (de Ligt et al. 2018). This formulation was applied to both armpits of 12 female volunteers. The total quantity applied weighed 1.5 g: this corresponds to the 90th percentile of the distribution of the quantities used in the population (SCCS 2018), and exhibited a radioactivity of ~100 Bq, equivalent to a ^{26}Al dose of 138 ng. After application, the subjects were asked to wear a cotton T-shirt for 24 h, and were then allowed to take a shower and to wash the underarm area. A bandage or gauze to cover the exposed skin area was not used in this study. Blood samples were taken at specific points in time over a period of 28 days following dermal application (Table 1), with the aim of reconstructing the blood concentration-time course of ^{26}Al. In addition, morning spot urine samples were collected sporadically (Table 1) to obtain some evidence on urinary excretion of ^{26}Al.

A crossover design was chosen for this study in order to investigate the influence of (i) daily application versus one-time application of antiperspirants and (ii) daily underarm shaving versus no shaving of the underarm area. To do so, three separate usage regimens were defined, within which exposure to the ^{26}Al-labelled antiperspirant formulation occurred once

(Figure 1): these involved the pre-/post-exposure daily use of a standard off-the-shelf (unlabelled) antiperspirant on unshaven (regime A) or shaven skin (regime B), as well as no use of either 'additional treatment' (regime C). To this end, the 12 subjects were split into three groups of four individuals. The groups differed from one another only in terms of the order in which they followed the three usage regimens (see Figure 1). After completing the regimens A, B and C, followed by a 4-week wash-out phase that involved no use of any antiperspirant, the subjects received a single intravenous dose[4]. This involved the bolus injection of 5 ml of a ^{26}Al-labelled (~1 Bq) aluminium citrate solution. Following this, blood and morning spot urine samples were taken and collected over a period of 28 days (Table 1).

Figure 1: Summary of the study design for the 2016 TNO study (after Ligt *et al.*, 2018).



After dermal administration, concentrations of ^{26}Al in blood were above the limit of quantification (0.122 fg/ml) in only 2 of 504 samples, which prevented the calculation of any concentration-time profiles. A determination of bioavailability using blood concentration-time curves was therefore not possible. Instead, the authors resorted to using the data from the morning spot urine samples collected following dermal administration in order to determine cumulative excretion in urine (see below). It proved possible to quantify ^{26}Al in 35% (87 of 252 samples) of these urine samples, although only the samples taken on days 1, 2 and 3 were generally quantifiable.

Determining the cumulative excretion of ^{26}Al in urine required the following: (i) the estimation of concentration levels for the samples that could not be quantified; (ii) an extrapolation of the ^{26}Al concentration in a single morning urine sample to the daily level of ^{26}Al excretion; and (iii) an estimation of ^{26}Al excretion by way of linear interpolation on the days on which no sample was taken. For the samples that could not be quantified, lower-bound and upper-bound estimations (best-case/worst-case approach) were made. For the lower-bound estimate, a value of zero was assumed for all values below the limit of quantification. For the upper-bound estimate, the limit of detection was assumed for values beneath the limit of detection, and the limit of quantification was assumed for values above the limit of detection but below the limit of quantification. To determine daily excretion of ^{26}Al, the concentration of ^{26}Al in a morning spot urine sample was multiplied by the daily quantity of urine produced, which was estimated from the creatinine concentration measured and an assumed daily creatinine excretion of 10 mmol. Dermal bioavailability was then determined from the cumulative urinary excretion following dermal and IV administration (de Ligt et al. 2018).

[4] One subject became pregnant during the study and withdrew prior to the IV administration.

For the various scenarios, the best-case approach yielded bioavailability values of 0.0056% (regimen A) to 0.0100% (regimen C) while the conservative worst-case approach yielded values of 0.0100 (regimen A) to 0.0144% (regimen C). As a result of the large variance in the data, the differences between the three regimens as regards bioavailability were not statistically significant.

TNO 2019

In this study, six female subjects completed a 2-week adaptation phase involving a daily wet shave and use of a standard off-the-shelf antiperspirant before receiving a single application to both armpits of a formulation containing ^{26}Al-labelled ACH that had been thickened with hydroxyethylcellulose. The total quantity applied weighed 1.5 g and had an activity of 2695 Bq, which corresponded to an applied quantity of 3732 ng of ^{26}Al. Following the application of 0.75 g to each armpit (approx. 100 cm² of underarm skin), the area treated was allowed to dry naturally before being covered with a non-occlusive gauze that was loosely attached over the application area. The subjects were then asked to wear a T-shirt for 24 h. The exposed area of skin was then washed and covered with a semi-occlusive gauze for another 24 h. After this 24 h period, the area of skin was washed once more. The wash solution, the other materials used, the gauzes and the T-shirts worn were then analysed to determine the proportion of non-absorbed ^{26}Al. For the IV dose, 5 ml of a ^{26}Al-labelled (~0.1 Bq) aluminium citrate solution was administered via a bolus injection.

Blood samples were then taken at specific time points (Table 1) for 28 days following dermal application. In addition, urine and faeces were collected in full over a period of 10 days (referred to urine collection (6-h and 12-h urine), 24-h urine, and 24-h faeces in the following); 24-h urine was also collected on days 14, 21 and 28 (table 1). On day 7 and day 35 following application, 'tape stripping' was also performed on one axilla, so as to determine residues of ^{26}Al in the horny layer. To do so, the stratum corneum was removed in individual layers using tape strips until the shiny surface of the viable epidermis became visible. A skin punch biopsy was also taken from the area of skin freed of its horny layer after 35 days, in order to determine the amount of ^{26}Al in the skin layers below the stratum corneum.

Since concentrations of ^{26}Al in blood were above the limit of quantification in only 12 of 84 samples, this reduced the usefulness of the resulting concentration-time profiles. Robust statements concerning bioavailability could not be derived in this study from the blood-concentration time profiles. Instead, the authors resorted to using the data from the collected urine samples.

Following dermal administration, it was possible to quantify ^{26}Al in 66% (59 of 90) of the urine samples collected over the entire observation period. Until day 6 (inclusive), the proportion of quantifiable urine samples was 90%. Following IV administration, the percentage for the entire period of time was 98% (88 of 90 samples). For the last samples taken (on day 28), the concentration of ^{26}Al in all samples was below the limit of detection (dermal administration) or near/below the limit of detection (IV administration). To calculate cumulative ^{26}Al excretion, values below the limit of quantification were set to the limit of quantification (upper-bound estimation). In case of one subject, the toxicokinetic data suggested that the intended intravenous administration probably occurred intramuscularly/subcutaneously. The data obtained from this subject were excluded from the descriptive statistics. Over the entire study period, an average of 0.00036% (dermal) and 70% (IV) of the applied dose was excreted in urine (mean value from 5 subjects).

By taking the proportion of ^{26}Al excreted in urine following dermal application and multiplying this with the proportion excreted in urine following IV administration, the bioavailable fraction

following dermal application could then be calculated for each of the remaining five subjects (see equation on page 6). The mean value for this bioavailable fraction was 0.00052%.

In faeces, 0.0014% of the dermal dose was recovered on average. Measurements conducted on the worn T-shirts, the gauzes, the wash solution and the utensils used resulted in a recovery rate of 70%. The largest proportion was found after 24 h in the wash solution (62%) and the T-shirts (6%). Based on the analysis of the tape strips, the recovery rate for the applied dose from the horny layer was 0.0097% (after 7 days) and 0.0090% (after 35 days). The skin punch biopsy (living epidermis and neighbouring dermis) returned a recovery rate of 0.00004% after 35 days (mean value from two quantifiable samples).

TNO 2019 – supporting study

To obtain information about the local fate of the non-absorbed aluminium and to determine the quantity lost to the environment, an additional, explorative study was conducted. Towards this end, a further 6 subjects, who had completed the same adaptation phase as designed for the main study, received an application of 1.5 g of the antiperspirant formulation to their axillae (0.75 g per 100 cm² of skin per armpit). The formulation had an activity of ~1 Bq, which corresponded to an applied quantity of 1.573 ng of ^{26}Al. After allowing 20 minutes to dry naturally, the exposed area of skin was then covered with semi-occlusive gauzes and the subjects put on a T-shirt. At various points in time following dermal application (20 min, and 1, 6 and 24 h), the horny layer was removed by repeated tape stripping from a new patch within the central vault of the axillae on each occasion, so as to obtain a depth profile of distribution within the stratum corneum. After the last tape-stripping at 24 h, a punch biopsy was taken from the area of skin from which the stratum corneum had just been removed. To obtain a mass balance, the quantity of ^{26}Al recovered from the tape-strip samples and punch biopsy was scaled to the total area of skin exposed and expressed as a proportion of the dose.

The first sample (after 20 min), taken from underarm skin dried naturally but not yet covered, produced the highest quantity of ^{26}Al recovered from the first tape strip. With each subsequent tape strip, the recovered quantity of ^{26}Al decreased in an exponential manner. As a result of the pronounced uneven surface of the skin of the axillae, one may assume that the quantities of ^{26}Al found in the first tape strips stemmed from both the horny layer and from the surface of the skin itself (from skin furrows). In the samples taken at later time points from the skin covered with a semi-occlusive gauze, the total quantity of ^{26}Al recovered decreased over time. The high recovery rate in the first tape strip sample, the overproportionally decreasing depth profile, and the declining quantities of ^{26}Al in the tape strips over time demonstrated that a considerable proportion of the applied formulation remained on the skin surface, and was then lost over time by contact with materials worn next to the skin (gauze, T-Shirt). Overall, the results showed that more than 95% of the applied dose remained external to the body within the first 24 hours after application.

In the skin punch biopsy, 0.08% of the applied quantity was recovered after 24 h. By way of comparison, the skin punch biopsy conducted in the main study found quantifiable ^{26}Al in only 2 of 6 samples after 35 days (equal to 0.00003% and 0.00004% of the dose). These data provide no indication that the skin acts as a ‘depot’ for aluminium.

Table 1: Summary of the study design for the human studies involving dermal application of ^{26}Al-labelled antiperspirants.

	Flarend et al. (2001)	TNO (2016)	TNO (2019) -
Number of subjects	2 (♂ + ♀)	12 (11) ♀	6 ♀
Application site	One axilla	Both axillae	Both axillae
Exposed skin area	77 cm²	2 × 100 cm² = 200 cm²	2 × 100 cm² = 200 cm²
Antiperspirant formulation	21% ACH (5.21% ^{27}Al) in an aqueous solution	25% ACH (6.25% ^{27}Al) thickened with 0.625% HEC	25% ACH (6.25% ^{27}Al) thickened with 0.625% HEC
Applied amount	0.246 g and 0.230 g	2 × 0.75 g = 1.5 g	2 × 0.75 g = 1.5 g
^{27}Al dose	13.3 mg and 12.4 mg	113 mg	83 mg(4)
^{26}Al dose (1)	7.75 ng and 8.31 ng	138 ng	3732 ng
Activity of applied overall quantity of ^{26}Al-labelled formulation	5.6 Bq and 6.0 Bq (2)	100 Bq	2695 Bq
Occlusive bandage	Yes	No	'Semi-occlusive'
Study regimen (shaving, prior use of standard off-the-shelf antiperspirant)	No use of antiperspirants before/during the study period, electric shave 2 days before application	3 treatment regimens (see text for details) with 4-week adjustment phase (before the first application)	Daily wet shave and use of a standard off-the-shelf antiperspirant in the 4 weeks before application
Blood collection	0, 6 and 14 h, and 1, 2, 3, 4, 5, 6, 7, 9, 11, 14, 18, 24, 32, 42 and 53 days after application	1, 2, 4, 8, 10 and 12 h, and 1, 2, 3, 7, 14, 21 and 28 days after application	1, 2, 4, 6, 8, 10 and 12 h, and 1, 2, 3, 7, 14, 21 and 28 days after application
Urine collection	24-h urine over the entire time frame until day 53 after application	Morning spot urine on day 1, 2, 3, 7, 14, 21 and 28 after application	Urine collection 0–6 h, 6–12 h and 12–24 h, then 24-h urine over the first 10 days, and on day 14, 21 and 28 after application
Faeces collection	None	None	24-h faeces over 10 days
Limit of detection (LOD)/quantification (LOQ)	LOD (blood and urine): ~0.01 fg/ml (3)	LOQ (blood/urine): 0.122/0.061 fg/ml LOD (urine): 0.034 fg/ml	LOQ (blood/urine): 0.118/0.109 fg/ml LOD: not reported
Materials analysed to determine the non-absorbed ^{26}Al	Bandages Tape strips Towelettes	Not reported	Gauzes Wash solution Tape strips T-shirts
Mass balance / Recovery rate for ^{26}Al	48% (♀) and 31% (♂)	Not reported	~70%

HEC: Hydroxyethylcellulose

(1) Calculated from the activity (in Bq) and the mass-related activity of ^{26}Al of 0.7221 Bq/ng. The mass-related activity was calculated after Wiechen et al. (2013) based on the half-life of ^{26}Al of 705000 years (Norris et al. 1983).

(2) Calculated from the reported activity (151 pCi and 162 pCi) and conversion factor: 27 pCi = 1 Bq (BfS 2019)

(3) This value was taken from Flarend and Elmore (1998), since no limit was reported in Flarend et al. (2001). According to Flarend and Elmore (1998), the limit of detection for accelerated mass spectrometry (AMS) for the measurement of ^{26}Al is reached at a ^{26}Al/^{27}Al isotope ratio of around 10^{-14}. During sample preparation, ^{27}Al

is added as a carrier isotope in macroscopic quantities, so any quantity of ^{27}Al already present in the sample can be discounted. For a carrier quantity of 1 mg of ^{27}Al, this results in a limit of detection for ^{26}Al of 0.01 fg/ml.

(4) Calculated from the average $^{26}Al/^{27}Al$ ratio of 4.36×10^{-5} of the antiperspirant formulation, the ^{26}Al dose and the molecular weights of ^{26}Al and ^{27}Al.

Conclusions

The three human studies on the bioavailability of aluminium from antiperspirants applied dermally provide a very heterogeneous set of results. Values range from 0.014% (Flarend et al. 2001) through 0.0056–0.0144% (TNO 2016) to 0.00052% (urine) and 0.0014% (faeces) (TNO 2019). Both random aspects and systematic factors need to be discussed to identify potential explanations for these differences.

In the study by Flarend et al. (2001), the small sample size may have exerted a certain degree of influence as a random component (in terms of sampling/selection bias). However, the BfR does not consider this parameter as the crucial influencing factor to explain the 27-fold higher absorption compared with the study by TNO (2019). Instead, the physical properties and composition of the formulation used provide the decisive contribution to the results here. Namely: an aqueous ACH solution was applied instead of a viscous cosmetic formulation. Apart from the comparatively high figure for dermal absorption itself, a further peculiarity in Flarend et al. (2001) is that the more or less constant rate of daily urinary excretion of ^{26}Al over a 14-day period, which is in contrast to the decline in both TNO (2016) and TNO (2019) after the first day post-dosing. This implies that ^{26}Al became bioavailable from a dermal depot in a stepwise/time-delayed manner. The reason for this could be a deeper penetration of the aqueous solution into the ducts of the sweat glands, which could have resulted in a prolonged systemic exposure. Despite only a single case of dermal application, this could explain the constant uptake rate over 14 days. Calculating back over this period would yield a dermal absorption rate of 0.001% per day.

Single application instead of daily application also leads to higher uptake. The study from TNO (2016) shows that in the case of regimen C, comparable to the study design from Flarend et al., the best-case approach would lead to roughly double the amount of aluminium being absorbed through the skin compared with regimen A or B (0.0100% vs 0.0056% and 0.0058%). Assuming the dermal uptake route is subject to saturation, the percentage of the quantity absorbed is ultimately dependent on the quantity as applied. Above a certain quantity of aluminium being applied, the absorption does not increase further once this saturation limit is reached. If aluminium is applied dermally in excess of this saturation limit, the bioavailable fraction will decrease.

In the study by TNO (2016), the antiperspirant formulation was applied in a 6-fold higher overall amount and with an approximately 20-fold higher activity in comparison with Flarend et al. (2001). The fact that, contrary to the expectation of the authors, the ^{26}Al concentration in the blood was not quantifiable is, in the view of the BfR, almost certainly a result of lower dermal availability due to the formulation's (standard commercial) viscous properties as well as analytical sensitivity, which was 1–2 orders of magnitude lower (Table 1). The decision to use instead the data from morning spot urine samples, which were collected sporadically and only partially analysable, requires a series of assumptions to be made in order to estimate the cumulative urinary excretion of ^{26}Al. The resulting estimate is associated with large uncertainties.

The BfR considers the time point when the first sample was taken, namely 24 h after dermal/intravenous administration, to be decisive in terms of the dermal absorption rate obtained in this way. The concentration of ^{26}Al in the first morning urine sample was used to estimate ^{26}Al excretion for the first 24 h. This window of time is a highly dynamic phase in which

the shapes of the urine concentration-time curves differ significantly for IV and dermal administration. While the first curve shows an exponential decay, the second curve follows an initially rising trajectory to a maximum before then declining. Data provided by the study from TNO (2019) indicate that the maximum for renal excretion of ^{26}Al is attained roughly 24 h after dermal application. Based on the data from the first morning urine sample, the excretion of ^{26}Al over the first 24 hours is therefore underestimated in the case of IV administration and overestimated for dermal application. This error is further compounded by using both values in a later calculation. The consequence is a significant overestimation of the excretion of ^{26}Al over the first 24 h, which is ultimately the main reason for overestimating dermal absorption.

In the study by TNO (2019), the activity in the antiperspirant formulation was increased by a factor of 25 compared with the activity in TNO (2016). While this did increase the proportion of quantifiable blood samples to a certain extent, the blood concentration-time profiles that can be derived from this study are of only limited reliability (see above). This study did provide, however, a robust set of data on the concentration of ^{26}Al in systematically collected urine, which could then be utilised in order to determine the cumulative excretion of ^{26}Al. Accordingly, the study by TNO (2019) can be used to derive a systemic bioavailability for aluminium in antiperspirants following dermal application of 0.00192%, which comprises 0.00052% and 0.0014% in urine and faeces, respectively.

The 2019 TNO study also provides other sets of valuable data that help to resolve some uncertainties that have persisted to date concerning the dermal absorption of ^{26}Al from antiperspirants. These data concerned the mass balance and recovery rate, the local fate of the non-absorbed aluminium, the depth profile of ^{26}Al distribution in the skin, and the question of whether skin could act as a depot for aluminium.

3.1.4 Risk characterisation

3.1.4.1 Dermal exposure

For the uptake of aluminium from antiperspirants via the skin, a bioavailability of 0.00192% is assumed, based on data from the 2019 TNO study.

According to the SCCS *Notes of Guidance*, daily exposure to antiperspirants equals 22.08 mg/kg body weight (SCCS 2018). For an aluminium content of 6.25% in a highly effective antiperspirant, this would yield an external dermal exposure of 1380 µg aluminium/kg body weight per day. From this, a daily systemic exposure dose (SED) of 0.026496 µg/kg body weight (= 1380/100% × 0.00192%) can be derived.

From the long-term study in rats conducted by Poirier et al. (2011) and assuming an oral bioavailability of 0.6% (Zhou et al. 2008), a systemic NOAEL of 180 µg/kg bw/d has been derived as a point of departure (PODsys).

For the antiperspirant, this yields a MoS (calculated as PODsys/SED) of 6793 (= 180 µg/kg bw/d divided by 0.026496 µg/kg bw/d).

If an oral bioavailability of 0.3% in rats was assumed, this would yield a PODsys of 90 µg/kg bw/d. While this would lead to a bisection of the MoS, the resulting margin of safety would still be far above the required value of 100.

3.1.4.2 Exposure by inhalation

When spray antiperspirants are used, dermal exposure to aluminium may be accompanied by unintentional exposure to aluminium from inhalation. The SCCS has completed a risk assessment for this route of exposure. The SCCS based this work on dossier data (Meech et al. 2011, cited in SCCS (2020)). Three separate and relevant aerosol fractions differing in terms of size distribution were considered here, which are capable of reaching the main compartments of the lungs (extra-thoracic, tracheo-bronchial and alveolar) (SCCS 2020). The quantity of bioavailable aluminium via inhalation resulting from the use of a standard off-the-shelf aerosol spray containing 2.86% aluminium amounts to 0.010582 µg Al/kg bw/d. For a 60-kg individual, this amounts to a systemic exposure of 0.63492 µg Al/d.

Regarding the methodology, SCCS refers to an experimental study from Schwarz et al. (2018), in which the exposure to aluminium via inhalation from sprays (without alcohol) is modelled and calculated under use conditions. According to Schwarz et al. (2018), less than 0.5 µg aluminium becomes systemically available per use from a spray containing 1.5% aluminium. If used twice daily, this corresponds to a daily dose of 0.01666 µg/kg body weight. If the higher concentration of 2.86% Al is utilised from the SCCS assessment, this yields a bioavailability of 0.03154 µg Al/kg bw/d. Assuming that the sprays used here do not differ significantly in terms of their patterns of aerosol generation from the spray considered by the SCCS, the study from Schwarz et al. confirms the SCCS calculations.

If inhalation is compared with the dermal route in terms of systemic exposure from antiperspirant sprays, the bioavailability from exposure by inhalation is several orders of magnitude higher (compared with a dermal bioavailability of 0.00192%) and so contributes significantly to overall exposure. Despite this, the MoS for this route of exposure is still within the range 20000 to 70000, since the quantities available via inhalation are so small.

Further information on the subject from the BfR website …

FAQ about aluminium in food and consumer-oriented products (FAQ from the BfR, updated on 13 December 2019):

https://www.bfr.bund.de/cm/349/faqs-about-aluminium-in-food-and-products-intended-for-consumers.pdf

Summary of publications about aluminium:
https://www.bfr.bund.de/en/a-z_index/aluminium-129853.html

BfR "Opinions app"

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About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. It advises the German federal government and German federal states ("Laender") on questions of food, chemical and product safety. The BfR conducts its own research on topics that are closely linked to its assessment tasks.

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