Scientific Committee on Consumer Safety

SCCS

OPINION ON

the safety of aluminium in cosmetic products

Submission II

The SCCS adopted this document
at its plenary meeting on 03-04 March 2020

ACKNOWLEDGMENTS

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This Opinion has been subject to a commenting period of a minimum eight weeks after its initial publication (from 16 December 2019 until 17 February 2020). Comments received during this time period are considered by the SCCS. For this Opinion, some changes occurred, in particular in sections 1, 3.2, 3.3.4.5, 3.3.8.1, 3.5, as well as in related discussion parts and conclusion (question 1). The list of references has also been updated.

1. ABSTRACT

In 2014, the SCCS was asked to review the safety of aluminium in cosmetic products. Aluminium containing ingredients were reported by cosmetic industry to be used in a lot of different categories of cosmetic products. Among them antiperspirants and deodorants, lipsticks and toothpastes were considered by the SCCS to be the main contributing sources of exposure via cosmetic products. The SCCS Opinion (SCCS/1525/14) concluded that due to the lack of adequate data on dermal penetration to estimate the internal dose of aluminium following cosmetic uses, risk assessment could not be performed, and asked for internal exposure to aluminium after skin application to be determined using a human exposure study under use conditions. The current SCCS Opinion is based on the new data and exposure assessment provided by the Applicant as part of Submission II.

The SCCS concludes the following:

1. In light of the new data provided, does the SCCS consider that Aluminium compounds are safe in

- *Antiperspirants,*
- *Other cosmetic products such as lipsticks and toothpastes?*

In the light of the new data provided, the SCCS considers that the use of aluminium compounds is safe at the following equivalent aluminium concentrations up to:

- 6.25% in non-spray deodorants or non-spray antiperspirants
- 10.60% in spray deodorants or spray antiperspirants
- 2.65% in toothpaste and
- 0.77 % in lipstick

2. Does the SCCS have any further scientific concerns regarding the use of Aluminium compounds in cosmetic products taking into account exposure from other sources?

The SCCS considers that the systemic exposure to aluminium via daily applications of cosmetic products does not add significantly to the systemic body burden of aluminium from other sources. Exposure to aluminium may also occur from sources other than cosmetic products, and a major source of aluminium in the population is the diet. This assessment has not taken into account the daily dietary intake of aluminium.

3. In the event that the estimated exposure to Aluminium from specific types of cosmetic products is found to be of concern, SCCS is asked to recommend safe concentration limits for the presence of Aluminium in those cosmetic products or other risk reducing measures.

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Keywords: SCCS, scientific opinion, aluminium, Regulation 1223/2009

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on the safety of aluminium in cosmetic products, preliminary version of 30-31 October 2019, final version of 03-04 March 2020, SCCS/1613/19

About the Scientific Committees

Two independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

These Committees are: the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and they are made up of scientists appointed in their personal capacity.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide Opinions on questions concerning health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Aluminium and its compounds are used in cosmetics products such as antiperspirants, lipsticks and toothpastes. In particular, the most extensively used aluminium compound in cosmetic products is aluminium chlorohydrate in antiperspirants. While aluminium Chlorohydrate is a cosmetic ingredient not regulated in the Cosmetic Regulation 1223/2009, other aluminium salts such as aluminium zirconium chloride hydroxide complexes and the aluminium zirconium chloride hydroxide glycine complexes are covered by entry 50 in Annex III of the Cosmetic Regulation for use as antiperspirants with specific conditions of use.

According to Cosmetics Europe, current conventional antiperspirants rely on a group of water soluble salts of aluminium and/or zirconium that possess similar insoluble gel-forming properties while lipstick and toothpastes generally contain water-insoluble aluminium ingredients such as aluminium colloidal colorant ‘lakes’ and insoluble minerals.

In 2013, the risk assessment issued by the Norwegian Scientific Committee for Food Safety showed that cosmetic products, and in particular antiperspirants, constitute a significantly larger contribution to the total systemic aluminium exposure compared to diet. As a result of this, the Commission requested the SCCS to evaluate the possible risk for human health arising from the presence of aluminium in cosmetics, considering the exposure from other sources, such as food and food supplements. The SCCS issued the opinion in 2014 (SCCS/1525/14) on the safety of aluminium in cosmetic products concluding that:

"*Aluminium is a known systemic toxicant at high doses. The SCCS is of the opinion that due to the lack of adequate data on dermal penetration to estimate the internal dose of aluminium following cosmetic uses, risk assessment cannot be performed. Therefore internal exposure to aluminium after skin application should be determined using a human exposure study under use conditions.*"

In October 2016, Cosmetics Europe submitted to the Commission services a new safety dossier to address the concerns expressed by the SCCS in particular by performing a clinical study on the absolute bioavailability of aluminium from dermal exposure of human volunteers to a representative antiperspirant formulation.

Terms of reference

1. In light of the new data provided, does the SCCS consider that Aluminium compounds are safe in
- *Antiperspirants,*
- *Other cosmetic products such as lipsticks and toothpastes?*

2. Does the SCCS have any further scientific concerns regarding the use of Aluminium compounds in cosmetic products taking into account exposure from other sources?

3. In the event that the estimated exposure to Aluminium from specific types of cosmetic products is found to be of concern, SCCS is asked to recommend safe concentration limits for the presence of Aluminium in those cosmetic products or other risk reducing measures.

3. OPINION

3.1 Chemical and Physical Specifications

Taken from previous Opinion (SCCS 2014)

In acidic aqueous solutions with pH <5, the ion Al^{3+} exists mainly as aluminium hexahydrate $[Al(H_2O)_6]^{3+}$. With increasing pH, a series of successive deprotonations of $[Al(H_2O)_6]^{3+}$ occur to yield $Al(OH)^{2+}$, $Al(OH)_2$ and soluble $Al(OH)_3$, with a corresponding decrease in the number of water molecules. Neutral solutions give an $Al(OH)_3$ precipitate which redissolves, owing to the formation of the aluminate anion $Al(OH)_4^-$; a mixture of these species occurs in the pH range of 5-7, but at pH > 6.2 $Al(OH)_4^-$ is the predominant soluble aqueous species (Martin, 1991).
According to a Cosmetics Europe survey of its members in 2013, more than 50 aluminium-containing substances are used as cosmetic ingredients. The different aluminium compounds have different physicochemical properties, such as solubility in aqueous medium, stability towards hydrolysis at different pH, electric charge etc. (see Appendix 1). These properties can greatly influence the toxicokinetic and toxicodynamic profile of aluminium delivery into the systemic circulation via different routes – oral, dermal and inhalation - and convey unique functions in cosmetic products. By far, the most extensively used aluminium compound in cosmetics is aluminium chlorohydrate in antiperspirants. Current conventional antiperspirants rely on a group of water soluble salts of aluminium and/or zirconium that possess similar insoluble gel-forming properties, such as: aluminium chloride ($AlCl_3$)(AC), aluminium chlorohydrate (ACH), activated aluminium chlorohydrate (AACH), zirconium - aluminium - glycine complexes (ZAG), activated zirconium - aluminium - glycine complexes (AZAG) and zirconium-aluminium complexes (ZACH). Aluminium chlorohydrate is often used in studies since it is one of the more commonly used salts, and can be considered as representative of the common gel-forming antiperspirant mode of action that is shared by this group of salts. Aluminium oxide (alumina) is also an aluminium compound that is a key component in the formation of certain cosmetic colloidal colourant 'lakes'. A 'lake' is any of a class of pigments composed of organic dyes that have been rendered insoluble by interaction with a compound of a metal, sometimes aluminium, but not always. Aluminium lakes of food colourants are permitted food additives in Europe. In cosmetics, lakes are typically used in make-up products such as lipsticks. Alumina and aluminium hydroxide can also be found in toothpaste products as an abrasive. Aluminium may also be present in small traces due to the natural occurrence in mineral based toothpaste ingredients, and sometimes in aluminium lake colourants or pigment minerals such as ultramarine. For the purposes of health risk assessment, the chemical measure of toxicological relevance is the body burden of total aluminium that is delivered systemically from the various sources of exposure. Therefore, this dossier presents an assessment of aluminium and its toxicity. Although focus is on three cosmetic product categories (antiperspirants, lipsticks and toothpastes) identified in the previous SCCS Opinion (SCCS, 2014), it is relevant to the safety assessment of all aluminium containing ingredients that may be used in other cosmetic products. In order to ensure reliable dosing, the critical toxicology studies used for hazard characterisation generally use the most bioavailable forms of aluminium substances, which is consistent with existing EU evaluations performed for aluminium in food and drinking water exposures. An overview on the most commonly used aluminium compounds in cosmetics is given in Annex 1.

Physicochemical properties of aluminium compounds used as cosmetic ingredients are summarised in Annex I.

SCCS comment
In Annex I, the correct CAS No for MICA containing aluminium is 12001-26-2.

3.2 Function and uses

Antiperspirants

Aluminium salts in antiperspirants, such as aluminium chlorohydrate, form insoluble aluminium hydroxide polymer gel plugs within sweat ducts to temporarily prevent sweat reaching the surface of the skin. These substances are soluble at very low pH in the formulation; however, once applied on the skin they form chemically inert complexes with basic components of sweat and skin. The relatively high molecular weight of the compounds, low 'Log P' and high positive charge limits 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 (Hostynek, 2003). These chemical properties limit the systemic delivery of aluminium via the intake skin.

Lipsticks

Aluminium colloidal colorant 'lakes' are mainly used in lipsticks. Colloidal colourants are prepared under aqueous conditions by reacting aluminium oxide with the organic pigments in order to make them insoluble. Aluminium oxide is usually freshly prepared by reacting aluminium sulphate 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 (bioaccessible) part will represent only a fraction.

Toothpastes

Insoluble minerals are used in toothpastes mainly to act as mild abrasives and to provide shine/gloss benefit through the polishing of the enamel. They are also used to improve rheology in striped toothpastes. Toothpastes may also contain aluminium colloidal colourant "lakes" and pigments.

3.3 Toxicological evaluation

The toxicology evaluation is focused on the toxicity of aluminium compounds, as may be relevant to the risk assessment of cosmetics ingredients containing aluminium. There is an extensive body of literature on the health effects and toxicity of aluminium; a number of extensive reviews and authoritative evaluations were published before 2014 (WHO IPCS 1997; Krewski et al., 2007; ATSDR, 2008; EFSA, 2008; FAO/WHO JECFA 2007; Environment Canada & Health Canada 2010; AFSSAPS 2011; FAO/WHO JECFA, 2012; VKM 2013; Willhite et al., 2014). A literature search was performed for relevant aluminium safety data post-2014.

For the 2017 Opinion of SCHEER on aluminium in toys, a literature search covering the period from 01/01/2008 until 31/01/2017 has been performed.

3.3.1 Acute toxicity

3.3.1.1 Acute oral toxicity

The data related to this part were assessed and commented upon by the SCCS in the previous Opinion (SCCS/1525/14, Revision of 18 June 2014). Only new elements, SCCS' comments and main conclusions are included in this section.

SCCS comment
The acute oral toxicity of those aluminium 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).

3.3.1.2 Acute dermal toxicity

According to ATSDR (2008):

'There is limited information on aluminium toxicity following dermal exposure. Application of aluminium compounds to the skin, such as aluminium chloride in ethanol, 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 (Lansdown, 1973).

In terms of systemic toxicity arising following dermal application, ATSDR state 'No studies were located regarding death in humans or animals after dermal exposure to various forms of aluminium.'

3.3.1.3 Acute inhalation toxicity

The data related to this part were assessed and commented upon by the SCCS in the previous Opinion (SCCS/1525/14, Revision of 18 June 2014). Only new elements, SCCS' comments and main conclusions are included in this section.

SCCS comment
The acute inhalation toxicity of aluminium oxide seems to be up to 1,000 mg Al/m^3 in male Fischer 344 rats (Thomson et al., 1986).

3.3.1.4 Acute intraperitoneal toxicity

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3.3.2 Irritation and corrosivity

3.3.2.1 Skin irritation

The data related to this part were assessed and commented upon by the SCCS in the previous Opinion (SCCS/1525/14, Revision of 18 June 2014). Only new elements, SCCS' comments and main conclusions are included in this section.

SCCS comment

The SCCS agrees with the applicant that use concentrations of aluminium compounds in antiperspirants (at doses up to 20% ACH) will not lead to skin irritation in consumers.

3.3.2.2 Mucous membrane irritation / Eye irritation

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3.3.3 Skin sensitisation and dermatitis

Aluminium is not regarded as a skin sensitiser. Aluminium chloride was tested in a murine local lymph node assay (LLNA) at doses up to 25% and there were no indications of a skin sensitisation potential (Basketter et al., 1999). A guinea pig maximisation test (GPMT) for aluminium chlorohydrate (ACH) dosed at 25%, found in the European Chemicals Agency database (ECHA, 1998), indicates that this substance is not sensitising. In addition, there is considerable history of use of aluminium containing cosmetic products with no indication in humans that aluminium is sensitising (AFSSAPS, 2011). In a few instances, sensitisation has been reported following application of aluminium compounds in children with a history of atopy (Goiset et al., 2018).

SCCS comment

The SCCS agrees that the available animal studies show that aluminium compounds used in antiperspirants are not skin sensitising. There is limited evidence that aluminium compounds can cause contact allergy in humans. However, taking into account the widespread use of these compounds, the SCCS considers this to be a rare phenomenon.

3.3.4 Dermal / percutaneous absorption

Dermal absorption of aluminium was initially investigated *in vitro* using mouse skin and *in vivo* in mice (Anane et al., 1995). An *in vitro* study was performed using *ex vivo* human skin (Pineau et al., 2012) and a limited single dose *in vivo* human study has also been performed (Flarend et al., 2001). All of these studies have limitations and following the 2014 SCCS Opinion, a new human clinical study was performed (TNO, 2016, 2019) to assess aluminium absorption from an antiperspirant, under typical consumer use conditions. This study is present in Annex 2.

3.3.4.1 *In vitro* animal skin absorption studies

The data related to this part were assessed and commented upon by the SCCS in the previous Opinion (SCCS/1525/14, Revision of 18 June 2014).

3.3.4.2 Animal skin absorption studies

The data related to this part were assessed and commented upon by the SCCS in the previous Opinion (SCCS/1525/14, Revision of 18 June 2014).

3.3.4.3 *In vitro* human ski absorption studies

The data related to this part were assessed and commented upon by the SCCS in the previous Opinion (SCCS/1525/14, Revision of 18 June 2014).

3.3.4.4 *In vivo* human skin absorption study – single dose

The data related to this part were assessed and commented upon by the SCCS in the previous Opinion (SCCS/1525/14, Revision of 18 June 2014).

3.3.4.5 *In vivo* human skin absorption study – single and repeat dose, in use concentrations

TNO study 2017

In 2014, the SCCS concluded that "internal exposure to aluminium after skin application should be determined using a human exposure study under use conditions." Following the SCCS request for an accurate clinical measurement of skin bioavailability, a clinical study has been performed using the radioisotope ^{26}Al to determine the 'absolute bioavailability' of aluminium from dermal exposure of human volunteers to a representative antiperspirant formulation under in use conditions (TNO, 2016). A brief summary of the study design and conclusions is provided below.
The objective of this first clinical study was to build upon the preliminary dermal study by Flarend et al., 2001, which was effectively a pilot for the TNO study with n=2 (one male, one female) subjects. The intravenous dosing study by Steinhausen et al., 2004, also acted as a pilot study and helped to identify appropriate sampling regimens. A more extensive single and repeat application study was designed that included intravenous dosing to determine the absolute bioavailability of aluminium from dermal exposure to a representative antiperspirant cosmetic formulation. It also addressed the previous concerns of the SCCS regarding the potential impact of shaving the axilla.

SCCS conclusion
After a careful analysis of the study (see SCCS comment in Annex 2), the SCCS considered that it was not appropriate to use it to derive absolute bioavailability. The SCCS concluded that, due to the gaps in the mass-balance of ^{26}Al and the lack of information about how missing amounts might be accounted for, it was impossible to use the results to derive a meaningful inference for skin absorption.
In 2017 the SCCS asked the cosmetics industry for a new clinical study and discussed further issues concerning study design and residual data gaps, particularly referring to the local fate of aluminium and the ability to determine a fraction absorbed (Fabs) value.
Based on that, a new clinical TNO study 2019 (studies 2A and 2B) was performed and results were made available to the SCCS in a dossier study, named 'Refined Safety Evaluation for Aluminium in Cosmetics, using new State-of-the-Art Human Dermal Bioavailability Data (2019)'.

Two new studies were included in this dossier:

- TNO Study 2A: A second follow-up human clinical study on the dermal bioavailability of aluminium was performed during 2018-2019. As was the case for the first study, the time restrictions for generating the new data for regulatory review meant that performing any pilot work was not possible. In view of the reliable detection methodology for urinary ^{26}Al in the first study, the latter acted as a pilot for study 2, where the level of radiolabel in the dermal dose was substantially increased to the maximum that could be dosed.

- TNO Study 2B: this study was performed to provide further support of the presumed extremely low penetration of aluminium through the stratum corneum, and to show that the skin does not act as a 'depot' for aluminium. A satellite study was performed that enabled a more focused investigation on the fate of aluminium on and in the skin.

Study 2A

Study 2A was conducted in a cohort of 6 female subjects with an increased proportion of radiolabel (~25-fold) incorporated into a single dermal dose, a complete urine collection, in 24 h intervals for 10 days, including 3 samples within the first 24 h, and analysis of Al levels on T-shirts, wash (including the gauze), as well as tape stripping and biopsies at the end of the sampling period.

The Samples included:

i) collection of total urine throughout the first 24 hours and up to Day 11 (which was not done in previous TNO study 1)

ii) collection of blood samples

iii) a collection of faeces from Day 1 to 11 in order to get more data on recovery and excretion

iv) analysis of Al on protective gauze & T-shirts, experimental equipment, armpit wash water

v) tape stripping and skin biopsies (where this did not compromise the primary objective due to deviation from real-life consumer exposure scenario)

Furthermore, the dermal dose of radiolabel was increased 25-fold, compared to TNO study 1, in an attempt to measure ^{26}Al in the blood after dermal exposure; the majority of blood samples in TNO Study 1 were below the limit of quantification (LOQ).

A fixed amount of 0.75 g antiperspirant formulation per axilla (1.5 g in total, containing ~2500 Bq [^{26}Al] as [^{26}Al]-ACH and ~20-25% ACH) was applied on each axilla approximately 100 ^{cm2,} on the first day of the first treatment period. For the i.v. dosing, 5 mL of [^{26}Al]-$AlCl_3$ in acetate/citrate-buffered physiological NaCl-solution (1 Bq) was administered on the first day of the second treatment period (Table 1a).

Study – Treatment	Amount	Concentration	Nominal dose	Nominal dose of ^{26}Al
2A - Topical (~2500 Bq)	1.5 g	1797 Bq/g	2695 Bq	3730317 pg
2A – IV (cohort 1)	5 mL	0.017 Bq/mL	0.086 Bq	120 pg
2A – IV (cohort 2)	5 mL	0.014 Bq/mL	0.072 Bq	100 pg
2B - Topical (~1 Bq)	1.5 g	0.76 Bq/g	1.14 Bq	1573 pg

Subjects 01-06 were included in Study 2A, subjects 07-12 were included in Study 2B; cohort 1 (Study 2A) comprised of subjects 01, 03, 04 and 05, cohort 2 (Study 2A) comprised of subjects 02 and 06

Table 1a: Overview of nominal dose applied in Study 2A and Study 2B

For the topical preparation, the average 26Al/27Al ratio for ACH preparation was comprised between 4.29 e^{-05} and 5.18 e^{-6}. For the IV preparation, the total amount of aluminium was 1 µg/mL.

On these specific days, the subjects stayed at the clinical unit overnight for additional pharmacokinetic sample collections. Approximately 48 hours (period 1) and 24 hours (period 2) after administration, the subjects were discharged. Any deviation within 10% of

the time-point determined in the study protocol (clinical period) or 4 hours (for follow-up visits) from the scheduled product administration time points was allowed.
Follow up visits were scheduled on day 4, 8, 15, 22, 29, 38, 39, 43, 50, 57, 64, and 71. Sample delivery by subjects was scheduled for: Day 5, 6, 7, 9, 10, 11, 40, 41, 42, 44, 45, 46. During the execution of the study, pharmacokinetic samples (blood, urine and/or faeces) were collected at each visit. Between visits, subjects collected urine and/or faeces samples at home up to 24h after product administration.

The fraction absorbed is calculated by dividing the dose-corrected fraction excreted following dermal exposure by the dose-corrected fraction excreted following IV dosing: this is multiplied by 100 so that the value can be expressed as a percentage rather than fraction:

Fabs = (Cumulative excretion of ^{26}Al in urine (% of dose) after topical application of ^{26}Al (nominal dose: 3.73 µg)) / (Cumulative excretion of ^{26}Al in urine (% of dose) after IV administration of ^{26}Al (nominal dose: ~110 pg)).

Study 2B

TNO Study 2(B) was performed to provide further support for the presumed extremely low penetration of aluminium through the stratum corneum, and to show that the skin does not act as a 'depot' for aluminium. A satellite study was performed that enabled a more focused investigation on the fate of aluminium on and in the skin. Such investigation using tape-stripping and skin biopsies could not be included in the main study (Part A), as it would have compromised the validity of measuring absolute bioavailability from dermal application to intact skin.
The primary objective was to provide valuable information on how much aluminium remains on the surface of the skin and within the stratum corneum, as well as to allow a better quantification of the amount of formulation lost to the environment.
For this purpose, an additional cohort of 6 female subjects was added to the protocol in part B. In this cohort, tape stripping was performed at unique sites at several time points within the first 24 hours after topical application of a low dose of ^{26}Al, followed by one skin punch biopsy after tape stripping at 24h within the area of the 24h tape strip. These assessments were designed to provide valuable information on how much aluminium remains on the skin surface and within the skin, as well as to allow a better quantification of what happens within the first 24 hours after application.

Subjects visited the clinical unit in the morning of day 1, on which a fixed amount of 0.75 g antiperspirant formulation (1.5 g in total, containing ~1 Bq [^{26}Al] as [^{26}Al]-ACH and ~20-25% ACH) was applied on each axilla approximately 100 cm^2. The subjects stayed in the clinic overnight for tape stripping and a skin punch biopsy procedure. Within the first 24 hours, tape stripping was performed on the axilla at 20 minutes, 1h, 4h, and 24h after applying the ^{26}Al formulation. Tape strips were collected from 4 distinct sites in the central vault of the axilla. A 3 mm skin punch biopsy was performed at 24 h. The end of the study (EOS) visit was performed on day 2.

Results of studies 2A and 2B

<u>Blood Data</u>
Concentrations of ^{26}Al were measured in whole blood and the area under the curve (AUC) was calculated for each subject, as per the methods described in the TNO Study 2 report. The blood concentration profiles for subjects are shown in Figure 1.

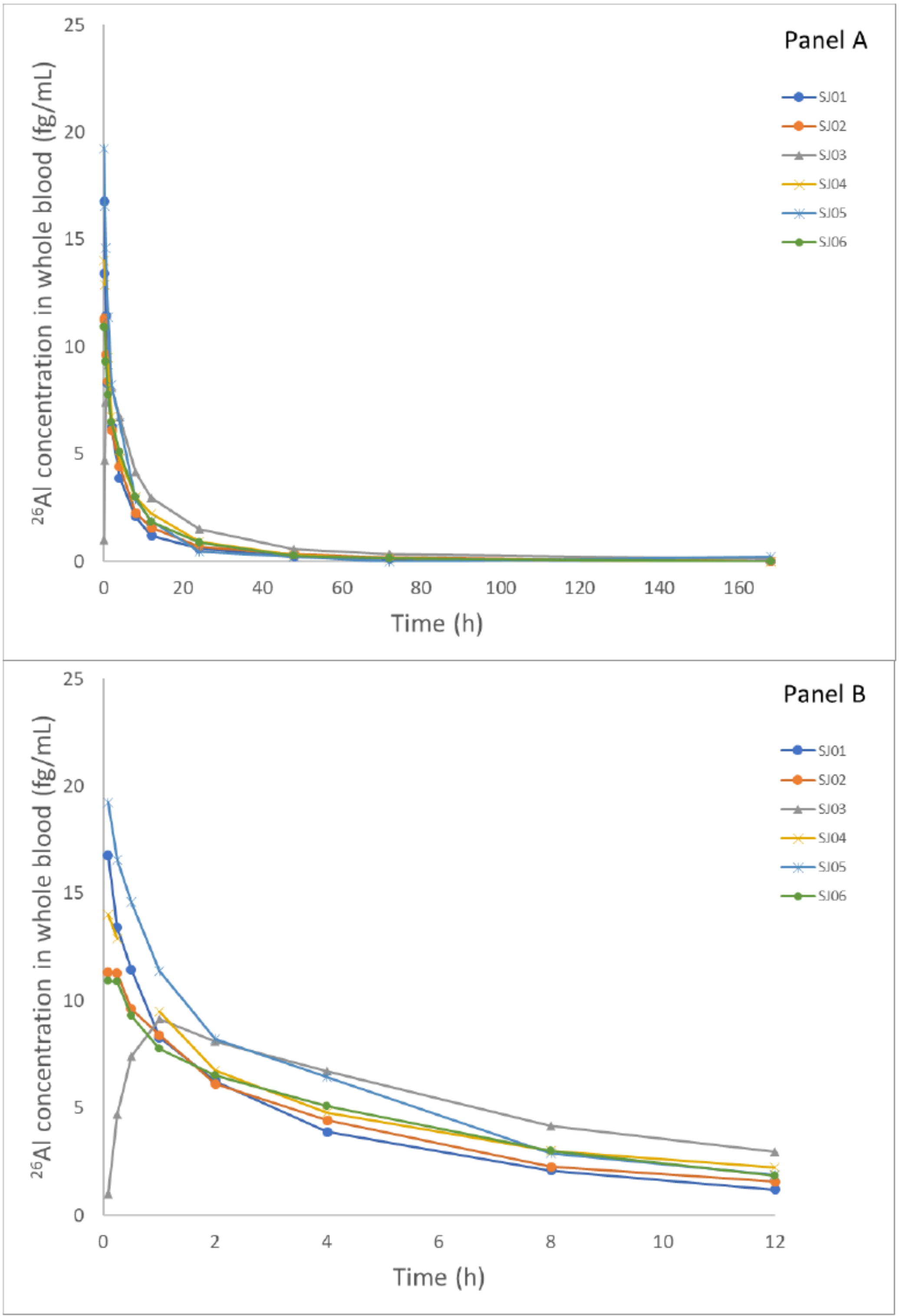

Figure 1 Study 2A: ^{26}Al concentrations in whole blood after IV injection: (A) 0-168h and (B) 0-12h (Panel B).

Note that for one subject (B-SJ03), the vein was missed in the intravenous dosing, and the dosing was actually performed as an intramuscular or subcutaneous dose, hence the different blood profile observed.

The majority of blood samples taken after dermal application of aluminium were below the lower limit of quantification (LLOQ). The LLOQ levels (in fg/mL) were 0.118 fg/mL for whole blood and 0.109 fg/mL for urine. The values have been derived from confidential information provided by the Applicant.

<u>Urine data</u>

Concentrations of ^{26}Al were measured in total urine and the fraction excreted was calculated for each subject, as per the methods described in the TNO Study 2 report. Figure 2 and Table 1 show the cumulative urinary excretion profiles for aluminium following intravenous and topical application. As can be seen, urinary excretion has been monitored until measures were consistently below the LLOQ.

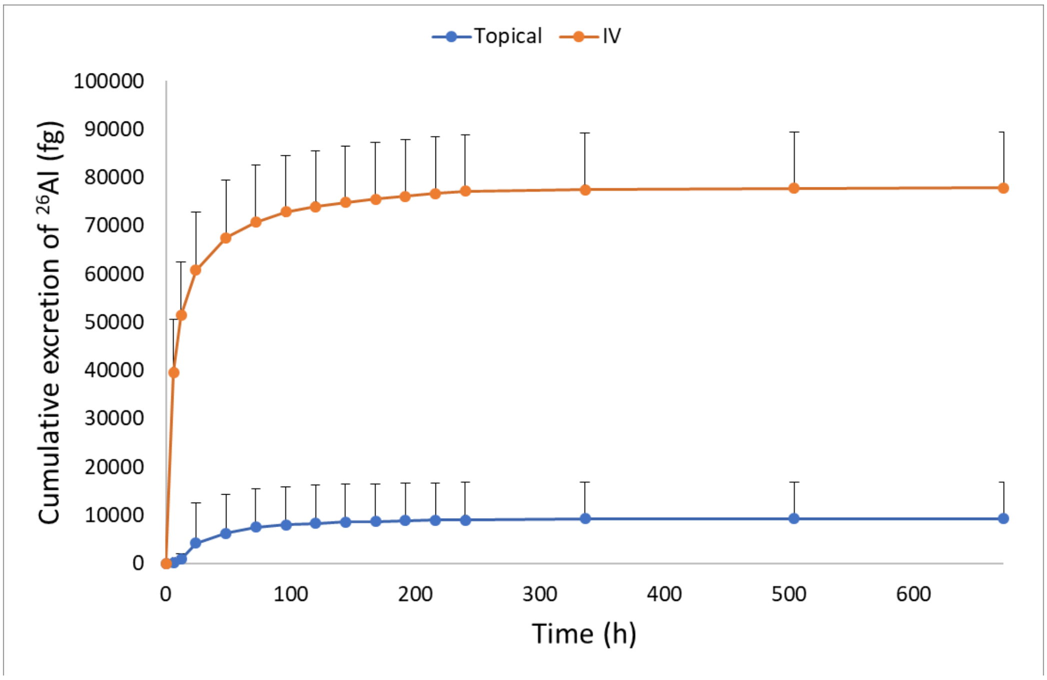

Figure 2 Study 2A: Cumulative urinary excretion of ^{26}Al after topical application or IV injection of ^{26}Al.

	Dermal fraction excreted	IV fraction excreted	Calculated fraction absorbed
SJ01	0.00029%	67.6%	0.00043%
SJ02	0.00072%	66.9%	0.00108%
SJ03	0.00015%	64.6%	0.00022%
SJ04	0.00019%	72.5%	0.00026%
SJ05	0.00031%	79.0%	0.00040%
SJ06	0.00029%	65.0%	0.00045%
Mean	0.00033%	69.3%	0.00047%
SD	0.00021%	5.55%	0.00031%
Mean (excl SJ03)	0.00036%	70.2%	0.00052%
SD (excl SJ03)	0.00021%	5.65%	0.00032%

Table 1 from Study 2A: Fraction of ^{26}Al excreted in urine following the administration of a topical and IV dose and the calculated fraction absorbed are shown. Values <LLOQ replaced with LLOQ.

Faeces Data

Attempts to quantitatively measure ^{26}Al in faeces were made for the first time in this study. Faecal excretion is not an expected route of elimination for aluminium after topical application (Priest et al., 2004; Kremsky et al., 2007). Using new preparation methods, these samples were the most technically challenging to analyse quantitatively. The non-occlusive nature of the study and the potential oral ingestion of very low levels of shed formulation increased the risk of contamination.

The individual measures of aluminium in faeces are provided in the TNO Study 2 report. The mean cumulative 'recovery' in faecal data over 240 hours was 0.0014%. It would be a misinterpretation to include this additional cumulative recovery from faeces, when using an absolute bioavailability method, since no paired faecal samples were collected following i.v. dosing for relative comparison.

Skin Biopsy and Tape Stripping Data

So as not to compromise the primary aim in Study 2A, a separate study of local fate and kinetics in and on the skin was carried out separately in Study 2B. This included an analysis of ^{26}Al in tape-strips at different time points and punch biopsies from the treated axillae, over a 24-hour period (three-millimeter punch biopsies are taken with a maximum of 2 biopsies per subject, one site in the axilla and one control site on the upper back). Some measures of tape strips and a final biopsy at 240 hours were taken in Study 2A, but a local skin profile over 24 hours immediately after dosing could not be taken in this study as it would have compromised other sample analysis.

Tape stripping data over 24 hours are shown (as femtograms (fg) of ^{26}Al per tape strip) in Figure 3 below. It is clear 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, and it was removed from the surface of the skin with time. Between 6-24 hours, a very small amount of measured aluminium could be measured in the tape strips.

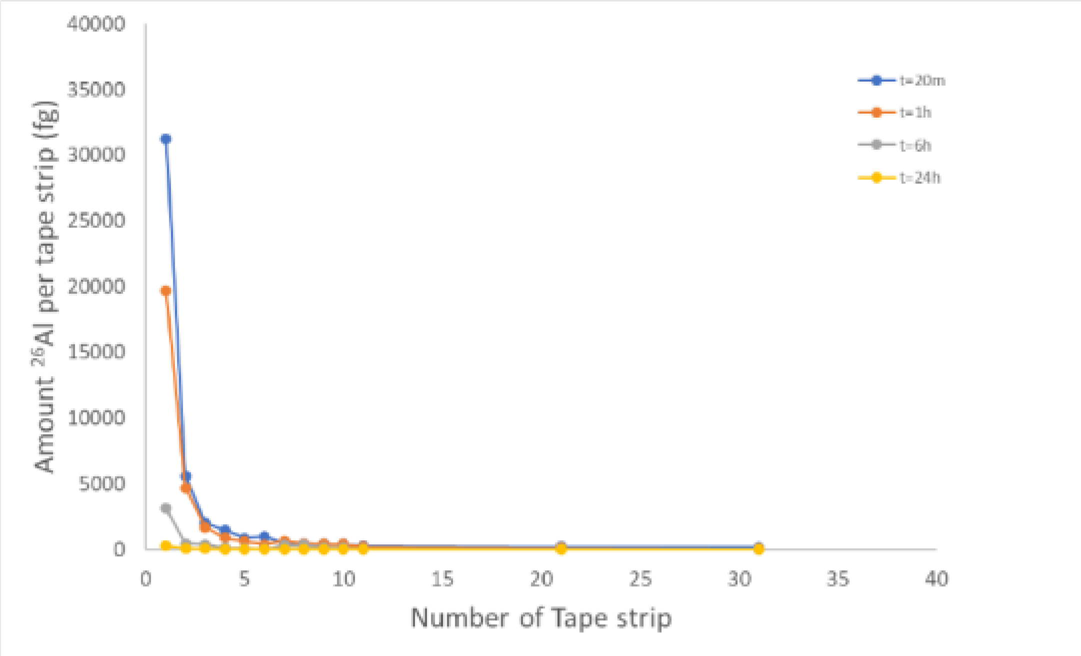

Figure 3 Study 2B: Representation of the amount ^{26}Al (in fg) recovered from tape strips (Reproduced from Figure 4 of the TNO study report).

In Study 2B a 3mm skin biopsy was taken at 24 hours. The recovery was 0.08% of the applied dose in this study. In contrast, in a skin biopsy taken at the end of Study 2A at 840h, only 2 samples (measuring at 0.00003% and 0.00004%) were greater than the LOQ. The recovery calculations were scaled up to the exposed skin area of presumably 200 cm^2.

Extraneous samples
Measurements of ^{26}Al were taken in all circumstances that could account for materials being 'lost to the environment'. These included: fingertips and other experimental equipment used to apply the test material to the axilla, skin wash at 24 and 48 hours and analyses of the semi-occlusive gauze, and T-shirts worn by the subjects at 24 and 48 hours. The recovery of ^{26}Al on these extraneous samples is reported in the TNO Study 2 report. Typically between 4-7% of the nominally applied dose was lost on the fingertips and other experimental equipment. The 'applied dose' used in calculations was therefore corrected for this loss of material given as 'net dose' in the TNO report.

Recovery data
It should be noted that for technical reasons this study is not designed to be a classical mass balance study. The data below provides an indication of the 'recovery' of ^{26}Al in all extraneous and biological samples in Table 2. As mentioned above, the 'applied dose' was corrected for material lost to fingertips and other experimental equipment, therefore the values below are percentages of the 'net dose'.

Sample	Recovery (% of dose) Mean ± SD	Recovery (% of dose) range
Skin wash 24h	62.0 ± 6.6	54.1 – 73.6
T-shirt 24h	6.0 ± 5.5	1.1 – 14.6
Skin wash 48h	1.6 ± 0.8	0.8 – 3.0
T-shirt 48h	0.09 ± 0.03	0.07 – 0.15
Tape strips (168h)	0.0097	0.0019 – 0.0417
Tape strips (840h)	0.0090	0.000004 – 0.0525
Skin biopsy (840h)	0.00004*	0.00003 and 0.00004*
Urine (total during 10 days)	0.0003	0.0001 – 0.0007
Faeces homogenate (total during 10 days)	0.0014	0.0008 – 0.0057
Subtotal	69.7 ± 6.4	58.7 – 76.8

Table 2 Study 2A: Overview of average % of the applied net dose in all samples

In Study 2B, a topical dose of ^{26}Al (1.5 g, 25% ACH, ~1 Bq) was applied to both axillae of 6 additional subjects (Table 1). At 4 different time points (20 min, 1h, 6h and 24h), tape strips were collected from 4 distinct axilla sites and analysed for the amount of ^{26}Al. After tape stripping (24h), a skin biopsy was taken within the tape stripped area and also analysed for the ^{26}Al content. At 20 minutes the majority of the recovered dose was found in the outer tape strip. The % of the applied dose decreased substantially with each sequential tape strip. After 1h, 6h, and 24h following dermal application, tape strips were taken from different sites in the central vault of the axilla. By 24 hours, the total amount recovered decreased to less than 2% of the normalised dose applied.

Conclusions

In this new study, the sensitivity was improved, with a ~25-fold higher level of isotope ^{26}Al in the applied topical dose, so that very low measures of aluminium in urine and blood are observable and quantifiable at levels above the limit of analytical quantification (LOQ). This level of radioactivity using ^{26}Al is the maximum ethically justifiable in a human clinical study.
Improved estimates of aluminium excreted in urine, a 24-hour total urine measurement and measurements over days to below the LLOQ, were evaluated.
Estimation of the aluminium concentration in blood was improved as more samples were measured above the lower LOQ (earlier observed) in TNO Study 2. However, it remains challenging to measure such low levels in blood samples.
Measurements of aluminium on T-shirts and experimental equipment provided robust evidence that the vast majority of the applied dose remains outside the body and is lost, on experimental equipment, clothing or direct loss from the surface of the skin to the

environment.
New measures of aluminium on and in the skin – tape stripping and skin biopsies - showed that the skin does not act as a 'depot' for aluminium and that the aluminium does not absorb into the skin in any appreciable amount. There was a little remaining in the upper layers, and evidence of inward flux through layers of the stratum corneum.
In addition, a satellite experiment (Study 2B), focused on the topical dose. Tape stripping and a skin biopsy were carried out, which showed that >95% of the applied dose remained external to the body.

The rapid equilibration between citrate and transferrin-bound aluminium (Nolte et al., 2001), suggested that differences in clearance between aluminium dosed IV as aluminium citrate and aluminium absorbed from dermally applied aluminium chlorohydrate would have a negligible impact on estimates of absorption using the absolute bioavailability method.

A refined value of fraction absorbed (Fabs) aluminium for risk assessment was determined: 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 mean dermal Fabs value of 0.00052% is regarded as an appropriate value to use in risk assessment.

SCCS comments
Recovery
The SCCS appreciates that the Applicant performed this new study to provide an estimate of the absolute bioavailability of aluminium.
The SCCS notes that the overall recovery of the ^{26}Al applied either topically or after IV injection (Study 2A) was found to be approximately 70%. This is a significantly higher recovery rate compared to the previously published clinical study, where the recovery was below 50% (Flarend et al., 2001). The Applicants consider that the reason for low recovery may be attributable to the 'loss' in the environment (it is possible that radioactive material moved from the surface of the skin to the T-shirt) and this missing quantity of aluminium is not systemically absorbed.

To verify this hypothesis, the Applicant provided a satellite study (Study 2B), where tape stripping was performed at unique sites at several time points within the first 24 hours after topical application of a low dose of ^{26}Al, followed by one skin punch biopsy after tape stripping at 24h. This study provides valuable information on how much aluminium remains on the skin surface and within the skin. It showed that more than 95% of the applied dose remained external to the body within the first 24 hours after application. The stratum corneum of the skin contains up to 20 layers. As shown in Figure 3 Study 2B, virtually all the radioactivity comes off in the first few tape strippings of skin, indicating that the applied labelled substance was confined to external layers of the skin.

In conclusion, considering Study 2B, the SCCS agrees with the Applicant's claim that the low recovery is associated with the losses of non-absorbed material, and this will have minimal impact on the estimation of the dermal absorption of aluminium.

In addition, recent articles have suggested that systemic exposure to aluminium via dermal cosmetics applications does not add significantly to the systemic body burden of aluminium. Chen et al., 2016, and Bretagne et al., 2017, showed that aluminium chlorohydrate formed plugs in the sweat glands of the skin. To test for plug formation, Chen et al., 2016, used imaging techniques, Bretagne et al., 2017, used microfluidic chips that contained aluminium. In a very recent study by Letzel et al., 2019, a potential self-limitation penetration process via the formation of plugs in the sweat glands has to be considered as lowest dermal absorption. These data provide 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 outside the body.

Calculation of absolute bioavailability of aluminium
It is not possible to calculate absolute bioavailability from the blood samples as the majority of blood samples taken after dermal application of aluminium was below the lower limit of quantification (LLOQ). The SCCS notes that no guideline exists for this approach and considers that it remains challenging to calculate the kinetic parameters with a majority of data below the LLOQ.

However, the SCCS considers the approach undertaken by the Applicant is adequate to calculate dermal bioavailability based on the ratio of cumulative fractions of the dose excreted in urine after topical and intravenous applications. The SCCS considers that there are differences in clearance between aluminium citrate (IV administration) and aluminium chlorohydrate (dermally applied).

A recent study published by Weisser et al., 2019, has demonstrated that parenterally administered Al citrate in rats is more rapidly cleared from plasma compared to other Al salts, such as chloride or lactate.

Nevertheless, due to the long follow up (28 days), these differences would have had a negligible impact on the estimates of absorption based on the method used by the Applicant. Under the conditions of the study, the SCCS agrees that dermal bioavailability of 0.00052% is an appropriate value for use in risk assessment.

3.3.5 Repeated-dose toxicity

A full and comprehensive review of all oral dosing repeated-dose studies was performed by EFSA (2008). The most pertinent information is summarised below. More recently (2017), in its Opinion on tolerable intake of aluminium with regards to adapting the migration limits for aluminium in toys, SCHEER performed a literature search covering the period from 01/01/2008 until 31/01/2017.

Data related to toxicity were assessed in the previous Opinion. Only new elements, SCCS' comments and conclusions are included in this section.

SCCS comments on Sub-chronic Rat/ dog oral Studies
When orally administered to rats, aluminium compounds (including aluminium nitrate, aluminium sulfate and potassium aluminium sulfate) have caused various effects, including decreased body weight gain and mild histopathological changes in the spleen, kidneys and livers of rats (104 mg Al/kg bw/day) and dogs (88-93 mg Al/kg bw/day) after subchronic oral exposure. Effects on nerve cells, testes, bone and stomach have been reported at higher doses. Severity of effects increased with dose.

SCCS comments on repeated-dose inhalation toxicity
Neurological examinations in the Steinhagen et al., 1978, publication have been limited to measurement of brain weight and/or histopathology of the brain; no function tests were performed.
The SCCS is of the opinion that the available information does not support concerns regarding potential toxicity of aluminium compounds by inhalation. The lung effects observed in humans and animals are suggestive of particle overload.

Repeated-dose dermal toxicity
There are no repeat dose toxicology studies available via the dermal route of exposure.

3.3.6 Mutagenicity / Genotoxicity

3.3.6.1 Mutagenicity / Genotoxicity *in vitro*

From the previous SCCS Opinion (SCCS/1525/14, Revision of 18 June 2014)

Aluminium compounds have produced negative results in most short-term *in vitro* mutagenic assays, including the Rec-assay using Bacillus subtilis, in Salmonella typhimurium TA92, TA 98, TA102, TA104 and TA1000 strains (with and without S9 metabolic activation), and in Escherichia coli (see Krewski et al., 2007). From *in vitro* studies of rat ascites hepatoma cells it was reported that aluminium chloride could serve as a stimulator for the crosslinking of chromosomal proteins (Wedrychowski et al., 1986a, 1986b, as reported in Krewski et al., 2007, ATSDR 2008). Studies on human blood lymphocytes showed that aluminium chloride could induce positive responses for both micronuclei formation and sister chromatid exchange (see Krewski et al., 2007).

More recently Lima et al., 2007, investigated the genotoxic effects of aluminium chloride in cultured human lymphocytes. Comet assay and chromosome aberrations analysis were used to evaluate DNA-damaging and clastogenic effects of aluminium chloride at different phases of the cell cycle. All tested concentrations (5 to 25 µM aluminium chloride) were cytotoxic, reduced the mitotic index, induced DNA damage and were clastogenic in all phases.

3.3.6.2 Mutagenicity / Genotoxicity *in vivo*

Roy et al., 1991, administered doses of aluminium sulphate and potassium aluminium sulphate in drinking water to male rats at doses ranging from 17 to 171 mg Al/kg bw/d for up to 21 days. The frequency of abnormal cells increased in direct proportion to both the dose and the duration of exposure to the aluminium salts. Most aberrations were chromatid breaks, with translocations recorded at higher doses.

EFSA (2008) concluded:
'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 sulphate was administered at high doses by gavage or by the intraperitoneal route. Several indirect mechanisms have been proposed to explain the variety of genotoxic effects elicited by aluminium salts in experimental systems. Cross-linking of DNA with chromosomal proteins, interaction with microtubule assembly and mitotic spindle functioning, induction of oxidative damage, damage of lysosomal membranes with liberation of DNase, have been suggested to explain the induction of structural chromosomal aberrations, sister chromatid exchanges, chromosome loss and formation of oxidized bases in experimental systems.' EFSA concluded, 'These indirect mechanisms of genotoxicity, occurring at relatively high levels of exposure, are unlikely to be of relevance for humans exposed to aluminium via the diet.'
With respect to cosmetics exposures, the SCCS 2014 Opinion states, 'The SCCS concurs with the EFSA panel conclusions. Aluminium compounds do not cause gene mutations in either bacteria or mammalian cells. Exposure to aluminium compounds does result in both structural and numerical chromosome aberrations both in *in vitro* and *in vivo* mutagenicity tests. SCCS also agrees that the DNA damage is probably the result of indirect mechanisms. The DNA damage was observed only at high exposure levels.'

SCCS comments
A recent and complete analysis of the genotoxic effects of aluminium has been performed by ANSES for ECHA (SEV-231-208-1-1_DEC_Final_Public_5450_en;

https://echa.europa.eu/documents/10162/a2dfbf85-287e-807b-5e2d-37f2d488b5d6). As a result, ECHA requested a combined *in vivo* mammalian erythrocyte micronucleus test and *in vivo* mammalian comet assay with additional specific investigation on oxidative DNA damage in rats by oral route, using aluminium sulphate.

Analysis of the available data, including recent open literature on genotoxicity of soluble aluminium salts (e.g. aluminium chloride, aluminium sulphate, aluminium chloride basic), confirms that:

- the salts 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 level of DNA damage in a comet assay *in vitro*
- it cannot be excluded that the salts may induce chromosomal aberrations *in vivo* (Par et al., 2017).

However, it has to be underscored that the positive results have been reported mostly in the open literature, but generally these studies have some limitations. The most commonly reported mode of genotoxic action was induction of oxidative stress by aluminium ions. The other suggested MoA was inhibition by Al ions of proteins involved in mitotic spindle function. Hence, the existence of a threshold mechanism for genotoxicity of Al ions can be assumed. Considering all the available evidence, the SCCS is of the opinion that aluminium is not likely to pose a risk of systemic genotoxic effects through the dermal exposure from cosmetics use.

3.3.7 Carcinogenicity

The International Agency for Research on Cancer (IARC) (IARC 1987, IARC 2010) concluded that "the available epidemiological studies provide limited evidence that certain exposures in the aluminium production industry are carcinogenic to humans, giving rise to cancer of the lung and bladder."

EFSA (2008) states 'However, the aluminium exposure was confounded by exposure to other agents including polycyclic aromatic hydrocarbons, aromatic amines, nitro compounds and asbestos. There is no evidence of increased cancer risk in non-occupationally exposed persons and IARC did not implicate aluminium itself as a human carcinogen.'

Carcinogenicity studies in animals (Schroeder and Mitchener, 1975a; Schroeder and Mitchener, 1975b; Frash et al., 1992; Oneda et al., 1994; Pott and Roller, 2005) were reviewed and summarised in the SCCS 2014 Opinion on aluminium, and therefore shall not be reviewed here.
SCCS in 2014, concluded 'There was no indication of carcinogenicity at high dietary doses (up to 850 mg Al/kg bw/day) in animal studies, and SCCS considers that carcinogenicity is not expected at exposure levels which are achieved via cosmetic use.'

Updated literature searches were performed for the period following the last SCCS review (2014 to 2015). Whilst preparing the final draft of this dossier, an additional issue-related paper was identified which had been published after the literature searches had been completed. The study of Mandriota et al., 2016, intended to demonstrate that aluminium concentrations, in the range of those measured in the human breast, fully transform cultured mammary epithelial cells, and concluded that aluminium salts could be environmental breast carcinogens. Xenografts of immortalised normal murine mammary gland (NMuMG) epithelial cells, which had been grown in a cell culture medium that had been treated with aluminium chloride (100 μM), were able to form metastatic tumours in immunocompromised 'severe combined immunodeficiency' (SCID) mice, and these

xenografts grew and metastasised more readily than xenograft tumours from untreated cells. This is consistent with their earlier paper where a similarly treated mammary cell line (MCF10A) showed anchorage-independent growth *in vitro* (Sappino et al., 2012).
This study has several limitations which impact the interpretation of the results, particularly with respect to the safety evaluation of aluminium-containing cosmetic products. The exposure scenario being comparable to direct injection of antiperspirant into breast tissue does not reflect real life exposure to antiperspirants. Furthermore, during typical consumer exposure to aluminium from antiperspirant cosmetic products, the speciation (aluminium can be found in different form) of aluminium would change as the small amount absorbed interacts with skin proteins and is influenced by the physiological pH. This is not comparable to the direct addition of aluminium chloride to a cell culture medium. Aluminium salts are well established flocculants used in drinking water treatment. Since aluminium chloride at 100 μM would exceed the limit of solubility in a buffered culture medium (pH 7.4), the flocculant behaviour would most probably have an impact on the presence of protein and essential metal ions in the culture medium. It is plausible that there might be some selection pressure placed on the cells grown under a cell culture medium that had been treated in this way.

As Sappino et al., 2012 note the mouse xenograft models used in the study are well established models for investigating the effects of cancer therapies and pharmaceuticals for which a standardised and reproducible model is required. Such models are neither well established nor validated for toxicological investigations and the relevance of the subtle changes in behaviour in the immunocompromised mouse models for human disease remains to be established. The authors themselves acknowledge the limitations of their study, and propose more epidemiological investigations of antiperspirant use, along with animal studies involving dermal exposure.

The SCCS reviewed the previous Sappino paper as part of its 2014 Opinion, concluding overall that “the available information does not support concerns regarding potential carcinogenicity of aluminium compounds”. The new study uses *in vivo* methods to draw similar conclusions to the previous publication and adds little to extend the earlier study. Again, the lack of consumer-relevant exposure means that this study is difficult to interpret in the context of safety assessment on antiperspirant.

Carcinogenicity of aluminium compounds has been investigated in three mice studies and two rat studies (Annex 1 to SCCS/1525/14, Revision of 18 June 2014). Two of the mice studies and one of the rat studies with aluminium potassium sulfate were performed according to protocols generally accepted for the evaluation of carcinogenicity. In the mice drinking water study, the incidence of leukemia lymphoma increased in the female mice, but not in the male mice, while in the mice feed study no carcinogenic effects were found. In the rat drinking water study, the tumour frequencies increased among male rats but not among the females. All of these three mice studies are old and insufficiently reported. In one mouse study, mesotheliomas were found after intraperitoneal injections and in a rat study, significant increases in benign and/or malignant lung tumours were observed with the 3 types of aluminium compounds studied by intratracheal instillations. It is not possible to draw conclusions in relation to potential carcinogenicity from both studies.

SCCS comment
The SCCS is of the opinion that based on the available information, aluminium from aluminium compounds is not considered to have potential carcinogenicity.

3.3.8 Reproductive toxicity

3.3.8.1 Fertility and reproductive toxicity

Data related to reproductive toxicity were assessed in the previous Opinion and therefore shall not be reviewed here. Only keys elements, SCCS' comments and conclusions are included in this section.

Developmental Toxicity

Although Al-induced maternal and/or embryonic effects were not observed when high doses of Al hydroxide were given by gavage to mice and rats (reviewed extensively in EFSA, 2008), some subtle signs of maternal and developmental toxicity were reported when Al hydroxide was given to mice concurrently with citric or lactic acids (Gomez et al., 1991). This observation stimulated Poirier et al., 2011, to perform a large neurodevelopmental toxicity study with aluminium citrate.
Poirier et al., 2011, reported a 12-month neuro-developmental toxicity study of aluminium citrate. The study in Sprague-Dawley rats was conducted according to a double-blind, vehicle-controlled randomised design by exposing offspring to aluminium citrate in-utero, through lactation, and then via drinking water post-weaning. The study was conducted according to Good Laboratory Practice (GLP) and was conducted to distinguish between cumulative neurodegenerative and cognitive changes from aberrant neural development alterations. Three dose levels were used: 30, 100, 300 mg Al/kg bw/day, in addition to control groups that received either water or a sodium citrate solution (27.2 g/L) compared to 27.2 g sodium citrate/L in the control group. Aluminium citrate was selected for the study since it is the most soluble and bioavailable aluminium salt. It is also the salt which is likely to be formed readily in the body when absorbed aluminium reacts with endogenous citrate.

Pregnant dams (n=20 per group) were exposed to aluminium citrate from gestational day 6 through lactation, and then the offspring (n = 80 per group) were exposed post-weaning until postnatal day 364.
Aluminium citrate was generally well tolerated in the dams at all doses, except the high dose (300 mg Al/kg bw/day) where diarrhea occurred in 8 of the treated dams.

In high-dosed pups the main toxic effects were observed in the urinary tract (damage and the formation of calculi (chalky secretions blocking the urinary tract)), resulting in high mortality in the male offspring (see Table 3 below). This caused a differential response in female and male pups. High-dose males were euthanised on study day 98 because of excessive clinical signs (including weight loss, diarrhoea, mild dehydration and poor hair coat).

Table 3: Rats with urinary tract lesions of hydronephrosis, ureteral dilation, obstruction and/or presence of calculi by sacrifice day group, treatment group and sex (Reproduced from Poirier et al., 2011).

Group	Sex	Collection time			
		Day 23 group	Day 64 group	Day 120 group	Day 364 group
Na citrate	M	0	1	0	0
	F	0	0	1	0
Control	M	0	0	0	0
	F	0	1	0	0
Low dose	M	0	0	0	1
	F	0	0	0	0
Mid dose	M	0	3	1	0
	F	0	1	0	0
High dose	M	0	11	7	5
	F	0	3	2	3

Increase of alkaline phosphatase and serum calcium levels has been observed especially at collection time point day 64. Parameters such as total protein, albumin and globulin were slightly lower (especially on day 64). Other clinical chemistry changes in males were consistent with the physiological effects resulting from a blocked urethra.
In terms of general development, landmarks of development (vaginal opening for females and preputial separation in males) were delayed in the sodium citrate control group and high-dose (300 mg aluminium citrate /kg bw/day) (see Table 4 below). Delayed sexual maturity was observed in the high-dose groups (300 mg Al/kg bw/day) of both sexes.

Table 4: Summary statistics for developmental landmarks by group and pup gender (vaginal opening for the females and preputial separation for the males)

Parameter	Sex	Statistic	Na citrate	Control	Low dose	Mid dose	High dose
Number of days to landmark	M	Mean	41.1	39.6	39.3	39.4	42.5
		SD	2.4	2.1	1.5	1.9	3.2
	F	Mean	35.3	31.3	32.1	32.4	39.7
		SD	2.9	2.1	2.5	2.1	5.6

Many behavioural effects were analysed in the study. However, aluminium exposure did not seem to be associated with any autonomic or sensimotor dysfunction. There was, however, a weak association between high Al exposure and reduced home cage activity, excitability.

No major neurological pathology or neurobehavioral effects were observed, other than in the neuromuscular subdomain in pups (reduced grip strength and increased foot splay). Thus, based on this effect, the lowest observed adverse effect level (LOAEL) was 100 mg aluminium citrate /kg bw/day and the no observed adverse effect level (NOAEL) was 30 mg aluminium citrate /kg bw/day.

In the same study, Poirier also evaluated the relative distribution of aluminium following repeated oral administration of various aluminium salts. Sprague–Dawley rats (n= 5 per sex per group) were orally gavaged with formulations of aluminium citrate, sulphate, nitrate, chloride and hydroxide, each delivering a dosage of 30 mg/kg body weight aluminium. Control animals were similarly dosed with deionised water. Animals were dosed daily for either 7 days or 14 days, followed by blood and organ collection. The distribution and concentrations of aluminium present in different tissues and organs, were measured by ICP-Mass Spectrometry. From this analysis, concentrations in the blood were much lower than those that distributed heterogeneously into other tissues and organs, in both females and males. However, as ^{26}Al was not used as a tracer, it is not possible to know the real bioavailability of the administered dose. Given effects were seen at the high dose and differences were seen in aluminium levels in blood and tissues, it can be said with confidence that aluminium was delivered systemically via the oral route in drinking water. However, the absolute oral bioavailability is unknown in this study. The authors conclude from their data that 'bioavailability of the three Al salts (chloride, sulfate and nitrate) and the Al hydroxide looks much lower than that of the Al citrate'.

SCCS comment
Based on the results of this neurodevelopmental toxicity study, the SCCS derives a NOAEL of 30 mg/kg bw/d, which will be used for MoS calculation. This is in line with SCHEER (2017), where the same NOAEL from the same study was used to derive migration limits for Al in toys.

3.3.8.2 Two generation reproduction toxicity

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3.3.9 Toxicokinetics

3.3.9.1 Toxicokinetics in laboratory animals

Data related to toxicokinetics in animals (absorption, distribution, metabolism and elimination) were considered in the previous Opinion (SCCS/1525/14, Revision of 18 June 2014) and therefore is not reviewed here. Only the keys elements, SCCS' comments, and conclusions are included in this section.

3.3.9.2 Toxicokinetics in humans

Oral Absorption
In the study on humans of Priest et al., 1996, the oral fraction absorbed of aluminium citrate in drinking water was 0.5%. In an earlier study on humans, where aluminium citrate was administered via drinking water, the fraction absorbed was calculated as being 0.22% (Priest et al., 1995). In a third study, Stauber et al., 1999, estimated the absorbed fraction of stable aluminium citrate from drinking water to be 0.36%. EFSA (2008) concluded that a value of 0.3% oral bioavailability was appropriate to use in human risk assessment for soluble aluminium in drinking water (i.e. without food) and 0.1% with food.

SCCS comments
Under the conditions of the EFSA study, the SCCS agrees that oral bioavailability of 0.1% is an appropriate value for use in risk assessment.

Taken together, all available data suggest that absorption of aluminium from lung deposits into the blood is low. For the purposes of lung exposure modelling and risk assessment, a

conservative value for aluminium uptake by the lung is 3% (Jones & Bennett, 1986; DeVoto & Yokel, 1994).
Human and animal studies cited in the current Opinion suggest that the urinary excretion of aluminium is multiphasic, and the TNO study 2019 has shown that after a single IV injection of ^{26}Al citrate in healthy subjects, more than 50% of the Al administered is excreted within the first 24h in the urine. It is known that the remaining amounts of ^{26}Al are eliminated extremely slowly (Priest, 2004).

3.3.10 Photo-induced toxicity

3.3.10.1 Phototoxicity / photo-irritation and photosensitisation

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3.3.10.2 Photomutagenicity / photoclastogenicity

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3.3.11 Human data

Breast cancer and aluminium containing cosmetics

Data related to breast cancer and cosmetics containing aluminium were developed in the previous Opinion and therefore shall not be reviewed here. Only keys elements, SCCS' comments and conclusions are included in this section.

In a case–control study (including 209 women with breast cancer and 209 healthy controls (Linhart et al., 2017), the authors suggest that the frequent use of underarm cosmetic products lead to an accumulation of aluminium in breast tissue. An increased risk for breast cancer was observed in women who reported to use antiperspirants more than once daily starting at an age below 30 years. Self-reported frequent historical use of underarm cosmetic products is apparently not a main source of aluminium in breast cancer.
This study is mainly based on correlation analyses and does not prove causal links (the authors state that "we cannot exclude a reverse causation effect, meaning that the breast tumor may accumulate aluminium.")

SCCS is of the opinion that the epidemiological studies do not support the hypothesis that the use of aluminium-containing cosmetics may affect the risk of breast cancer.

Effects of aluminium on the CNS

Several publications are related to effects of aluminium on the central nervous system and a possible relationship between aluminium exposure and mental diseases. The central nervous system is particularly sensitive to metal-induced oxidative stress and impact of aluminium on cell signalling, neurotransmission, and cell redox status has been the most investigated critical effect for the nervous system (Verstraeten et al., 2008; Chaitanya et al., 2012; Shrivastava, 2012; Yuan et al., 2012). The greatest complications of aluminium toxicity are neurotoxic effects such as neuronal atrophy in the locus ceruleus, substantia nigra and striatum (Neeshu et al., 2016).

Aluminium and neurodegenerative diseases

The neurotoxic effects of aluminium have been postulated to have links with Alzheimer's disease. The encephalopathy effects seen in kidney dialysis patients who have been highly exposed to aluminium (Alfrey et al., 1976) might have led to suspicions that aluminium could have effects in the brain. However, after significant investigation, it is generally accepted that there is no causal link between aluminium and Alzheimer's disease (Wisniewski et al., 1991). The 2011 AFSSAPS report reviewed the epidemiological data available at that time, concluding that there is no evidence that aluminium-based antiperspirants are associated with putative systemic toxic endpoints, such as Alzheimer's disease (AFSSAPS, 2011). More broadly, JECFA considered that "Although recent studies do not definitively rule out a positive association between aluminium in drinking-water and Alzheimer disease, the information available remains inconsistent and does not support a causal association" (JECFA, 2011). The World Health Organisation (WHO) reached the conclusion that increased aluminium intake is very unlikely to be a causal factor for Alzheimer's disease (IPCS, 1997).

SCCS in 2014 concluded that 'SCCS considers that aluminium (Al) is a known neurotoxicant in animal and circumstantial evidence has linked this metal with several neurodegenerative disorders like Alzheimer's disease (Miu and Benga, 2006; Percy et al., 2011), Parkinson's disease (Oyanagi, 2005) and other chronic neurodegenerative diseases (Bondy, 2010), but no causal relationship has yet been proven. Relevant publications published afterwards also came to the conclusion that there is no consistent and convincing evidence to associate the chemical forms of aluminium and concentrations found in food and drinking water in North America and Western Europe with increased risk for Alzheimer's disease (SCHEER, 2017).

Aluminium-Induced Bone Disease (AIBD)

A single medical case report was identified that reported on toxic effects resulting from antiperspirant exposure (Guillard et al., 2004). The patient suffered from bone pain and anaemia, which the author considered to be caused by her daily use of an antiperspirant cream, and possibly associated with shaving-related damage to the skin barrier. However, case reports are often difficult to interpret and it is not possible to determine from this report whether the effects described were caused by or coincidental to the antiperspirant use; until yet no causal relationship has yet been proven.

3.3.12 Special investigations

Other source of exposure

The SCCS notes that antiperspirant use has a minor impact on the body burden of aluminium (due to its very low dermal bioavailability as shown in the current Opinion), in contrast to uptake via nutrition or vaccination.
In its 2017 Opinion, SCHEER identified several sources of aluminium exposure including cosmetic products. Aluminium is found in pharmaceuticals (anti acid, vaccine adjuvant) and in flame retardants in different materials, including children's toys. According to Klotz et al., 2017, an aluminium dose of 0.1–0.8 mg is absorbed after IM application of a vaccine approved in Europe, and concerns have been expressed whether vaccines may pose a risk to infants. In the US, Mitkus et al., 2011, calculated and compared the body burden of aluminium from vaccines and diet throughout an infant's first year of life. The authors concluded that episodic exposures to vaccines do not contribute significantly to the body burden of aluminium compared to others sources (food).

Effects of aluminium on the immune system

In its 2017 Opinion, SCHEER quoted a review from Zhu et al., 2013. These authors analysed the effects of aluminium (with focus on aluminium-containing adjuvant in vaccine) on components of the immune function (autoimmunity, oral tolerance, expression of the immune cells, hypersensitivity and erythrocyte immune function). The authors stated that the effects of aluminium on the immune function are controversial, and consider the need for further investigations to explore if aluminium has immunotoxic effects.
The SCCS is of the opinion that no clear conclusions can be drawn regarding the effects of aluminium on the immune system.

3.3.13 Consumer Exposure assessment

Dermal exposure

Antiperspirants

Cosmetics Europe data show that average (median) consumers apply 0.82 g/day of non-spray deodorant/antiperspirant, rising to 1.5 g/day for 90th percentile high-level consumers (Hall et al., 2007). Following the SCCS Notes of Guidance (10th Revision), the 90th percentile product exposure for non-spray deodorants/antiperspirants can be expressed on a bodyweight basis as 22.08 mg product/kg bw/day (SCCS/1602/18).

Thus, at 6.25% aluminium (from aluminium chlorohydrate or ACH) for a high-performing non-spray antiperspirant, assuming exposure at 22.08 mg product/kg bw/day, the dermal exposure to aluminium would be 1.38 mg aluminium chlorohydrate /kg bw/day (0.0625 x 22.08 mg/kg/day). Using the dermal fraction absorbed value of 0.00052%, from the human clinical TNO Study 2, where ACH was applied under in-use conditions in females, the systemic exposure of aluminium via dermal application of non-spray antiperspirants is 0.007 µg/kg bw/day.

This is expressed mathematically in the following calculation for systemic exposure dose (SED) as per the SCCS 10th Notes of Guidance (SCCS/1602/18).

$$\boxed{SED = E_{product} \times \frac{C}{100} \times \frac{DA_p}{100}}$$

Where:
SED (mg/kg bw/day) Systemic Exposure Dose

$E_{product}$ (mg/kg bw/day) Estimated daily exposure to a cosmetic product per kg body weight, based on the amount applied and the frequency of application (for calculated relative daily exposure levels for different cosmetic product types (SCCS/1602/18).

C (%) Concentration of the substance under study in the finished cosmetic product on the application site

DAp (%) Dermal Absorption expressed as a percentage of the test dose assumed to be applied in real-life conditions

Therefore, for non-spray antiperspirants:
SED = 22.08 (mg/kg bw/day) x 6.25/100 x 0.00052/100 = 0.007 µg/kg bw/day

The mean cumulative 'recovery' in faecal data was 0.0014%. When the SCCS took into account the amount of radiolabelled aluminium found in urine and faeces, a value of dermal bioavailability of 0.00192% could be estimated (0.00052% +0.0014%).
Therefore, for non-spray antiperspirants, taking account the amount of radiolabelled aluminium found in urine and faeces, for the estimations of dermal bioavailability was:
SED = 22.08 (mg/kg bw/day) x 6.25/100 x 0.00192/100 = 0.0265 µg/kg bw/day
Using the dermal fraction absorbed value of 0.00192% from the human clinical study, where ACH was applied under in use conditions in females, the systemic exposure of aluminium via dermal application of non-spray antiperspirants is 0.0265 µg/kg bw/day.

For spray antiperspirants, which are generally non-ethanol based formulations due to incompatibility of antiperspirant actives and alcoholic formulations, dermal product exposure is 10 mg product/kg bw/day (SCCS, 2018). This product exposure value excludes the propellant (Steiling et al., 2012). Taking the formulation that had the highest experimental respirable dose measurement, the 'Compressed 2' product contained 27% non-volatiles (with 70% propellant and 3% fragrances). Since aluminium is 2.86% of the full Compressed 2 formulation, aluminium would be 10.6% of the non-volatile fraction. Therefore, 1.06 mg/kg bw/day of aluminium is applied to the skin (10.6% of 10 mg/kg bw/day). Taking the dermal absorption of 0.00052% from the second TNO skin absorption study, the associated systemic exposure via the skin would be 0.006 µg/kg bw/day (0.00052% of 1.06 mg/kg bw/day).

Therefore, for spray antiperspirant products:

SED = 10 (mg/kg bw/day) x 10.6/100 Al x 0.00052/100 = 0.006 µg/kg bw/day

Using the dermal fraction absorbed value of 0.00052% from the human clinical study, where ACH was applied under in use conditions in females, the systemic exposure of aluminium via dermal application of spray antiperspirants is 0.006 µg/kg bw/day.

The mean cumulative 'recovery' in faecal data was 0.0014%. When the SCCS took into account the amount of radiolabelled aluminium found in urine and faeces, a value of dermal bioavailability of 0.00192% could be estimated (0.00052% +0.0014%).
Therefore, for spray antiperspirants, taking account the amount of radiolabelled aluminium found in urine and faeces, for the estimations of dermal bioavailability was:

SED = 10 (mg/kg bw/day) x 10.6/100 Al x 0.00192/100 = 0.0204 µg/kg bw/day

Using the dermal fraction absorbed value of 0.00192% from the human clinical study, where ACH was applied under in use conditions in females, the systemic exposure of aluminium via dermal application of spray antiperspirants is 0.020 µg/kg bw/day.

The calculated values above of SED from antiperspirants containing 6% ACH are used in the safety evaluations in Tables 5 (a,b) and 6 (a,b).

Oral exposure

Lipsticks

In the Norwegian Scientific Committee for Food Safety Risk Assessment (Norwegian VKM, 2013), 11 marketed lipstick/lip gloss products were assayed for the total aluminium content. The median value of total aluminium in lipsticks was 0.77% and the maximum level found was 2.8%.

Using the VKM cited maximum level as a worst case evaluation. The daily intake from the maximal 2.8% Al in lipstick would be 2.8% x 0.9mg product/kg bw/day = 0.0252 mg Al/kg/day(SCCS,2018). If one assumes the bioaccessible fraction is 7%, then the bioaccessible amount is 0.00176 mg Al/kg/day in soluble form. Assuming (conservatively) that 0.3% absorbs across the gut wall (EFSA, 2008), then 0.00528 µg/kg bw/day maximally could be systemically bioavailable.

Using the Norwegian VKM cited median level as a realistic safety evaluation, the daily intake from the median 0.77% Al in lipstick would be 0.77% x 0.9 mg product/kg bw/day = 0.00693 mg Al/kg/day. If one assumes the bioaccessible fraction is 7%, then the bioaccessible amount is 0.485 µg Al/kg/day in soluble form. Assuming (conservatively) that 0.3% absorbs across the gut wall (EFSA, 2008), then 0.0015 µg/kg bw/day maximally could be systemically bioavailable.

The intake value of 0.0015 µg/kg bw/day is used in the safety evaluation. This is based upon the median level of aluminium in lipstick, with the conservative assumption of complete 100% ingestion of applied product and the conservative assumption (based upon data) of 7% oral bioavailability, which was calculated using lipstick ingredients and is expected to be even lower from a waxy lipstick product matrix.

Toothpaste

Using the SCCS Notes of Guidance 10th revision (SCCS/1602/18) for toothpaste, the estimated daily exposure is 2.75 g/day for the 90th percentile high level consumer and it is assumed that 5% of the toothpaste used to clean teeth is swallowed, resulting in 2.16 mg product/kg bw/day for a 60kg adult (SCCS, 2018).
Based on a survey of Cosmetic Europe members in 2013, toothpaste currently on the EU market contains a maximum level of 5% aluminium oxide (equivalent to 2.65% aluminium). Thus of 2.16 mg product/kg bw/day, 57µg Al/kg bw/day would be ingested.
Using an oral bioavailability value for Al oxide of 0.1%, the systemic exposure dose for adults (60 kg) is calculated to be 0.057 µg Al/kg bw/day. This value is used in the safety evaluation.

Inhalation exposure

Meech et al., 2011, used an experimental measure of lung exposure to assess the intake from inhalation exposure. The same values used in risk assessment are:
Respirable in deep lung = 0.00781 µg/kg bw/day.
Respirable dose deposited in upper respiratory tract = 0.00234 µg/kg bw/day.
Non-respirable dose = 0.000432 µg/kg bw/day.
The methodology used in the 2016 dossier next to the respirable dose method has also been recently published in Schwarz et al., 2018.

3.5 SAFETY EVALUATION (including calculation of the MoS)

The Margins of Safety for each of the three cosmetic product types, antiperspirants, lipstick and toothpaste are presented in Table 5 a (considering non-spray antiperspirants) and Table 6 a (considering spray antiperspirants). Each product is considered individually in terms of the MoS for systemic effects.
A total systemic body burden has been calculated assuming that all 3 product types are used on the same day.

Taking the NOAEL of 30 mg aluminium citrate/kg bw/day from the neurodevelopmental rat study (Poirier et al., 2011) and adjusting by the rat oral bioavailability (0.6%) of aluminium citrate (Poirier et al., 2011, Zhou et al., 2008), the systemic exposure at the NOAEL is estimated to be **180 µg Al/kg bw/day**. This value is used as a point of departure for the safety assessment.

Table 5a: Overall margin of safety calculations for antiperspirant non-spray products (dermal exposure only), lipstick and toothpaste and a total body burden calculation to account for potential simultaneous exposure.

Product type	**Systemic Exposure (internal dose) µg Al/kg bw/day**	**MoS (based on an internal dose POD of 180 µg Al/kg bw/day)**
Dermal exposure		
Antiperspirant (roll-on/stick)	0.007	25,714
Oral exposure		
Lipstick	0.0015	120,000
Toothpaste	0.057	3,158
Total Systemic Body Burden	0.0655	2,748

When the SCCS took into account the amount of radiolabelled aluminium found in urine and faeces for the estimations of dermal absorption (e.g. a dermal absorption of 0.00192%), it did not alter the overall safety assessment (Table 5 b):

Table 5b: Overall margin of safety calculations for antiperspirant non-spray products (dermal exposure only), lipstick and toothpaste and a total body burden calculation to account for potential simultaneous exposure and considering dermal absorption of 0.00192%.

Product type	**Systemic Exposure (internal dose) µg Al/kg bw/day**	**MoS (based on an internal dose POD of 180 µg Al/kg bw/day)**
	Dermal exposure	
Antiperspirant (roll-on/stick)	0.0265	6,792
	Oral exposure	
Lipstick	0.0015	120,000
Toothpaste	0.057	3,158
Total Systemic Body Burden	0.085	2,117

Table 6a: Overall margin of safety calculations for antiperspirant spray products (dermal and inhalation exposure), lipstick and toothpaste and a total body burden calculation to account for potential simultaneous exposure.

Product type	**Systemic Exposure (internal dose) µg Al/kg bw/day**	**MOS (based on an internal dose POD of 180 µg Al/kg bw/day)**
	Dermal exposure	
Antiperspirant (spray)	0.006	30,000
	Oral exposure	
Lipstick	0.0015	120,000
Toothpaste	0.057	3158
	Inhalation exposure (systemic)	
Antiperspirant sprays/aerosols (Respirable in deep lung)	0.00781	23,047
Antiperspirant sprays/aerosols (Respirable deposited in upper respiratory tract)	0.00234	76,923
Antiperspirant sprays/aerosols (Non-respirable)	0.000432	416,667
Total Systemic Body Burden	0.075	2,400

When the SCCS took into account the amount of radiolabelled aluminium found in urine and faeces for the estimations of dermal absorption (e.g. a dermal absorption of 0.00192%), it did not alter the overall safety assessment (Table 6 b):

Table 6b: Overall margin of safety calculations for antiperspirant spray products (dermal and inhalation exposure), lipstick and toothpaste and a total body burden calculation to account for potential simultaneous exposure and considering dermal absorption of 0.00192%.

Product type	Systemic Exposure (internal dose) µg Al/kg bw/day	MOS (based on an internal dose POD of 180 µg Al/kg bw/day)
Dermal exposure		
Antiperspirant (spray)	0.0204	8,823
Oral exposure		
Lipstick	0.0015	120,000
Toothpaste	0.057	3158
Inhalation exposure (systemic)		
Antiperspirant sprays/aerosols (Respirable in deep lung)	0.00781	23,047
Antiperspirant sprays/aerosols (Respirable deposited in upper respiratory tract)	0.00234	76,923
Antiperspirant sprays/aerosols (Non-respirable)	0.000432	416,667
Total Systemic Body Burden	0.0895	2,011

3.6 DISCUSSION

Function and uses
A variety of aluminium salts, complexes and mineral compounds are used as cosmetics ingredients, e.g. as antiperspirants, toothpaste or in lipstick (see Annex I).

Physicochemical properties
Physicochemical properties of aluminium compounds used as cosmetic ingredients are given in Annex I; in this Annex the correct CAS No for MICA containing aluminium is 12001-26-2

General toxicity
The toxicological evaluation is focused on the toxicity of aluminium compounds relevant to the risk assessment of cosmetics ingredients containing aluminium. There is an extensive body of literature on the health effects and toxicity of aluminium; a number of extensive reviews and authoritative evaluations were published before 2014 (WHO IPCS 1997; Krewski et al., 2007; ATSDR, 2008; EFSA, 2008; FAO/WHO JECFA 2007; Environment

Canada & Health Canada 2010; AFSSAPS 2011; FAO/WHO JECFA, 2012; VKM 2013; Willhite et al., 2014).

For the 2017 SCHEER Opinion on aluminium in toys, a literature search covering the period from 01/01/2008 until 31/01/2017, was performed. The evaluation by JECFA (2011) was based on new data which included a developmental toxicity study specifically evaluating neurobehavioural endpoints (Poirier et al., 2011). The LOAELs identified in these studies were consistent with the body of data reviewed previously by the other committees; however, the oral developmental toxicity study in rats provided a suitable and robust NOAEL for risk assessment (30 mg/kg bw/day). By applying the standard uncertainty factor of 100 to this NOAEL and considering the bioavailability of aluminium citrate, the JECFA considered it appropriate to revise the PTWI (provisional tolerable weekly intake) upward to 2 mg/kg bw/week. This new data by the JECFA Committee therefore supersedes its earlier Opinions in 2008, and does not contradict the 2008 EFSA Opinion. The SCCS agrees on the NOAEL of 30 mg/kg bw/day used by JECFA for risk assessment.

Irritation/sensitisation

Local dermal effects have been observed when aluminium compounds (10% w/v chloride, nitrate) have been applied to the skin of mice, rabbits and pigs over five-day periods (once per day) including epidermal damage, hyperkeratosis, acanthosis and microabcesses (Lansdown, 1973). In this study, these effects were not seen with aluminium acetate, hydroxide or chlorohydrate compounds.

Aluminium compounds are widely used in antiperspirants without acute harmful effects to the skin. Some people, however, may be unusually sensitive to topically-applied aluminium compounds. Skin irritation has been reported in human subjects following the application of aluminium chloride hexahydrate in ethanol used in a high-dose (20% ACH) formulation for the treatment of axillary or palmar hyperhidrosis (excessive sweating) (Ellis and Scurr, 1979; Goh, 1990; Reisfeld & Berliner, 2008) and after use of a crystal deodorant containing alum (Gallego et al., 1999).

Although some high-strength antiperspirants used in hyperhidrosis treatments, using aluminium chloride, have been associated with irritation of the axilla, the long history of cosmetic antiperspirant use would suggest that irritation of the axilla is uncommon. There are several examples of cosmetic product formulations that include raw materials that are irritant in isolation, yet acceptable amongst consumers (e.g. surfactants, menthol).

The SCCS agrees that the available animal studies show that aluminium compounds used in antiperspirants are not skin sensitising. There is limited evidence that aluminium compounds can cause contact allergy in humans. However, taking into account the widespread use of these compounds, the SCCS considers this to be a rare phenomenon.

Dermal absorption

In the new study described in the Opinion, the Applicant provided an estimate of the aluminium bioavailability after dermal exposure. The SCCS agrees that a dermal Fabs value of 0.00052% is an appropriate value to use in risk assessment.

Mutagenicity/Genotoxicity

The most commonly reported mode of genotoxic action is induction of oxidative stress by aluminium ions. The other suggested MoA is inhibition by Al ions of proteins involved in mitotic spindle function. Hence, an existence of a threshold mechanism for Al ions can be assumed. Considering all the data, the SCCS is of the opinion that under the scenarios of dermal exposure in cosmetics, aluminium is not likely to pose a risk of genotoxic effects.

The SCCS is aware of the request addressed by ECHA for combined *in vivo* mammalian erythrocyte micronucleus test and *in vivo* mammalian Comet assay with additional specific investigation on oxidative DNA damage in rats by oral route, using aluminium sulphate.

Carcinogenicity
Carcinogenicity studies in animals have been reviewed by SCCS and are summarised in the Annex of the previous Opinion ((SCCS/1525/14, Revision of 18 June 2014). There was no indication of carcinogenicity at high dietary doses (up to 850 mg Al/kg bw/day) in animal studies, and the SCCS considers that carcinogenicity is not expected at exposure levels that are achieved via cosmetic use.

Toxicokinetics
Aluminium compounds present in food and drinking water are poorly absorbed through the gastrointestinal tract in animals and humans.
Several small scale human studies estimated aluminium absorption efficiencies of 0.07–0.39% following administration of a single dose of the radionuclide aluminium-26 (^{26}Al) in drinking water (Hohl et al., 1994; Priest et al., 1998; Stauber et al., 1999; Steinhausen et al., 2004). Fractional absorption was estimated by measuring aluminium levels in urine; it is likely that most of these studies (with the exception of Stauber et al., 1999) underestimated gastrointestinal absorption because the amount of aluminium retained in tissues or excreted by non-renal routes was not factored into the absorption calculations. Several animal studies also utilised ^{26}Al to estimate aluminium bioavailability from drinking water. When aluminium levels in urine and bone were considered, absorption rates of 0.04–0.06% were estimated in rats (Drueke et al., 1997; Jouhanneau et al., 1993); when liver and brain aluminium levels were also considered, an absorption rate of 0.1% was estimated (Jouhanneau et al., 1997). Another study that utilised a comparison of the area under the plasma aluminium concentration-time curve after oral and intravenous administration of ^{26}Al estimated an oral aluminium bioavailability of 0.28% (Yokel et al., 2001).
Two human studies examined the bioavailability of aluminium in the diet. An absorption efficiency of 0.28–0.76% was estimated in subjects ingesting 3 mg aluminium lactate/day (0.04 mg Al/kg/day) or 4.6 mg aluminium citrate/day (0.07 mg Al/kg/day) (Greger and Baier 1983; Stauber et al., 1999). When 125 mg Al/day (1.8 mg Al/kg/day) as aluminium lactate in fruit juice was added to the diet, aluminium absorption decreased to 0.094% (Greger and Baier, 1983). Yokel and McNamara (2001) suggested that the bioavailability of aluminium from the diet is 0.1% based on daily urinary excretion levels of 4–12 µg and average aluminium intake by adults in the United States of 5,000–10,000 µg/day.
Considering the available human and animal data as discussed above, it is likely that the oral absorption of aluminium can vary 10-folds, based on the chemical form alone. Although bioavailability appears to generally parallel to water solubility, insufficient data are available to allow direct extrapolation from solubility in water to bioavailability. Additionally, due to the available dietary ligands, such as citrate, lactate, and other organic carboxylic acid complexing agents, the bioavailability of any particular aluminium compound can be markedly different in the presence of food than under empty stomach conditions.

Aluminium retention in the body
The SCCS notes that aluminium has several half-lives corresponding to the different distribution phases preceding the terminal elimination half-life. The terminal half-life of aluminium is not known.
Human and animal studies cited in the current Opinion suggest that the urinary excretion of aluminium is biphasic and have shown that after a single IV injection of ^{26}Al citrate in healthy subjects, more than 50% of the Al administered is excreted within the first 24h in the urine. In conclusion, even if aluminium accumulation cannot be ruled out after dermal exposure, any significant accumulation in the body is unlikely following daily use of cosmetic products.

Human data
The SCCS considers that aluminium is a known neurotoxicant in animals. Circumstantial evidence has linked this metal with several neurodegenerative disorders, like Alzheimer's disease (Miu and Benga, 2006; Percy et al., 2011), Parkinson's diseases (Oyanagi, 2005)

and other chronic neurodegenerative diseases (Bondy, 2010), but no causal relationship has yet been proven.

4. CONCLUSION

1. In light of the new data provided, does the SCCS consider that Aluminium compounds are safe in

- *Antiperspirants,*
- *Other cosmetic products such as lipsticks and toothpastes?*

In the light of the new data provided, the SCCS considers that the use of aluminium compounds is safe at the following equivalent aluminium concentrations up to:

- 6.25% in non-spray deodorants or non-spray antiperspirants
- 10.60% in spray deodorants or spray antiperspirants
- 2.65% in toothpaste and
- 0.77 % in lipstick

2. Does the SCCS have any further scientific concerns regarding the use of Aluminium compounds in cosmetic products taking into account exposure from other sources?

The SCCS considers that the systemic exposure to aluminium via daily applications of cosmetic products does not add significantly to the systemic body burden of aluminium from other sources. Exposure to aluminium may also occur from sources other than cosmetic products, and a major source of aluminium in the population is the diet. This assessment has not taken into account the daily dietary intake of aluminium.

3. In the event that the estimated exposure to Aluminium from specific types of cosmetic products is found to be of concern, SCCS is asked to recommend safe concentration limits for the presence of Aluminium in those cosmetic products or other risk reducing measures.

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5. MINORITY OPINION

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6. REFERENCES

Afssaps (2011) Agence Française de Sécurité Sanitaire des Produits de Santé. Evaluation du risque lié à l'utilisation de l'aluminium dans les produits cosmétiques, 43 pages (report in French).

Allen C, Alfrey AC, LeGendre GR, Kaehny WD (1976). The dialysis encephalopathy syndrome. Possible aluminium intoxication N Engl J Med. 294(4):184-8.

Alfrey AC, Hegg A, Craswell P (1980) Metabolism and toxicity of aluminium in renal failure. Am J Clin Nutr. 33(7):1509-16.

Altmann P, Cunningham J, Dhanesha U, Ballard M, Thompson J, Marsh F (1999) Disturbance of cerebral function in people exposed to drinking water contaminated with aluminium sulfate: retrospective study of the Camelford water incident, Br. Med. J., 1999, 319, 807–811.

Anane R, Bonini M, Grafeille JM, Creppy EE. (1995) Bioaccumulation of water soluble aluminium chloride in the hippocampus after transdermal uptake in mice. Arch Toxicol. 69(8):568-71.

Atomic Energy of Canada Limited (AECL 2010) The Bioavailability of Ingested Al-26 Labelled Aluminium and Aluminium Compounds in the Rat, GNP-121100-REPT-001 (Reported in EFSA Journal 2011;9(5):2157

ATSDR (2008). Toxicological profile for aluminium. Atlanta GA.: U.S. Department of Health and Human Services, Public Health Service. pp357.

Basketter DA, Lea LJ, Cooper KJ, Ryan CA, Gerberick GF, Dearman RJ, Kimber I (1999) Identification of metal allergens in the local lymph node assay Am J Contact Dermat. 10(4):207-12.

BfR (2014) Bundesinstitut fur Risikobewertung. Aluminium in Antitranspirantien. Stellungnahme Nr. 007/2014

Bondy SC. (2010).The neurotoxicity of environmental aluminium is still an issue. Neurotoxicology. 2010 Sep;31(5):575-81.

Bretagne A, Cotot F, Arnaud-Roux M, Sztucki M, Cabane B, Galey JB. (2017) The mechanism of eccrine sweat pore plugging by aluminium salts using microfluidics combined with small angle X-ray scattering. Soft Matter. May 24;13(20):3812-3821. doi: 10.1039/c6sm02510b.

Bundesgesundheitsblatt (1998): Opinion of the Human Biomonitoring Commission of the German Federal Environmental Agency Published in German in: Bundesgesundhbl., Bd. 41 (6), (1998), 271.

Carthew, P., Griffiths, H., Keech, S. and Hartop, P., 2002. Safety assessment for hairspray resins: risk assessment based on rodent inhalation studies. Inhalation Toxicology, 14:401–416.

Casarett & Doull, 2008. Toxicology: The Basic Science of Poisons, p. 519.

Chen X, Gasecka P, Formanek F, Galey JB, Rigneault H. *In vivo* single human sweat gland activity monitoring using coherent anti-Stokes Raman scattering and two-photon excited autofluorescence microscopy. Br J Dermatol. 2016 Apr;174(4):803-12. doi: 10.1111/bjd.14292. Epub 2016 Jan 9. PubMed PMID: 26574296

Colomina, M.T., Roig, J.L., Torrente, M., Vicens, P., Domingo, J.L., 2005. Concurrent exposure to aluminium and stress during pregnancy in rats: effects on postnatal development and behaviour of the offspring. Neurotoxicol. Teratol. 27, 565-574.

Cranmer JM, Wilkins JD, Cannon DJ, et al.,et al.,, 1986. Fetal-placental-maternal uptake of aluminium in mice following gestational exposure: Effect of dose and route of administration. Neurotoxicology 7(2):601608.

Darbre PD. (2009) Underarm antiperspirants/ deodorants and breast cancer. Breast Cancer Res. 2009; 11(Suppl 3): S5.

Darbre PD. (2005) Aluminium, antiperspirants and breast cancer. J Inorg Biochem. 99: 1912-1919.

Darbre PD. (2006). Metalloestrogens: an emerging class of inorganic xenoestrogens with potential to add to the oestrogenic burden of the human breast. J Appl Toxicol, 26, 191–7.

Darbre PD, Pugazhendhi D, Mannello F. (2011). Aluminium and human breast diseases. J Inorg Biochem, 105, 1484–8.

Darbre PD, Mannello F, Exley C. (2013) Aluminium and breast cancer: Sources of exposure, tissue measurements and mechanisms of toxicological actions on breast biology. J Inorg Biochem. 128:257-61.

Day JP, Barker J, Evans LJA, Perks J, Seabright PJ, Ackrill P, Lilley JS, Down PV and Newton GWA (1991) Aluminium absorption studied by 26Al tracer, Lancet 337, 1345.

Denton J, Freemont AJ & Ball J (1984) Detection and distribution of aluminium in bone. J. Clin. Pathol. 37, 136–142.

DeVoto & Yokel (1994) The biological speciation and toxicokinetics of aluminium. Environ Health Perspect, Nov;102(11):940-51.

Domingo, J.L., Llobet, J.M., Gómez, M., Tomas, J.M. and Corbella, J., (1987a). Nutritional and toxicological effects of short-term ingestion of aluminium by the rat. Res Commun Chem Pathol Pharmacol 56, 409-419.

Domingo, J.L., Paternain, J.L., Llobet J.M., Corbella, J., 1987b. The effects of aluminium ingestion on reproduction and postnatal survival in rats. Life Sciences, 41, 1127-1131.

Drew RT, Gupta BN, Bend JR, et al.,et al.,, 1974. Inhalation studies with a glycol complex of aluminiumchloride-hydroxide. Arch Environ Health 28(6):321-326. [as cited in ATSDR, 2008]

Eastwood JB, Levin GE, Pazianas M, Taylor AP, Denton J, Freemont AJ (1990) Aluminium deposition in bone after contamination of drinking water supply, Lancet, 336, 462–464.

European Commission, 1996. Technical guidance documents in support of the commission directive 93/67/EEC on risk assessment for new notified substances and the commission regulation (EC) 1488/94 on risk assessment for existing substances

ECHA (1998) Guinea pig maximization test (GPMT), conducted GLP and OECD guideline 406. http://echa.europa.eu/registration-dossier/-/registered-dossier/16009/7/5/2

Edwardson JA (1991) The pathogenesis of cerebral b-amyloid deposition and the possible role of aluminium, in Alzheimer’s Disease and the Environment, ed. Lord Walton of Detchant, Royal Society of Medicine, London, 1991, p. 24.

EFSA (2008). Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC). Safety of aluminium from dietary intake. The EFSA Journal. 6(7); 754: 1-34

EFSA 2011 Statement of EFSA on the evaluation of a new study related to the bioavailability of aluminium in food. EFSA Journal. 9(5):2157

Ellis H, Scurr JH. (1979) Axillary hyperhidrosis - topical treatment with aluminium chloride hexahydrate. Postgrad Med J. 55(654):868-9.

Ellis HA, Pang MMC, Mawhinney WHB, Skillen AW (1988) Demonstration of aluminium in iliac bone: correlation between aluminon and solochrome azurine staining techniques with data on flameless absorption spectrometry. J. Clin. Pathol. 41, 1171–1175.

Environment Canada & Health Canada (2010) Priority substances list assessment report follow up to the state of science report 2000: aluminium chloride, aluminium nitrate, aluminium sulphate. Available at https://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=491F0099-1

Exley C, Charles LM, Barr L, Martin C, Polwart A, Darbre PD.(2007). Aluminium in human breast tissue. J. Inorg. Biochem. 101: 1344-1346.

Fakri S, Al-Azzawi A, Al-Tawil N. (2006). Antiperspirant use as a risk factor for breast cancer in Iraq. Mediterr Health J, 12, 478–82.

Finley B, Proctor D, Scott P, Harrington N, Paustenbach D, Price P (1994) Recommended dsitributions for exposure factors frequently used in health risk assessment. Risk Anal. 14, 533-553.

Flarend R, Bin T, Elmore D and Hem SL (2001). A preliminary study of the dermal absorption of aluminium from antiperspirants using aluminium-26. Food Chem. Toxicol. 39(2): 163-168.

Flendrig JA, Kruis H and Das HA (1976) Aluminium and dialysis dementia, Lancet 307 (7971), 1235.

Frash VN, Vanchugova NN, Rukoleeva SN, Zykova VA, Grebennikov SA, Shcherbakov SV. Oncogenic action of some nonfibrous mineral dusts. Biull Eksp Biol Med 1992;114:1878–1882.

Gallego H, Lewis EJ, Crutchfield CE (1999) Crystal deodorant dermatitis: irritant dermatitis to alum-containing deodorant. Cutis.; 64(1):65-6.

Ganrot PO. 1986. Metabolism and possible health effects of aluminium. Environ Health Perspect 65:363-441.

Gitelman HJ. Aluminium exposure and excretion. Sci Total Environ 1995;163:129–135.

Goh CL (1990). Aluminium chloride hexahydrate versus palmar hyperhidrosis evaporimeter assessment. Inter J Dermatol. 29: 369-370.

Golub MS, Han B, Keen CL. 1996. Iron and manganese uptake by offspring of lactating mice fed a high aluminium diet. Toxicology 109(2-3):111-118.

Golub, M.S., Germann, S.L., 2001. Long-term consequences of developmental exposure to aluminium in a suboptimal diet for growth and behavior of Swiss Webster mice. Neurotoxicol Teratol. 23, 365-372.

Gómez, M., Domingo, J.L., Llobet, J.M., Tomas, J.M. and Corbella, J. 1986. Short-term oral toxicity study of aluminium in rats. Arch Pharmacol Toxicol. 12, 145-151. (Cited in WHO, 1997).

Greger, J.L. and Sutherland, J.E., 1997. Aluminium exposure and metabolism. Crit. Rev. Clin. Lab. Sci. 34, 439-474.

Guillard O, Fauconneau B, Olichon D, Dedieu G, Deloncle R (2004) Hyperaluminemia in a woman using an aluminium-containing antiperspirant for 4 years. Am J Med.117(12):956-9.

Guo, C.H., Lu, Y.F., Hsu, G.S.H., 2005. The influence of aluminium exposure on male reproduction and offspring in mice. Environ. Toxicol. Pharmacol. 20, 135-141.

Hall B., Tozer S., Safford B., Coroama M., Steiling W., Leneveu-Duchemin M.C., McNamara C., Gibney M. (2007) European consumer exposure to cosmetic products, a framework for conducting population exposure assessments. Food and Chemical Toxicology 45(11):2097-108.

Hall B., Steiling W., Safford B., Coroama M., Tozer S., Firmani C., McNamara C., Gibney M. (2011) European consumer exposure to cosmetic products, a framework for conducting population exposure assessments, Part 2. Food and Chemical Toxicology 49, 407-21.

Hepp. N.M. 2012. Determination of total lead in 400 lipsticks on the US market using a validated microwave-assisted digestion, inductively coupled plasma mass spectophotometry method. J., Cosmet, Sci., 63, 159-176.

Heyder, J., Gebhart, J., Rudolf, G., Schiller, C.F. and Stahlhofen, W., 1986. Deposition of particles in the human respiratory tract in the size range 0.005-15 µm. J. Aerosol Sci., 17, 811-825.

Hicks, J.S., Hackett, D.S. and Sprague, G.L., 1987. Toxicity and aluminium concentration in bone following dietary administration of two sodium aluminium phosphate formulations in rats. Food Chem. Toxicol. 25(7), 533-538 (Cited in WHO, 1997).

Hostynek JJ (2003) Factors determining percutaneous metal absorption. Food Chem Toxicol 41(3):327-45.

IARC (International Agency for Research on Cancer). (1987). Aluminium production. Overall evaluation of carcinogenicity: An updating of IARC Monographs, (Vol 1–41). Suppl 7. Lyon: World Health Organization, pp. 89–91.

IARC (International Agency for Research on Cancer). (2010). Occupational exposures during aluminium production. IARC Monographs 100F. Lyon: World Health Organization, pp. 215-224.

JECFA (2007). Aluminium from all Sources, including Food Additives. Safety evaluation of certain food additives and contaminants: Prepared by the sixty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series. 58: 119-207. http://apps.who.int/iris/bitstream/10665/43645/1/9789241660587_eng.pdf

JECFA (2012). Aluminium-containing food additives (addendum). Safety evaluation of certain food additives and contaminants: Prepared by the seventy-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series. 65: 3-86. http://whqlibdoc.who.int/publications/2012/9789241660655_eng.pdf

Jones KC, Bennett BG. (1986) Exposure of man to environmental aluminium-an exposure commitment assessment. Sci Total Environ 52:65-82.

Katz, A.C., Frank, D.W., Sauerhoff, M.W., Zwicker, G.M. and Freudenthal, R.I., 1984. A 6-month dietary toxicity study of acidic sodium aluminium phosphate in beagle dogs. Food Chem Toxicol 22, 7-9.

Krewski D, Yokel RA, Nieboer E, Borchelt D, Cohen J, Harry J, Kacew S, Lindsay J, Mahfouz AM, Rondeau V. J (2007) Human health risk assessment for aluminium, aluminium oxide, and aluminium hydroxide. Toxicol Environ Health B Crit Rev.10 Suppl 1:1-269.

Kumar, S. (2001) Acute toxicity of aluminium chloride, acephate, and their coexposure in male Wistar rat. Int. J. Toxicol., 20, 219–223.

Lansdown AB (1973) Production of epidermal damage in mammalian skins by some simple aluminium compounds. Br J Dermatol 89:67-76. [as cited in ATSDR, 2008]

Lee, A. H., (2005). Why is carcinoma of the breast more frequent in the upper outer quadrant? A case series based on needle core biopsy diagnoses. The Breast, 14: 151-152

Letzel M, Drexler H, Göen T, Hiller J. Impact of Daily Antiperspirant Use on the Systemic Aluminium Exposure: An Experimental Intervention Study. Skin Pharmacol Physiol. 2019 Sep 25:1-8.

Liao YH, Yu HS, Ho CK, et al.,et al.,, 2004. Biological monitoring of exposures to aluminium, gallium, indium, arsenic, and antimony in optoelectronic industry workers. J Occup Environ Med 46(9):931-936.

Lima PDL, Leite DS, Vasconcellos MC, Cavalcanti BC, Santos RA, Costa-Lotufo LV, et al.,et al.,, (2007). Genotoxic effects of aluminium chloride in cultured human lymphocytes treated in different phases of cell cycle. Food Chem Toxicol, 45, 1154–9.

Lippmann M (1977) Regional deposition of particles in the human respiratory tract, In: Handbook of Physiology, Section 9: Reactions to Environmental Agents, Lee DHK, Falk HL, Murphy SD, Giger SR (eds), American Physiological Society, Bethesda, MD, 213.

Llobet JM, Domingo JL, Gomez M, et al.,et al.,, 1987. Acute toxicity studies of aluminium compounds: Antidotal efficacy of several chelating agents. Pharmacol Toxicol 60:280-283.

Llobet, J.M., Colomina, M.T., Sirvent, J.J., Domingo, J.L., Corbella, J., 1995. Reproductive toxicology of Aluminium in male mice. Fund. App. Toxicol. 25, 45-51.

MAK (2012) Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, 2012. In: Deutsche Forschungsgemeinschaft (DFG) (Ed.), List of MAK and BAT Values 2012: Maximum concentrations and biological tolerance values at the workplace. Report 48, Wiley-VCH, Weinheim.

MAK (2014). Aluminium. The MAK Collection for Occupational Health & Safety, Wiley-VCH Verlag GmbH & Co. KGaA

Mandriota S, Tenan M, Ferrari P, Sappino A-P (2016) Aluminium chloride promotes tumorigenesis and metastasis in normal murine mammary gland epithelial cells. Molecular Cancer Biology, e-publication 7 Sept 2016.
http://dx.doi.org/10.1002/ijc.30393

Mannello F, Tonti GA, Medda V, Simone P, Darbre PD. (2011). Analysis of aluminium content and iron homeostasis in nipple aspirate fluids from healthy women and breast cancer-affected patients. J. Appl. Toxicol. 31: 262-269.

Markesbery WR, Ehmann WD, Alauddin M, Hossain TIM (1984) Brain trace element concentrations in aging. Neurobiol Aging, 5, 19-28.

Martin, R.B, 1991. "Aluminium in biological systems" in "Aluminium in Chemistry Biology and Medicine, Vol 1, Nicolini, M., Zatta, P.F., Corain, B., (eds) Cortina International Verona Raven Press/New York, 3-20.

McAughey J, Newton D, Talbot R, Day JP, Fifield K, Priest N (1998) Uptake and excretion of inhaled 26Al-aluminium oxide, AEA Technology Report No. AEA-2221.

McGrath KG. (2003). An earlier age of breast cancer diagnosis related to more frequent use of antiperspirants/deodorants and underarm shaving. Eur J Cancer Prev, 12(6), 479–85.

McGrath KG. (2009). Apocrine sweat gland obstruction by antiperspirants allowing transdermal absorption of cutaneous generated hormones and phermones as a link to the observed incidence rates of breast and prostate cancer in the 20th century. Med Hypotheses, 72, 665–74.

Meech L (2011) Antiperspirant Simulated Use Evaluation, Study Report DS 110156.

Meek ME, Boobis AR, Crofton KM, Heinemeyer G, Van Raaij M, Vickers C (2011) Risk assessment to combined exposures of multiple chemicals: A WHO/IPCS Framework. Reg Tox Pharm 60, S1-S14.

Mirick DK, Davis S, Thomas DB. (2002) Antiperspirant use and the risk of breast cancer. J Natl Cancer Inst. 94(20): 1578-80.

Miu AC, Benga O (2006). Aluminium and Alzheimer's disease: a new look. Alzheimers 10 (2-3):179-201.

NF EN 71-3 (2002). Safety of toys - Part 3: Migration of certain elements (includes Amendment A1:2002 + Corrigendum AC:2002)

Namer M, Luporsi E, Gligorov J, Lokiec F, Spielman M. (2008). The use of deodorants/antiperspirants does not constitute a risk factor for breast cancer. Bull Cancer. 95(9):871-80.

Nieboer, E., Gibson, B.L., Oxman, A.D. and Kramer, J.R., 1995. Health effects of aluminium: A critical review with emphasis on aluminium in drinking water. Environ. Rev. 3, 29-81.

Nolte E, Beck E, Winklhofer C, Steinhausen C (2001) Compartmental model for aluminium biokinetics. Human Exp Toxicol 20, 111-117.

Ogden, T.L. and Birkett, J.L., 1978. An inhalable dust sampler for measuring hazard from total airborne particulate. Annals Occup. Hyg., 24, 41-50.

Ogoshi, K., Yanagi, S., Moriyama, T., Arachi, H., 1994. Accumulation of Aluminium in Cancers of Liver, Stomach, Duodenum and Mammary Glands of Rats. J. Trace Elem. Electrolytes Health Dis., 8: 27-31

Oneda S, Takasaki T, Kurowaki K, et al.,et al.,, 1994. Chronic toxicity and tumorigenicity study of aluminium potassium sulfate in B6C3F1 mice. *In Vivo* 8(3):271-278.

Ott SM, Maloney NA, Klein GL, Alfrey AC, Ament ME, Coburn JW, Sherrard DJ (1983) Aluminium associated with low bone formation in patients receiving chronic parenteral nutrition. Ann. Intern. Med 98: 910.

Oyanagi K. (2005). The nature of the parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam and magnesium deficiency. Parkinsonism Relat Disord. 11 Suppl 1: S17-23.

Paz LNF, Moura LM, Feio DCA, Cardoso MSG, Ximenes WLO, Montenegro RC, Alves APN, Burbano RR, Lima PDL. Evaluation of *in vivo* and *in vitro* toxicological and genotoxic potential of aluminium chloride. Chemosphere. 2017 May;175:130-137. doi: 10.1016/j.chemosphere.2017.02.011. Epub 2017 Feb 3. Erratum in Corrigendum to "Evaluation of *in vivo* and *in vitro* toxicological and genotoxic potential of aluminium chloride" [Chemosphere 175 (2017), 130-137]. [Chemosphere. 2018]

Percy ME, Kruck TP, Pogue AI, Lukiw WJ. (2011). Towards the prevention of potential aluminium toxic effects and an effective treatment for Alzheimer's disease. J Inorg Biochem. 105(11): 1505-12.

Pettersen, J.C., Hackett, D.S., Zwicker, G.M. and Sprague, G.L., 1990. Twenty-six week toxicity study with KASAL (basic sodium aluminium phosphate) in beagle dogs. Environ Geochem. Health 12, 121-123.

Pierre F, Baruthio F, Diebold F, Biette P. Effect of different exposure compounds on urinary kinetics of aluminium and fluoride in industrially exposed workers. Occup Environ Med 1995;52:396–403.

Piggot GH, Gaskell BA, Ishmael J (1981) effects of long term inhalation of alumina fibres in rats. Br J Exp Pathol 63(3): 323-331.

Pineau A, Guillard O, Fauconneau B, Favreau F, Marty MH, Gaudin A, Vincent CM, Marrauld A, Marty JP (2012). *In vitro* study of percutaneous absorption of aluminium from antiperspirants through human skin in the Franz™ diffusion cell. J Inorg Biochem 110:21-26.

Poirier J, Semple H, Davies J, Lapointe R, Dziwenka M, Hiltz M and Mujibi D. (2011). Double-blind, vehicle-controlled randomized twelve-month neurodevelopmental toxicity study of common aluminium salts in the rat. Neuroscience. 193: 338-362.

Pott and Roller (2005). Carcinogenicity study with nineteen granular dusts in rats. Eur J Oncol, 2005; 10: 249-81.

Priest ND (2004). The biological behaviour and bioavailability of alulminium in man, with special reference to studies emplying aluminium-26 as a tracer: review and study update. J. Environ. Monit. 6, 375-403.

Priest ND, Newton D, Day JP, Talbot RJ, Warner AJ.(1995) Human metabolism of aluminium-26 and gallium-67 injected as citrates. Hum Exp Toxicol. 14(3):287-93.

Priest ND, Talbot RJ, Austin JG, Day JP, King SJ, Fifield K, Cresswell RG. (1996). The bioavailability of 26Al-labelled aluminium citrate and aluminium hydroxide in volunteers. Biometals; 9(3):221-8.

Raabe, O.G., 1982. Comparison of the criteria for sampling ‘inhalable’ and ‘respirable’ aerosols. Ann. Occup. Hyg., 26(1-4), 33-45.

Reisfeld R, Berliner KI (2008) Evidence-based review of the nonsurgical management of hyperhidrosis. Thorac Surg Clin. 18(2):157-66.

Riihimäki V, Valkonen S, Engström B, Tossavainen A, Mutanen P, Aitio A. (2008) Behavior of aluminium in aluminium welders and manufacturers of aluminium sulfate--impact on biological monitoring Scand J Work Environ Health. 34(6):451-62.

Riihimäki V, Aitio A. (2012) Occupational exposure to aluminium and its biomonitoring in perspective Crit Rev Toxicol. 42(10):827-53.

RIVM, National Institute for Public Health and the Environment, ConsExpo, Available through: http://www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp, 2012

Rodrigues-Peres RM, Cadore S, Febraio S, Heinrich JK, Serra KP, Derchain SF, Vassallo J, Sarian LO. (2013) Aluminium concentrations in central and peripheral areas of malignant breast lesions do not differ from those in normal breast tissues. BMC Cancer. 13: 104.

Rothe et al.,et al.,, (2011) Special aspects of cosmetic spray safety evaluations: principles on inhalation risk assessment. Toxicol Lett 205(2):97-104.

Roy AK, Sharma A, Talukder G. 1991a. Effects of aluminium salts on bone marrow chromosomes in rats *in vivo*. Cytobios 66 : 105-111.

Roy, A.K., Talukder, G. and Sharma, A., 1991b. Similar effects *in vivo* of two aluminium salts on the liver, kidney, bone, and brain of Rattus norvegicus. Bull. Environ Contam Toxicol 47, 288-295.

Salem, H., Katz, S.A., 2006. Inhalation Toxicology, 2nd ed. CRC Taylor & Francis, BocaRaton, USA (ISBN-10: 0849340497).

SCCS (2014) Opinion on the safety of aluminium in cosmetic products. SCCS/1525/14 Revision of 18 June 2014.

SCCS (2018): The SCCS Notes of Guidance for the Testing of Cosmetic ingredients and Their Safety Evaluation. 10th Revision ed.

Schwarz, K., Pappa, G., Miertsch, H. et al.,et al.,, A methodology for the assessment of inhalation exposure to aluminium from antiperspirant sprays. Arch Toxicol 92, 1383–1392 (2018).

Schönholzer et al.,et al.,,, 1997 Intestinal absorption of trace amounts of aluminium in rats studies with 26aluminium and accelerator mass spectrometry. Clinical Science. 92:379-383.

Schroeder HA, Mitchener M. 1975a. Life-term studies in rats: Effects of aluminium, barium beryllium and tungsten. J Nutr 105(4):421-427.

Schroeder HA, Mitchener M. 1975b. Life-term effects of mercury, methyl, mercury, and nine other trace metals on mice. J Nutr 105:452-458.

Singal, M., Pandian, M., Joachim, F., Corea, N., Jones, L., & Smith, L. (2010). Estimating Inhalation Exposure to Fragrance Materials in Air Freshening Products using a Two-Zone Residential Indoor Air Dispersion Model. 2010 Society of Toxicology 49th Annual Meeting & ToxExpo. SaltLake City, Utah.

Sjögren B, Lidums V, Hakansson M, et al.,et al.,, 1985. Exposure and urinary excretion of aluminium during welding. Scand J Work Environ Health 11(1):39-43.

Sjögren B, Elinder CG, Irgren A, McLachlan DRC, Riihimaki V (1997) Occupational aluminium exposure and its health effects, Chapter 9 in Research Issues in Aluminium Toxicity, ed. R. A. Yokel, R. A. and M. S. Golub, Taylor & Francis, Washington pp. 165–183.

Somova, L.I., Missankov, A. and Khan, M.S., 1997. Chronic aluminium intoxication in rats: dosedependent morphological changes. Methods Find. Exp. Clin Pharmacol 19, 599-604.

Sorenson JRJ, Campbell IR, Tepper LB, et al.,et al.,, 1974. Aluminium in the environment and human health. Environ Health Perspect 8:3-95.

Stauber JL, Florence TM, Davies CM, et al.,et al.,, 1999. Bioavailability of Al in alumtreated drinking water. J Am Water Works Assoc 91(11): 84-93.

Steiling, W., Buttgereit, B., Hall, B., O'Keeffe, L., Safford, B., Tozer, S. and Coroama, M., 2012. Skin exposure to deodorant/antiperspirants in aerosol form. Food and Chemical Toxicology. 50:2206-2215.

Steiling W., Bascompta M., Carthew P., Catalano G., Corea N., D'Haese A., Jackson P., Kromidas L., Meurice P., Rothe H. and Singal M. (2014) Principle Considerations for the Risk Assessment of Sprayed Consumer Products Toxicology Letters, 227, 41 – 49.

Steinhagen, W.H., Cavender, F.L., Cockrell, B.Y. (1978). Six month inhalation exposures of rats and guinea pigs to aluminium chlorohydrate. Journal of Environmental Pathology and Toxicology, 1:267-277.

Steinhausen C, Kislinger G, Winklhofer C, Beck E, Hohl C, Nolte E, Ittel TH,Alvarez-Brückmann MJ. Investigation of the aluminium biokinetics in humans: a 26Al tracer study. Food Chem Toxicol. 2004 Mar;42(3):363-71.

Talbot RJ, Newton D, Priest ND, Austin JG, Day JP (1995) Inter-subject variability in the metabolism of aluminium following intravenous injection as citrate. Human and Exp. Toxicol. 14, 595–599.

Thomson SM, Burnett DC, Bergmann JD, et al.,et al.,, 1986. Comparative inhalation hazards of aluminium and brass powders using bronchopulmonary lavage as an indicator of lung damage. J Appl Toxicol 6(3):197209.

TNO (2016) Assessment of bioavailability of aluminium, as aluminium chlorohydrate, in humans after topical application of a representative antiperspirant formulation using a

[26Al] microtracer approach. Study report Error! Unknown document property name. Study commissioned by the Cosmetics Industry via Cosmetics Europe.

TNO (2019) Assessment of bioavailability of aluminium in humans after topical application of a representative antiperspirant formulation using a [26Al] microtracer approachUnknown document property name. Study commissioned by the Cosmetics Industry via Cosmetics Europe

U.S. Department of Labor, 2006. MSHA Handbook Series. Mine Safety and Health Administration. Metal and Nonmetal Mine Safety and Health Chapter 5: mineral dusts - gravimetric method. October 2006, Handbook Number PH06-IV-1(1).

Valkonen S, Aitio A (1997) Analysis of aluminium in serum and urine for the biomonitoring of occupational exposure. Sci Total Environ. 20;199(1-2):103-10.

VKM 2013 Norwegian scientific Committee for Food Safety, Risk assessment of the exposure to aluminium through food and the use of cosmetic products in the Norwegian population, 5 April 2013

Weisser K, Göen T, Oduro JD, Wangorsch G, Hanschmann KO, Keller-Stanislawski B. (2019) Aluminium toxicokinetics after intramuscular, subcutaneous, and intravenous injection of Al citrate solution in rats. Arch Toxicol. 2019 Jan;93(1):37-47. doi: 10.1007/s00204-018-2323-8. Epub 2018 Oct 9.

WHO IPCS (International Programme on Chemical Safety). (1997). Aluminium. Environmental Health Criteria 194. United Nations Environment Programme. Geneva: World Health Organization, pp. 1–214. Available at:
http://www.inchem.org/documents/ehc/ehc/ehc194.htm

Wilhelm, M., Jäger, D.E. and Ohnesorge, F.K., 1990. Aluminium toxicokinetics. Pharmacol.Toxicol. 66, 4-9.

Willhite CC, Karyakina NA, Yokel RA, Yenugadhati N, Wisniewski TM, Arnold IMF, Momoli F, Krewski D (2014) Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminium, aluminium oxides, aluminium hydroxide and its soluble salts. Criticl reviews in Toxicology, 44:sup4, 1-80.

Wisniewski HM (1991) About the association of aluminium and Alzheimer's disease–a commentary, in Aluminium in Chemistry, Biology and Medicine, ed. M. Nicolini, P. F. Zatta and B. Corain, Raven Press, New York, pp. 115–117.

Wright, B.M., 1950. A new dust feed mechanism. J. Sci. Instr., 27:12-15.

Yokel RA. 1985. Toxicity of gestational aluminium exposure to the maternal rabbit and offspring. Toxicol Appl Pharmacol 79(1):121-133.

Yokel RA, McNamara PJ. 1985. Aluminium bioavailability and disposition in adult and immature rabbits. Toxicol Appl Pharmacol 77(2):344-352.

Yokel RA, Allen DD, Ackley DC (1999) The distribution of aluminium into and out of the brain, J. Inorg. Biochem. 76, 127–132.

Yokel RA. (2000). The toxicology of aluminium in the brain: a review. Neurotoxicology, 21, 813–28.

Yokel RA, McNamara PJ (2001) Aluminium toxicokinetics: an updated minireview. Pharmacol Toxicol. 88(4):159-67.

Yousef, M.I., El-Morsy, A.M.A., Hassan, M.S., 2005. Aluminium-induced deterioration in reproductive performance and seminal plasma biochemistry of male rabbits: protective role of ascorbic acid. Toxicology 215: 97-107.

Yu, C.P., 1996. Extrapolation modeling of particle deposition and retention from rats to humans. In Particle Overload in the Rat Lung and Lung Cancer. Implications for risk assessment, eds. J. L. Mauderly and R. J. McCunney, pp. 279-291. London; Taylor & Francis.

Zhou Y, Harris WR, Yokel RA (2008) The influence of citrate, maltolate and fluoride on the gastrointestinal absorption of aluminium at a drinking water-relevant concentration: A 26Al and 14C study. J Inorg Biochem;102(4)798–808.

7. GLOSSARY OF TERMS

See SCCS/1602/18, 10th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 141

8. LIST OF ABBREVIATIONS

See SCCS/1602/18, 10th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 141

ANNEX 1: Cosmetics Ingredients containing aluminium

Aluminium salts, complexes and mineral compounds used as cosmetics ingredients

Chemical Name	INCI Name	CAS Number	Common synonyms	Chemical formula	Mol Wt	LogP	Water solubility (g/l)	Physical Form
Simple Inorganic Salts								
Aluminium Sulphate	Aluminium sulfate	10043-01-3	Alum; E520	$Al_2(SO_4^{2-})_3$	342.15	-	soluble	white crystal/powder
Aluminium Potassium Sulphate	Potassium alum	10043-67-1	Potassium alum; E555	$KAl(SO_4^{2-})_2$	258.19	-	slightly soluble	white powder
Aluminium Ammonium Sulphate	Ammonium alum	7784-25-0	Ammonium alum	$NH_4Al_2(SO_4^{2-})_2$	237.15	-1.031 (est)	very soluble	white powder
Simple Organic Salts								
Aluminium Lactate	Aluminium lactate	18917-91-4	Aluctyl	$Al[CH_3(OH)CO_2^-]_3$	294.19	-2.43 to -1.90	soluble	white/yellow powder
Aluminium Citrate	-	31142-56-0	Aluminium citrate	$(NH_4^+)_5[Al_3(H_{-1}Cit)_3(OH)(H_2O)[NO_3^-]\bullet 6H_2O$	216.08	-1.48	soluble	white powder
Aluminium Glycinate	Dihydroxyaluminium aminoacetate	13682-92-3	Dihydroxy aluminium aminoacetate	$Al(OH)(CH_2NH_2CO_2^{2-})$	135.05	-1.85	insoluble	fine powder
Aluminium Benzoate	Aluminium benzoate	555-32-8	Aluminium tribenzoate	$Al(C_7H_6O_2^-)_3$	390.32	1.895 /3.923 10	very slightly soluble	white crystal/powder
Chlorohydrates								
Aluminium chloride hexahydrate	-	7784-13-6	Hydrated aluminium chloride	$AlCl_3\bullet 6H_2O$	241.43	-	soluble	colorless/ white
Aluminium chlorohydrate (ACH)	-	1327-41-9	aluminium hydroxychloride , aluminium chlorhydroxide	$Al_2Cl(OH)_5$	138.50	-	soluble	-
Aluminium chlorohydrate 80% solid	-	-	-	-	-	-	-	-
Aluminium sesquichloro-hydrate	-	173763-15-0	-	$Al_2(OH)_yCl_z$ x nH_2O (z=1,1 1,3, y=6x)	-	-	-	-
Zirconium - aluminium - glycine complexes (ZAG)								
Aluminium Zirconium Trichlorohydrate Glycine	Aluminium zirconium trichlorohydrex	134375-99-8	Aluminium zirconium trichlorohydrex	$Al_8Zr(OH)_{13}Cl_3.xH_2O$ with glycerin	-	-	soluble	white powder

	gly		gly					
Aluminium Zirconium Tetrachlorohydrate Glycine	Aluminium zirconium tetrachlorohydrex gly	134910-86-4	Aluminium zirconium tetrachlorohydrex gly	$Al_4Zr(OH)_{12}Cl_4$ Gly x nH_2O	-	-	soluble	white powder
Aluminium Zirconium Octachlorohydrate Glycine	Aluminium zirconium octachlorohydrex gly	174514-58-0	Aluminium zirconium octachlorohydrex Gly; Complex reaction product obtained from the reaction of aluminium zirconium octachlorohydrate (Al8Zr(OH)20Cl8 .xH2O) and glycine	$C_2H_8AlClNO_4Zr^{+5}$	263.75	-	-	white powder
Zirconium-aluminium complexes (ZACH)								
Aluminium Zirconium Tetrachlorohydrate	-	-	-	-	-	-	-	-
Aluminium Zirconium Pentachlorohydrate	-	173762-83-9	-	$AlCl_5ZrH_2$	-	-	-	-
Water insoluble Minerals, Glasses and Clays								
Aluminium hydroxide (Gibbsite)	Aluminium hydroxide	21645-51-2	Aldrox; alumina hydrate; gibbsite	$Al(OH)_3$	78.00	-	insoluble	white amorphous powder
Aluminium magnesium hydroxide	-	39366-43-3	Aluminium magnesium pentahydroxide	AlH_5MgO_5	136.32	-	-	-
Aluminium oxide (Alumina, aluminium sesquioxide)	Alumina	1344-28-1	-	Al_2O_3	101.96	-	insoluble	white crystal/powder
Perlite (Volcanic Glass, 12–15% Al2O3)	Perlite	93763-70-3/ 130885-09-5	Sodium Potassium Aluminium Silicate	Natural volcanic glass with higher amounts of water (2-5%). White to light gray, glassy.	-	-	insoluble	white powder
Bentonite (volcanic ash derived clay; E 558)	Bentonite	1302-78-9	Taylorite; Wilkinite; Alumino silicate; Sodium	$Al_2H_2O_6Si$	180.06	-	insoluble	gray powder

			montmorillonite ;					
Hectorite (Na0:3(Mg; Li)3Si4O10(OH)2; 0.6% Al2O3)	Hectorite	12173-47-6	Hectorite (clay mineral)	$Na_{0.3}(Mg,Li)_3Si_4O_{10}(OH)_2$	283.25	-	insoluble	white powder
Synthetic Sapphire	Synthetic Sapphire	-	-	$Al_2O_3 + Cr_2O_3$		-	insoluble	
Cobalt Aluminium Oxide	Cobalt Aluminium Oxide	1345-16-0	Aluminium cobalt oxide; C.I. Pigment Blue 28; Cobalt aluminate blue spinel , C.I.77346	Al_2CoO_4	176.89	-	insoluble (< 0.1 mg/L)	blue powder
Aluminium silicate (Kaolin and clay minerals; E 559; CI 77004)	Kaolin	1332-58-7	-	$Al_2Si_2O_5(OH)_4$	259.76	-	insoluble	white powder
Kaolin (Al2Si2O5(OH)4; Clay silicate mineral)	Kaolin	1332-58-7	-	$Al_2Si_2O_5(OH)_4$	259.76	-	insoluble	white powder
Topaz (Silicate of aluminium and fluorine; Al2SiO4(F,OH)2)	Topaz	1302-59-6	Pycnite	$Al_2SiO_4(F,OH)_2$	182.25	-	-	-
Aluminium calcium sodium silicate (Andesine)	-	-	-	$(Na,Ca)Al_{1\text{-}2}Si_{3\text{-}2}O_8$	268.60	-	-	-
Sodium potassium aluminium silicate	Sodium potassium aluminium silicate	66402-68-4 /12736-96-8	Silicic acid, aluminium potassium sodium salt	$(Na,K)AlSi_3O_8$	301.34	-	insoluble	white powder
Sodium silver aluminium silicate	Sodium silver aluminium silicate	-	-	-	-	-	insoluble	white powder
Aluminium Calcium Sodium Silicate	Aluminium Calcium Sodium Silicate	1344-01-0	Silicic acid, aluminium calcium sodium salt	$AlCaNaO_4Si^{+2}$	182.13	-	73 mg/l	white powder
Magnesium aluminium silicate (Argila)	Magnesium aluminium silicate	1327-43-1	Silicic acid, aluminium magnesium salt	$AlMgO_4Si^+$	143.37	0.650	2.24 mg/L	white powder
Aluminium Magnesium Silicate	Magnesium aluminium silicate	1327-43-1	Silicic acid, aluminium magnesium salt	$AlMgO_4Si^+$	143.37	0.650	2.24 mg/L	white powder
Alumina Magnesium	-	50958-44-6	aluminium	$AlMgO_4Si^+$	143.37	-	-	-

Metasilicate			magnesium tetraoxidosilane					
Potassium Aluminium Silicate (Moonstone Powder)	Mica	12001-26-2	Potassium aluminium silicate; Mica; Muscovite	$KAl_2[AlSi_3O_{10}](OH)_2$	398.31	-	-	white powder
Ammonium Silver Zinc Aluminium Silicate	Ammonium Silver Zinc Aluminium Silicate	-	-	$Ag_2Al_2H_8N_2O_21Si_7Zn_2$	969.14	-	-	-
Pumice (volcanic glass)	Pumice	1332-09-8	Amorphous aluminium silicate	-	-	-	-	-
Loess (aeolian/wind-blown silt)	Loess	-	-	-	-	-	-	-
Calcium aluminium borosilicate (Al2O3, 14.5%)	Calcium aluminium borosilicate	65997-17-3	-	-	-	-	Insoluble	white solid
Talc (Magnesium Silicate, containing a small portion of aluminium silicate)	Talc	14807-96-6	Talc ($Mg_3H_2(SiO_3)_4$) (CI 77718); Talcum	$Mg_3(Si_4O_{10})(OH)_2$	379.27	-	Insoluble	-
Mica (CI 77891; silicate minerals of varying chemical composition)	CI 77891	13463-67-7	Titanium dioxide	TiO_2	79.87	-	Insoluble	white solid
Carbohydrates								
Aluminium starch octenylsuccinate (E1452)	Aluminium starch octenylsuccinate	9087-61-0	Starch, hydrogen 2-(octen-1-yl)butanedioate, aluminium salt	$C_{21}H_{44}O_3$	344.57		poorly soluble in water	white powder
Aluminium Sucrose Octasulfate	Aluminium Sucrose Octasulfate	54182-58-0	Aluminium, hexadeca-mu-hydroxytetracosahydroxy[mu8-[1,3,4,6-tetra-O-sulfo-beta-D-fructofuranosyl] alfa-D-gluycopyranoside tetrakis(hydrogen sulfato)(8-)]] hexadeca-	$R\text{-}(CH_2OSO_3^-)_8$ $[Al_2(OH)_5^+]_8$ R = sucrose $C_{12}H_{54}Al_{16}O_{75}S_8$	2086.74		insoluble	white powder
Fatty acids salts								
Aluminium dimyristate	Aluminium dimyristate	56639-51-1	Hydroxybis(myristato-O)aluminium	$2[C_{14}H_{28}O_2]Al.HO$	498.71	-	slightly soluble in water	white powder
Aluminium distearate	Aluminium distearate	300-92-5	Stearic acid aluminium salt	$C_{36}H_{71}AlO_5$	610.93	-	insoluble	white powder
Aluminium stearate	Aluminium stearate	7047-84-9	Aluminium hydroxide	$C_{18}H_{37}AlO_4$	344.47	8.216 7.97	0.00272 mg/L @	white powder

			stearate; aluminium monostearate; Dihydroxyaluminium stearate				25 °C (est)	
Aluminium tristearate	Aluminium tristearate	637-12-7	Stearic acid, aluminium salt	$C_{54}H_{105}AlO_6$	877.39	-	insoluble	white powder
Aluminium octadecanoate	Aluminium tristearate	637-12-7	aluminium(3+) ion trioctadecanoate	$C_{54}H_{105}AlO_6$	877.39	10.81 7.15	1.02e-05 mg/mL	white powder
Hydroxyaluminium Distearate	Aluminium distearate	300-92-5	-	$C_{36}H_{71}AlO_5$	610.93	-	insoluble	white powder
Aluminium magnesium hydroxystearate	-	-	Aluminium magnesium 18-hydroxyoctadecanoate	$C_{36}H_{70}AlMgO_6^{+3}$	649.65	-	-	-
Aluminium stearoyl glutamate	Aluminium stearoyl glutamate	-	Aluminium 2-(1-oxooctadecylamino)pentanedioate (1:3)	$C_{23}H_{43}AlNO_5$	426.21	-	slightly soluble in water	solid

ANNEX 2: Assessment of bioavailability of aluminium in humans after topical application of a representative antiperspirant formulation using a [^{26}Al] microtracer approach

Study Design and Test Material Preparation

In order to address the SCCS' request for data, the study was designed to:

a) Assess the absolute bioavailability of aluminium in healthy female subjects after topical application of a representative antiperspirant formulation
b) Explore the impact of shaving of the axilla on the dermal bioavailability of aluminium
c) Explore the impact of regular product use on the dermal bioavailability of aluminium
Details of the clinical studies by Flarend et al., and this new study (TNO, 2016) are provided below:

Table 3: Comparison of the clinical details between Flarend et al and the TNO (2016) study

	Flarend [2]	TNO (2016)
Number of subjects	2	12
Dose	6 Bq ^{26}Al in an aqueous solution	100 Bq ^{26}Al in a representative topical formulation
Application site	Left axilla	Both axillae (50 Bq ^{26}Al each)
Dosing regimen	Single	Single and repeated*
Application details	Occlusion with bandage for maximally 7 days and daily tape stripping of the axilla (resulting in skin irritation for one of the subjects)	Non-occlusion: subjects were wearing T-shirts during the first 24 hours and to minimise loss of radiolabel to the environment
Shaving regimen	2 days prior to application electric shaving	Adaptation period of 4 weeks with either daily wet shaving** or no shaving at all
Route of administration/study design	Single topical administration	Three topical and one IV administration/cross over design

* dosing after adaptation period without antiperspirants considered to represent a single dose of ACH and dosing after adaptation period with daily use of antiperspirants considered to represent repeated dosing
** shaving was performed on the morning of ^{26}Al application at the clinical site

A ^{26}Al labelled topical formulation, which was representative of an aluminium chlorohydrate (ACH) containing antiperspirant cosmetic product, was prepared:

7µg ^{26}Al-HCl (obtained from Los Alamos Laboratory) was used to prepare ^{26}Al-citrate for the intravenous dose. A lab scale batch of ^{26}Al-ACH was prepared meeting commercial specifications for pH, density, Al:Cl ratio and molecular weight profile. The proportion of ^{26}Al:^{27}Al in the ACH test material was 1:820,000 (i.e. 0.138 µg ^{26}Al applied in 113 mg total aluminium) meaning that, every atom of ^{26}Al detected in the TNO 2016 study would represent 820,000 atoms of aluminium entering the body from the test antiperspirant. The homogeneity of label incorporation (^{26}Al:^{27}Al) was confirmed across molecular weight bands, with mean radioactive concentration 116.8 Bq/g. A simple roll-on test formulation was prepared containing 25% ^{26}Al-ACH (6.25% Al), thickened with 0.625% hydroxyethylcellulose to achieve typical commercial viscosity. A proportion of 1.5g/day of a test formulation was applied to the axilla using positive displacement pipette.

Twelve subjects were recruited for the study; 11 completed the study and one withdrew prior to the IV administration as she became pregnant during the study.

Four treatment periods were included in the study:

A – topical application of ^{26}Al-ACH after daily use of Al-containing antiperspirant without shaving, representing typical repeated exposure.
B – topical application of ^{26}Al-ACH after daily use of Al-containing antiperspirant and daily shaving, representing repeated exposure with worst-case daily shaving behaviour.
C – topical application of ^{26}Al-ACH without daily use of Al-containing antiperspirant without shaving, representing single exposure, to allow direct comparison with the previous human study [2].
D – IV administration of ^{26}Al-$AlCl_3$ for the assessment of absolute bioavailability.
Prior to each of the three topical treatments with ^{26}Al-ACH, a 4-week adaptation was scheduled depending upon which treatment group the subjects were allocated to; e.g. to apply unlabelled antiperspirant and/or whether or not to shave on a daily basis. There were n=4 subjects per group, and each subject served as their own control. All subjects were treated with an intravenous dose (D) at the end of the study.
The key aspects of the cross-over study design are illustrated in Figure 1 below.

i)

ii)

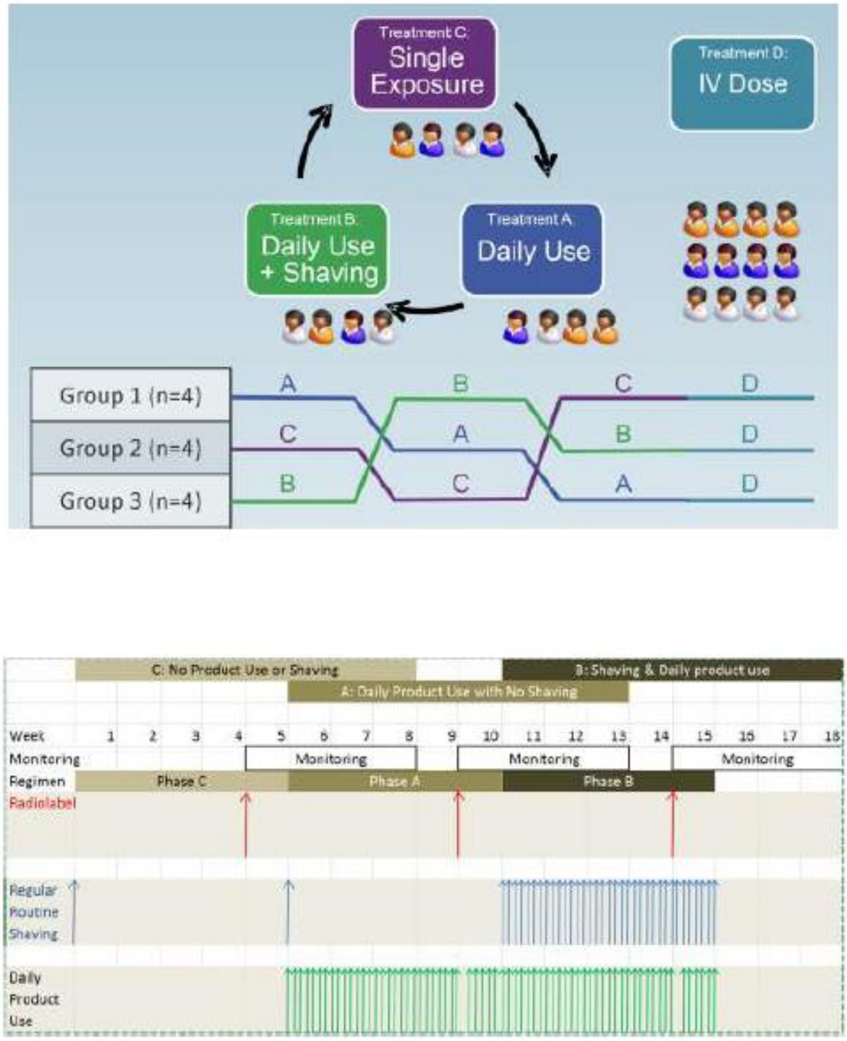

Figure 1 (i) The basic cross-over study design for three groups of n =4 human volunteers and (ii) an example of the detailed study regimen for Group 2 (n =4) - C, A, B, D (not showing the intravenous stage (D).

Results from blood and urine measurements:

^{26}Al was measured in the blood and urine of treated subjects, using an accelerator mass spectrometry method developed by TNO. Blood and urine were also analysed for non-radioactive ^{27}Al using inductively coupled plasma high resolution mass spectroscopy (ICP MS). The full details of blood and urine sample collection and preparation are provided in the full report (Annex I).
The highly sensitive lower limit of quantification (LLOQ) for AMS measurements of ^{26}Al in blood was 0.122 fg/ml and in urine samples the LLOQ was 61 ag/ml. Whole blood samples were analysed (not plasma), to avoid any potential impact of protein binding in the analysis. Samples were taken at -30, 5, 15, 30, 1, 2, 4, 6, 8, 10, 12, 24 hours, then 3, 4, 8, 15, 22 and 29 days, post dose administration. Whilst ^{26}Al was readily detectable in blood samples following IV exposure (which was 1/100th the amount of dermal exposure), all blood measures following dermal exposure were lower than the LLOQ, except for two samples (treatment B, subject 11, 2 hr value: 0.13 fg/ml and treatment C, subject 7, 6 hr value: 0.14 fg/ml). Since ^{26}Al had been detectable in the Flarend pilot study, the low levels of

quantifiable ^{26}Al were unexpected because the dose of ^{26}Al used in this study was 20 times higher than that used in the Flarend pilot study and the LLOQ was the same.
As a back-up in the study, and to provide some evidence on urinary excretion, spot urine samples were taken in the study at 24 hours, 3, 4, 18, 15, 22 and 29 days post-dose and normalised to creatinine concentration. Whilst creatinine correction can be used to correct spot urine samples for differences in urine volume output between volunteers and time points, it cannot correct for the likely aluminium concentrations that would have been excreted in bladder voidings prior to the 24 hours spot test. This means that the quantity of aluminium excreted in the early part of the first 24 hours is unknown. For the IV doses, the impact of missing the first 12+ hours of excretion is substantial since the majority of the IV dose of ^{26}Al is lost from the blood in the minutes and hours post dose (Figure 2 below), meaning that using 24 hour spot urine to estimate IV dose is likely a substantial underestimate of internal exposure.
For the dermally applied samples, the impact is likely much smaller since the absorption kinetics across the skin would be slower, meaning the 24 hours spot urine samples would better reflect internal exposure. Since the IV data is the benchmark for assessing the absolute bioavailability in this study design, the uncertainty introduced by using spot urine measurements would overestimate dermal absorption, thus the uncertainty adds to the conservatism in this assessment.
Following IV exposure, levels of ^{26}Al in blood and urine were seen to decrease rapidly (Figure 2a and 2b below).

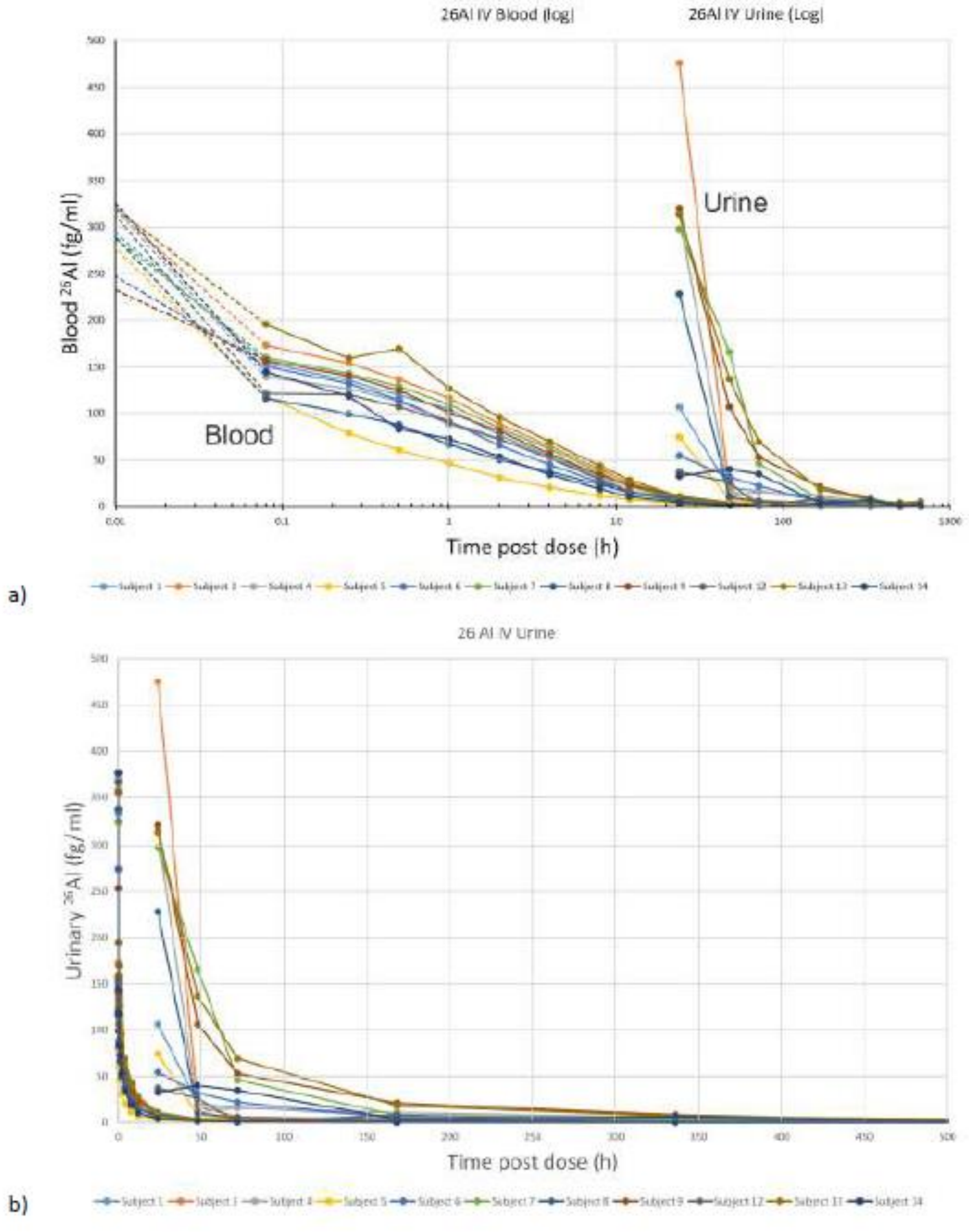

Figure 2 Blood and urine measurement (fg/ml) of ^{26}Al following intravenous dosing in 11 human volunteers a) on a logarithmic scale and b) on a linear scale.

Acknowledging the limitations and consequent conservatism of using the spot urine samples, a quantitative approach to estimating dermal fraction absorbed was taken using the urine data. Whereas only two blood measurements had quantifiable ^{26}Al, approximately 30% of urine samples (where material becomes more concentrated in the bladder over hours) had quantifiable ^{26}Al following dermal exposure, allowing for a more reliable estimate of dermal bioavailability using the urine data. An approach was taken to estimate fraction absorbed where, for samples in which no aluminium was detectable, a value of either zero, 50 % LOD or the LOD was used, and similarly for those samples where the measurements were unquantifiable, either zero, 50% LLOQ or the LLOQ was used. Table 4 below shows the estimations for dermal fraction absorbed taking these approaches.

Table 4 Percentages of the applied topical dose absorbed following three different topical treatment periods (A, B and C – see Figure 1(i) below), and all data taken together, as calculated by non-compartmental methods from urinary excretion data. Mean, sd, coefficient of variation (%) and minimum and maximum observation among 11 subjects are given. Lower, half LLOQ based and upper estimate represent strategies to deal with urine concentrations below LLOQ (see Annex I for details).

Application	A	B	C	All
Lower estimate: values <LLOQ replaced with 0				
mean	0.0056	0.0058	0.0100	**0.0071**
sd	0.0055	0.0107	0.0195	0.0129
%cv	97	184	195	181
min	0.0007	0.0004	0.0000	0.0000
max	0.0167	0.0363	0.0611	0.0611
Half LLOQ based estimate: values <LLOQ replaced with ½LLOQ; values < LOD replaced with ½LOD				
mean	0.0078	0.0081	0.0122	**0.0094**
sd	0.0064	0.0113	0.0192	0.0131
%cv	81	140	158	140
min	0.0021	0.0022	0.0020	0.0020
max	0.0200	0.0410	0.0625	0.0625
Upper estimate: values <LLOQ replaced with LLOQ; values < LOD replaced with LOD				
mean	0.0100	0.0103	0.0144	**0.0116**
sd	0.0075	0.0120	0.0191	0.0134
%cv	75	117	133	116
min	0.0031	0.0032	0.0030	0.0030
max	0.0234	0.0456	0.0639	0.0639

Figure 1(i)

The approach of using the Half LLOQ as a conservative replacement value for non-quantifiable samples, has been used previously in aluminium risk assessment by the Norwegian VKM, and is regarded equally in this risk assessment as adequately conservative. Therefore, a value of 0.0094% dermal fraction absorbed will be taken forward into the risk assessment.

The study design demonstrated no significant difference between single and daily application on systemic exposure, as well as no evidence of an impact of daily shaving on the absolute dermal bioavailability of aluminium after topical application of a representative antiperspirant formulation. The results of this study are consistent with the observations by Flarend et al., and also indicate the *in vitro* human skin absorption study by Pineau et al., overestimates absorption.

In addition to measuring ^{26}Al by Accelerator Mass Spectrometer (AMS) for the absolute bioavailability determination, total aluminium was measured in study samples using Inductively Coupled Plasma Mass Spectrometry (ICP MS). The data for individual subjects in shown in Figure 3.

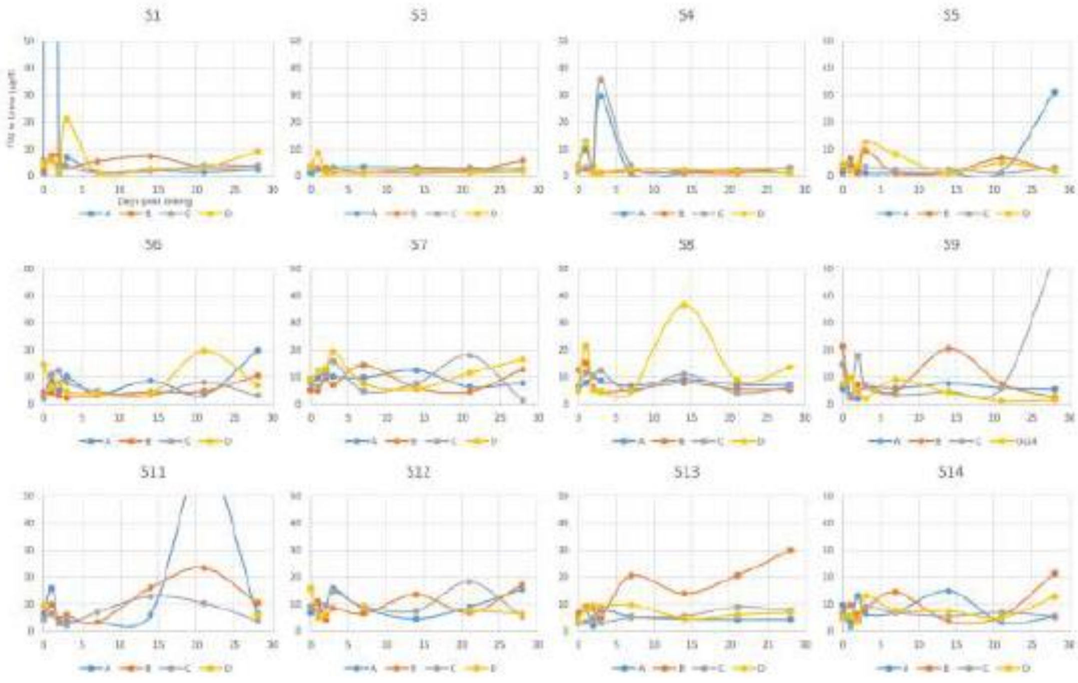

Figure 3 Comparison of ^{27}Al measures (µg/L) in the urine of individual human volunteers, measured in spot samples days after dosing, in the TNO study (2016).

This ‘background’ aluminium in the body represents overall exposure including food, drink, and other environmental sources. This would also represent release or turnover of internal aluminium burden (e.g. bone) that may have accumulated over long periods of time. These total aluminium measurements provide an additional line of evidence to suggest antiperspirants make only a minor contribution to systemic exposure. Average levels in urine of 9.5 µg/L were consistent with the published German Human Biomonitoring Commission reference value of 15 µg/L. Although urinary aluminium levels varied substantially between subjects, and over time within each subject, there was no difference between dermal phases A and B, where ^{27}Al containing antiperspirants use was mandatory, and dermal phase C where antiperspirant use was prohibited. There was also no obvious impact of applying the test antiperspirant formulation (6.25% Al) at the 90th percentile amount (1.5 g in total). Clearly, the contribution from antiperspirant use is small compared to the ‘noise’ of other exposures. This provides supporting evidence that antiperspirant use is likely a minor source of exposure, with minimal impact on body burden.

SCCS comment

The SCCS has asked for detailed data/information on the fate and mass-balance of the test compound because the speciation of Al in blood, after dermal absorption of $^{26}AlCl_3$is not clear, and that the clearance of aluminium from the dermal or IV routes could be different. In the absence of this information, it will not be appropriate to conclude on the absolute bioavailability.

The SCCS has also noted that different approaches are available to determine/estimate bioavailability. For example, the approach based on mass-balance refers to an experiment where the dermal absorption is inferred from the amount removed from the skin following the exposure period, together with urinary and faecal excretion data. A limitation of this approach to estimate Al bioavailability is that it would not take into account the Al retained, excreted by non-renal routes, or excreted by the kidneys after study completion.

The second approach is based on comparison of the areas under the plasma concentration-time curve after dermal and intravenous administration. However, this might not have been appropriate for dermal absorption study of Al because although Al could be readily measured in blood following IV administration and AUCs calculated, none of the 204 blood samples collected in the current study were above LLOQ (0.12 fg/ml) following dermal application making it impossible to determine AUC for this route of administration.
Another approach is based on inference of absorption from urinary excretion of the applied dose. On these lines, a value of 0.0094% dermal fraction absorbed was determined in the current study. However, this fraction is not defined as the cumulative fraction of the dose excreted upon topical application at the end of the study but as the ratio of cumulative fractions of the dose excreted between topical and intravenous applications. Instead, an alternative approach was used to calculate dermal bioavailability based on the ratio of cumulative fractions of the dose excreted in urine between topical and intravenous applications. Therefore, for the reason given below, the data provided do not allow calculation of the fractions of the dose excreted in urine:
Approximately 70% of urine samples were below LLOQ and LOD (the applicant replaced samples below LLOQ and LOD by LLOQ and LOD, or half of those values). The SCCS notes that no guideline exists for this approach and considers that calculation of kinetic parameter with a majority of data below the LLOQ remains a challenge.
The collection of urine should have continued until all Al has been completely excreted (five times the half-life). The SCCS notes that aluminium kinetic scientific publications show that complete elimination of Al would require more time than the duration of the clinical study. The SCCS also notes that the clinical study duration was not sufficient to see complete elimination of AI as aluminium kinetic may be different following the dermal route when compared to the oral route.
Spot urine samples were taken in the study at 24 hours, 3, 4, 18, 15, 22 and 29 days (as a back-up in the study), this means that the quantity of aluminium excreted in the early part of the first 24 hours is unknown, and this presents a major limitation in the calculation of fraction of the dose excreted in urine after IV administration (see below with the Talbot et al study, where 60% of Al was eliminated in urine during the first 24 h).
The Al concentration in urine was estimated from urine samples at different time points and not collection over 24h. This calculation is based on the typical (not measured) 24 h urine production (L/day), estimated by dividing the typical creatinine excretion of 10 mmol/day (not measured) by the measured creatinine concentration (mmol/L) in the urine (data not provided). Next each measured 26Al concentration is multiplied by the 24 h urine production (estimated) and divided by the applied dose, to derive the fraction of the dose excreted in that 24 h window. The exact Al concentration therefore remains unknown.
The alternative approach adopted in this study is based on the premise that urinary excretion is directly proportional to plasma concentration. But the relationship between serum concentration and renal clearance remains to be established.

The assumption underlying this approach is that the ratio of renal clearance (or total clearance) is the same for the IV and dermal administration. However, the SCCS is of the opinion that there is evidence in published literature that clearance could differ according to the route of administration and the speciation:
1-The publication from Talbot et al 1995 and Steinhausen et al 2004 investigated the aluminium kinetics in humans. In the Talbot study, following 84 ng injection of ^{26}Al citrate (n = 6 subjects), aluminium is predominantly excreted in urine. It has been reported that 59% of ^{26}Al is excreted in the first 24 hours post-injection. In the Steinhausen study, following 1 ng injection of $^{26}AlCl_3$ (n= 2 subjects), aluminium is also excreted in urine. It has been reported that 25 and 28% of ^{26}Al is excreted after 5 days post-injection.
It also appears that the difference in clearance of aluminium exists according to speciation during administration of $AlCl_3$ versus Aluminium citrate.
2-In plasma, the predominant binding ligands for Al are transferrin and citrate, with a percentage of association of 90 % and 10 %, respectively. (Yokel et al, 2000). Citrate

forms a small molecular weight complex with Al that appears to enhance Al distribution and elimination when compared to Al transferrin.
3-After dermal absorption, Al could be released into blood as Al transferrin as well Al citrate, but due to the avid transferrin binding for Al, it is likely that Al-transferrin would account for the majority of the Al that distributes to the tissues. Al binding by transferrin in this way would prevent rapid clearance.
In the same clinical study provided by the applicant, after IV administration, Al is already binding to citrate, and for one part of this complex clearance could be more rapid.
Therefore, the speciation of Al in blood, after dermal absorption of $^{26}AlCl_3$ is not clearly understood, and clearance of aluminium could be different according to the dermal or the IV administration, leading to inappropriateness of the calculation of absolute bioavailability.
