Scientific Committee on Consumer Safety

SCCS

OPINION ON

the safety of aluminium in cosmetic products

The SCCS adopted this opinion at its 5th plenary meeting

of 27 March 2014

About the Scientific Committees

Three 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.

They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

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 all types of 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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1. BACKGROUND

DG Health and Consumers, unit B2 Health Technology and Cosmetics, received in September 2011 a report submitted by the 'Agence française de sécurité sanitaire des produits de santé (AFSSAPS)' which raises concern on the use of aluminium in antiperspirants and deodorants. Other Member States asked to pay attention to aluminium present in other cosmetic products, such as lipsticks and toothpastes.

In October 2012, the Commission received a 'Scientific discussion paper on systemic exposure to Aluminium from dermal exposure to soluble salts' by Cosmetics Europe, in which they provide information on the wide variety of cosmetic ingredients containing Aluminium, which perform several different functions in several product types. In particular, the contribution from Cosmetics Europe focuses on the following:

Water-soluble aluminium containing ingredients that include: Simple Inorganic salts; Simple Organic Salts; Aluminium Benzoate, Chlorohydrates. These ingredients can be used in skin care products. Functions reported in Cosing are astringent, buffering agent, deodorant, antiperspirant.

Water-insoluble aluminium containing ingredients that include: Minerals, Glasses and Clays; Aluminium Lakes; Carbohydrates; Fatty acids salts.
The Insoluble Minerals, Glasses and Clays are typically added to cosmetic products as bulking agents, coloured pigments, and sometimes as mild abrasives. Aluminium colloidal colorants 'lakes' are mainly used in lipsticks.

According to Cosmetics Europe, the several physico-chemical properties of aluminium in the different chemical compounds seem to make it difficult to determine dermal and oral bioavailability, leading to uncertainty in the exposure assessment.

In June 2013, the Commission received a dossier on "the risk assessment of Aluminium exposure through food and the use of cosmetic products in the Norwegian population" by the Norwegian Scientific Committee for Food Safety. Shortly summarized, the exposure to aluminium through food and the use of cosmetic products in the Norwegian population was calculated and compared to two toxicological reference values: the tolerable weekly intake (TWI) of 1 mg Al/kg bw/week established by EFSA (2008), and the provisional tolerable weekly intake (PTWI) of 2 mg Al/kg bw/week established by JECFA (2011). The TWI/PTWI values are based on studies of developmental neurotoxicity in laboratory animals. In cosmetics, lipstick/lip gloss, antiperspirants and a few brands of whitening toothpaste were considered the relevant sources of exposure to aluminium. The Norwegian risk assessment aims at showing that cosmetic products, and in particular antiperspirants, contribute considerably more than diet to the total systemic exposure to aluminium in persons using such products.

2. TERMS OF REFERENCE

1. *In view of the above, SCCS is requested to assess the possible risk for human health from the presence of Aluminium in cosmetics, in particular in products such as antiperspirants and deodorants, lipsticks and toothpastes, considering the exposure from other sources, such as food and food supplements.*

2. *In the event 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

More than twenty-five aluminium compounds can be used in cosmetic products. The aluminium chlorohydrate is one of the most widely used, especially as antiperspirant.

Confusion exists with respect to the correct terminology for underarm deodorants that are actually present on the market since they often contain ingredients typical to both deodorants and to antiperspirants..

DEODORANTS are cosmetic products that prevent body odour caused by the bacterial breakdown of transpiration (sweating) in armpits, feet, and other areas of the body. The bacteria (mostly own skin flora) feed in particularly on the sweat from the apocrine glands and on dead skin and hair cells, releasing substances in their waste, which are the primary cause of body odour. Underarm deodorants are popular and their typical composition consists of perfume, antibacterial substances and substances that neutralize unpleasant odour, or a combination of these ingredients. Deodorants may act directly or indirectly. Such an indirect action might be the result of hydrolysis by the sweat of more complex compounds into antibacterial components (eg. benzyl benzoate releasing benzyl alcohol and benzoic acid) or by encapsulation of actives, creating as such a depot effect releasing only active ingredients when there is contact with sweat.

ANTIPERSPIRANTS are cosmetics that diminish or significantly reduce the amount of sweat by formation of little plugs in the upper part of the eccrine sweat ducts as such reducing the moist environment in which skin bacteria thrive. The pH plays a role in this process. Typical ingredients are Al-derivatives (Al-chloride, Al-chlorohydrate, Al-Zr-complexes, etc) that also exhibit astringent properties which add to their antiperspirant function.

3.2. Function and uses

Aluminium metal is used as a structural material in the construction, automotive and aircraft industries, in the production of metal alloys, in the electric industry, in cooking utensils and in food packaging. Aluminium compounds are used as antacids, antiperspirants and food additives (ATSDR, 2008).

Aluminium is present in a wide range of consumer products (Cosmetics Europe, 2012), including but not limited to the product types highlighted in the dossier of AFSSAPS, i.e. antiperspirants, lipsticks and toothpastes.

A large variety of different aluminium containing compounds is used in cosmetics including simple inorganic and organic salts, chlorohydrates, minerals, glasses and clays, aluminium lakes, carbohydrates and fatty acids salts.

Antiperspirants

Aluminium salts in antiperspirants, such as chlorohydrates, form insoluble aluminium hydroxide polymer gel plugs within sweat ducts to temporarily prevent sweat reaching the surface of the skin.

Lipsticks

Aluminium colloidal colorants 'lakes' are mainly used in lipsticks. Colloidal colorants are prepared under aqueous conditions by reacting aluminium oxide with the pigments in order to make them insoluble (EFSA, 2008). Aluminium oxide is usually freshly prepared by reacting aluminium sulfate or aluminium chloride with sodium carbonate or sodium bicarbonate or aqueous ammonia. Due to the complex molecule structures and high molecular weights of organic lakes, the aluminium represents only a small part of the weight of the raw material of which the extractable part will represent only a fraction. Aluminium content in the lakes usually ranges from 0.01 to 10 %, but a lake with 18 % aluminium has also been found on the market.

Toothpastes

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

Given the ubiquitous nature of aluminium in the environment, it is also reasonable to expect aluminium to be present as a minor component in many naturally derived ingredients (both botanical and mineral).

Table 1. Aluminium compounds which may be used in cosmetic products based on the CosIng list –INCI names

Ingredients without restrictions	Restricted ingredients (Annex III)
Aluminium Sulfate= ALUMINUM SULFATE	
Aluminium Bromohydrate= (INCI) ALUMINUM BROMOHYDRATE	
Aluminium Chloride = (INCI) ALUMINUM CHLORIDE	
Aluminium Chlorohydrate = (INCI) ALUMINUM CHLOROHYDRATE	
Aluminium Chlorohydrex = (INCI) ALUMINUM CHLOROHYDREX	
Aluminium Chlorohydrex Peg = (INCI) ALUMINUM CHLOROHYDREX PEG	Aluminium Zirconium Octachlorohydrate=ALUMINUM ZIRCONIUM OCTACHLOROHYDRATE
Aluminium Chlorohydrex Pg = (INCI) ALUMINUM CHLOROHYDREX PG	Aluminium Zirconium Pentachlorohydrate=ALUMINUM ZIRCONIUM Pentachlorohydrate
Aluminium Citrate= (INCI) ALUMINUM CITRATE	Aluminium Zirconium Pentachlorohydrex Gly =ALUMINUM ZIRCONIUM
Aluminium Dichlorohydrate = (INCI) ALUMINUM DICHLOROHYDRATE	Aluminium Zirconium Tetrachlorohydrate=ALUMINUM ZIRCONIUM Pentachlorohydrex Gly
Aluminium Dichlorohydrate Peg = (INCI) ALUMINUM DICHLOROHYDRATE PEG	Aluminium Zirconium Tetrachlorohydrex Gly=ALUMINUM ZIRCONIUM Tetrachlorohydrex Gly
Aluminium Dichlorohydrate Pg = (INCI) ALUMINUM DICHLOROHYDRATE PG	Aluminium Zirconium Trichlorohydrate=ALUMINUM ZIRCONIUM Trichlorohydrate
Aluminium Sesquichlorohydrate = (INCI) ALUMINUM SESQUICHLOROHYDRATE	Aluminium Zirconium Trichlorohydrex Gly=ALUMINUM ZIRCONIUM Trichlorohydrex Gly
Aluminium Sesquichlorohydrex Peg = (INCI)ALUMINUM SESQUICHLOROHYDRATE PEG	
Sodium Alum	
Sodium Aluminium Chlorohydroxy Lactate = (INCI) SODIUM ALUMINUM CHLOROHYDROXY LACTATE	
Sodium Sesquichlorohydrex Pg = (INCI) ALUMINUM SESQUICHLOROHYDRATE PG	

3.3. Toxicological Evaluation

Many reports have been published which include extensive review of the effects of aluminium on health (EFSA, 2008, 2011, ATSDR, 2008, JECFA, 2008, 2011...). Both EFSA (2008) and JECFA (2011) commented on the lack of specific toxicological data for food additives containing aluminium and on the limitations of the available animal studies. The more recent evaluation, the 2011 JECFA evaluation, was based on new data which included a multigenerational study and 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 developmental study 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, the JECFA considered it appropriate to revise the PTWI 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.

Below is a brief summary taken from these previous reports:

No studies were located regarding dermal effects in humans after dermal exposure to various forms of aluminium.

Acute toxicity
The acute oral toxicity of those aluminium compounds for which data are available (bromide, nitrate, chloride and sulfate) is moderate to low, with LD50 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).

Local effect
Aluminium compounds are widely used in antiperspirants without harmful effects to the skin (Sorenson *et al.* 1974). Some people, however, are unusually sensitive to topically applied aluminium compounds. Skin irritation was reported in subjects following the application of aluminium chloride hexahydrate in ethanol used for the treatment of axillary or palmar hyperhidrosis (excessive sweating) (Ellis and Scurr 1979; Goh 1990) or the use of a crystal deodorant containing alum (Gallego *et al.* 1999).

Systemic toxicity after repeated exposure
No studies were located regarding dermal effects in animals following intermediate- or chronic- duration dermal exposure to various forms of aluminium.

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

The main toxic effects of aluminium that have been observed in experimental animals are neurotoxicity and nephrotoxicity. Neurotoxicity has also been described in patients dialysed with water containing high concentrations of aluminium, but epidemiological data on possible adverse effects in humans at lower exposures are inconsistent (see chapter 3.6.2.).

Based on a neuro-developmental toxicity study of aluminium citrate administered via drinking water to rats, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a Provisional Tolerable Weekly Intake (PTWI) of 2 mg/kg bw (expressed as

aluminium) for all aluminium compounds in food, including food additives. The Committee on Toxicity of chemicals in food, consumer products and the environment (COT) considers that the derivation of this PTWI was sound and that it should be used in assessing potential risks from dietary exposure to aluminium.

Reproductive and developmental toxicity

Taken from COT (2013)

Studies of reproductive toxicity in male mice (intraperitoneal or subcutaneous administration of aluminium nitrate or chloride) and rabbits (administration of aluminium chloride by gavage) have demonstrated the ability of aluminium to cause testicular toxicity, decreased sperm quality in mice and rabbits and reduced fertility in mice. No reproductive toxicity was seen in females given aluminium nitrate by gavage or dissolved in drinking water. Multi-generation reproductive studies in which aluminium sulfate and aluminium ammonium sulfate were administered to rats in drinking water, showed no evidence of reproductive toxicity (COT, 2013).

High doses of aluminium compounds given by gavage have induced signs of embryotoxicity in mice and rats – in particular, reduced fetal body weight or pup weight at birth and delayed ossification (EFSA, 2008). Developmental toxicity studies in which aluminium chloride was administered by gavage to pregnant rats showed evidence of fetotoxicity, but it was unclear whether the findings were secondary to maternal toxicity (FAO/WHO, 2012).
Poirier et al. (2011) carried out a twelve-month neuro-developmental toxicity study of aluminium citrate administered via the drinking water to Sprague-Dawley rats, which was conducted according to Good Laboratory Practice (GLP). Aluminium citrate was selected for study since it is the most soluble and bioavailable aluminium salt. Pregnant rats were exposed to aluminium citrate from gestational day 6 through lactation, and then the offspring were exposed post-weaning until postnatal day 364. An extensive functional observational battery of tests was performed at various times. Evidence of aluminium toxicity was demonstrated in the high (300 mg/kg bw/day of aluminium) and to a lesser extent, the mid-dose groups (100 mg/kg bw/day of aluminium). In the high-dose group, the main effect was renal damage, resulting in high mortality in the male offspring. No major neurological pathology or neurobehavioural effects were observed, other than in the neuromuscular subdomain (reduced grip strength and increased foot splay). Thus, the lowest observed adverse effect level (LOAEL) was 100 mg/kg bw/day and the no observed adverse effect level (NOAEL) was 30 mg/kg bw/day. Bioavailability of aluminium chloride, sulfate and nitrate and aluminium hydroxide was much lower than that of aluminium citrate (Poirier et al., 2011). This study was used by JECFA as key study to derive the PTWI.

Genotoxicity

Taken from EFSA (2008)

Aluminium compounds were non-mutagenic in bacterial and mammalian cell systems, but some produced DNA damage and effects on chromosome integrity and segregation in vitro. Clastogenic effects were also observed in vivo when aluminium sulfate was administered at high doses by gavage or by the intraperitoneal route. Several indirect mechanisms have been proposed to explain the 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 DNAase, have been suggested to explain the induction of structural chromosomal aberrations, sister chromatid exchanges, chromosome loss and formation of oxidized bases in experimental systems. The EFSA Panel noted that 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.

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.

Carcinogenicity

The International Agency for Research on Cancer (IARC) has 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." 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.

The database on carcinogenicity of aluminium compounds is limited. The majority of available studies are old and reports contain little experimental detail. Dose levels of aluminium were generally low and the EFSA Panel concluded that it was not possible to reach a conclusion on the carcinogenicity of aluminium from these studies. The Panel also noted the absence of epidemiological evidence for carcinogenicity of aluminium compounds used therapeutically. IARC concluded that aluminium itself is unlikely to be a human carcinogen, despite the observation of an association between inhalation exposure to aluminium dust and aluminium compounds during production/processing and cancer in workers.

Overall the EFSA Panel concluded that aluminium is unlikely to be a human carcinogen at exposures relevant to dietary intake.

Carcinogenicity studies in animals have been reviewed by SCCS and are summarized in Annex 1.

There was no indication of carcinogenicity at high dietary doses (up to 850 mg Al/kg bw/day) in animal's studies, and SCCS considers that carcinogenicity is not expected at exposure levels which are achieved via cosmetic use.

3.4. Dermal / percutaneous absorption

For cosmetic uses of aluminium, the majority would be applied in formulations where the aluminium would be insoluble, which means that very little of the applied aluminium might be bioaccessible for skin absorption. The notable exception being antiperspirants where the aluminium is soluble at low pH in the formulation, before being rendered insoluble as it is neutralised by the sweat on the skin's surface and within the sweat ducts (Cosmetic Europe, 2012).

Taken from ATSDR (2008)
There are limited human data on the dermal absorption of aluminium. Aluminium compounds are common additives in underarm antiperspirants. The active ingredient is usually an aluminium chlorohydrate salt, which is thought to form an obstructive plug of aluminium hydroxide within the sweat duct (Hostynek *et al.* 1993; Reiber *et al.* 1995).

A preliminary study of the dermal absorption of aluminium from antiperspirants using aluminum-26 has been performed (Flarend *et al.* 2001). After repeated exposure for 6 days to aluminum chlorohydrate 21 % (about 13 mg of aluminium) to each axilla under occlusive dressing in two volunteers (one man and a woman), on skin previously tape stripped twice, blood and urine samples were collected. Aluminium was detected in the blood 6 hours after the first application and remained detectable for 15 days. The results of this study estimate that the proportion of aluminium is absorbed averaged 0.012%. The shortcomings of this study are that it was not done in accordance with good practice (GCP) and it was performed using only 2 volunteers.

A case of hyperaluminaemia (3.88 +/- 0.07 µmol/L) in a 43-year-old woman who applied about 1g of an aluminium chlorhydrate-containing antiperspirant cream on each shaved underarm every morning for 4 years was reported by Guillard *et al.* (2004). A decrease in aluminium concentration in plasma and urine was observed, reaching the reference range in the third (for urine) and eighth (for plasma) month after antiperspirant use was discontinued.

SCCS comment
Beside this case report, for which only brief details are available, there is no evidence for a link between hyperaluminaemia and antiperspirant uses.

Dermal absorption studies were not located for animals; however a study by Anane *et al.* (1995) found increased levels of aluminium in the urine of mice exposed to 0.1 or 0.4 µg/day aluminium chloride (0.01– 0.04 µg Al/day) applied daily to a 4 cm^2 shaved area for 130 days. Interpretation of this study is limited due to the lack of control measures to prevent the animals from licking their fur and thus ingesting aluminium.

In a recently published study (Pineau *et al.*, 2012), dermal absorption of aluminium from three cosmetic formulations of antiperspirant was studied by using human full skin biopsies mounted in FranzTM diffusion cell. This study is reported in detail below:

Guideline: OECD 428 guideline, 2004 and SCCP 2003
Species/strain: Caucasian human skin, from skin bank (Poitiers, France)
Membrane integrity: transepidermal water loss
Group size: five samples (2 cells per donor, 5 donors for all tests).
Method: in vitro, Franz diffusion cell (static type);
Test substance: three cosmetic formulations provided by Unilever Laboratories (Seacroft, Leeds, UK):

> Aerosol base: 38.5% aluminium chlorohydrate- $Al_2(OH)5Cl,2H_2O$, corresponding to 9.59% Al): 2.59+/- 0.28 mg/cm^2 applied, corresponding to 248.45+/-27.09 ug/cm^2 Al
> Roll-on emulsion: (14.5% aluminium chlorohydrate- $Al_2(OH)5Cl,2H_2O$, corresponding to 3.61% Al): 4.55 +/- 0.28 mg/cm^2 applied, corresponding to 164.30+/-10.21 ug/cm^2 Al
> Stick 21.2% aluminium chlorohydrate- $Al_2(OH)5Cl,2H_2O$, corresponding to 5.28% Al): 3.1 +/- 0.64 mg/cm2 applied, corresponding to 163.80+/-33.77 ug/cm^2 Al

Batch: batch numbers are not given
Purity: not stated
Test item: as above
Dose volume: volume not stated, weights are given

Receptor fluid: phosphate-buffered saline (pH 7.4) containing 0.1% sodium azide as preservative with 5% Brij 98 polyoxyethylene olelyl ether as non-ionic solubilizer
Method of Analysis: Zeeman electrothermal spectrophotometry using a Perkin-Elmer atomic absorption spectrophotometer model 'Analyst 600'
GLP: not stated
Study period: 6 hours, 12 hours, 24 hours

Results:

Table 2

Total amounts of aluminum (µg/cm²) recovered [mean± SD, n = 10 cells/formulation (2 cells/donor, 5 donors)].

	Viable epidermis (E) [a]	Dermis (D) [a]	Receptor Fluid (RF) 24 h [a]	Total skin absorption (E + D + RF) [a]
	µg/cm²	µg/cm²	µg/cm²	µg/cm²
Normal skin				
«Aerosol» base	1.49 ± 2.09	0.28 ± 0.18	0.07 ± 0.01	1.84 ± 2.23
«Roll-on» emulsion	0.30 ± 0.35	0.16 ± 0.05	0.07 ± 0.01	0.53 ± 0.38
Stick	1.30 ± 1.25	0.41 ± 0.27[†]	0.10 ± 0.05	1.81 ± 1.45
Blank samples (n = 5)	0.022 ± 0.004	0.13 ± 0.04	0.082 ± 0.006	0.23 ± 0.04
Stripped skin				
Stick	9.42 ± 7.82[##]	2.01 ± 1.14[##]	0.07 ± 0.03[#]	11.50 ± 8.90[##]
Blank samples (n = 5)	0.05 ± 0.02	0.18 ± 0.05	0.09 ± 0.01	0.32 ± 0.07

[#]$p < 0.01$, [##]$p < 0.005$, [##]$p < 0.0001$ compared to stick normal skin.
[a] In all the samples (n = 10 diffusion cells/formulation). Aluminum amounts were detected and quantified.

Table 3

Total amounts of aluminum (µg/cm²) recovered [mean ± SD, n = 10 cells/formulation (2 cells/donor, 5 donors)].

	Horny layer (S1) [a]	Horny layer (S2–S3) [a]	Full horny layer (S) [a]	Total skin quantity (S + viable epidermis + dermis)
	µg/cm²	µg/cm²	µg/cm²	µg/cm²
Normal skin				
«Aerosol» base	2.20 ± 2.14	1.78 ± 1.76	3.98 ± 3.89	5.75 ± 6.17
«Roll-on» emulsion	1.36 ± 1.24	0.88 ± 0.65	2.24 ± 1.87	2.69 ± 2.27
Stick	2.70 ± 1.15*	1.73 ± 0.71	4.43 ± 1.79*	6.14 ± 3.31*
Blank samples (n = 5)	0.000 ± 0.000	0.044 ± 0.017	0.044 ± 0.017	0.20 ± 0.06
Stripped skin				
Stick				11.43 ± 9.00
Blank samples (n = 5)				0.32 ± 0.08

[a] In all the samples (n = 10 diffusion cells/formulation). Aluminum amounts were detected and quantified.
* $p < 0.05$ compared to «roll-on» emulsion normal skin.

Receptor fluid measurements showed no significant difference between controls and either normal or damaged skin.

The amount of aluminium deposited in skin and the amount that penetrated the skin differed between the three cosmetic formulations tested (see Tables 2 and 3, from Pineau et al, 2012). The total absorption of aluminium in the viable epidermis, dermis and receptor fluid was as follows:

Aerosol base:	1.84+/-2.23 ug/cm²
Roll-on emulsion:	0.53+/-0.38 ug/cm²
Stick:	1.81+/-1.45 ug/cm²

However, more aluminium was captured by the *stratum corneum* (horny layers: see Table 3). The use of tape-stripped skin with the 'stick' demonstrated higher skin absorption at 11.50+/-8.90 ug/cm², illustrating the function of the *stratum corneum* as a barrier.

SCCS comment
Aluminium salts in antiperspirants, such as chlorohydrates, form insoluble aluminium hydroxide polymer gel plugs within sweat ducts to temporarily prevent sweat reaching the surface of the skin. Aluminium salts in antiperspirants 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. This limits the bioaccessibility of aluminium on living skin.

Aluminium in antiperspirants is thought to work by (a) precipitating inside the eccrine sweat ducts as insoluble aluminium hydroxide, and (b) altering sweating by either a direct constrictor effect on the eccrine duct lumen or via an anticholinergic action.

The publication from Pineau *et al.* (2012) reports a study performed by the cosmetic industry some years ago (2007) at the request of Afssaps. The authors used transepidermal water loss to confirm the viability of the epidermis they used in their study. The study is

limited by the lack of an intact vasculature. There are many other shortcomings in this absorption study. Aluminium levels were measured by validated methods (Electrothermal Atomic Absorption Spectrophotometry with Zeeman effect, EAAS); however, there was large variability in measured aluminium in all samples (standard deviations were typically 63% of the measured value in all treated samples) and there was also large variation in mass balance values (51±10% to 141±29%), which means this study falls outside the SCCS criteria for validity. The mass balance values were omitted when the PMIC study was published (Pineau *et al.* 2012), preventing public scrutiny of this key criterion for a valid study.

The available studies are of poor quality and have not been carried out according to the current requirements. In the absence of any better data to estimate skin penetration of aluminium, the SCCS considers that aluminium absorption after dermal exposure is still very poorly understood. A conclusion on internal exposure to aluminium following cosmetic use cannot be drawn.

3.5. Toxicokinetics

Aluminium present in food and drinking water is poorly absorbed through the gastrointestinal tract. The bioavailability of aluminium is dependent on the form in which it is ingested and the presence of dietary constituents with which the metal cation can complex (see Section 3.5.1). Ligands in food can have a marked effect on absorption of aluminium, as they can either enhance uptake by forming absorbable (usually water soluble) complexes (e.g., with carboxylic acids such as citric and lactic), or reduce it by forming insoluble compounds (e.g., with phosphate or dissolved silicate).

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 (26Al) 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 utilized 26Al 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 utilized a comparison of the area under the plasma aluminium concentration-time curve after oral and intravenous administration of 26Al 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 Al/day (0.04 mg Al/kg/day) or 4.6 mg Al/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-fold based on chemical form alone. Although bioavailability appears to generally parallel water solubility, insufficient data are available to directly extrapolate from solubility in water to bioavailability. Additionally, due to 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.

3.6. Special investigations

3.6.1. Breast cancer and aluminium containing cosmetics

Based on the observation of a high incidence of breast cancer in the upper outer quadrant adjacent to the usual area of application of deodorants and/or antiperspirants, some scientific teams have advanced the hypothesis of a possible link between antiperspirants and breast cancer.

In 2005, Darbre et al. published works indicating a link between the use of underarm cosmetics such as aluminium-based antiperspirants and breast cancer.

In 2007, aluminium was measured in human breast tissue in a study which separated a tissue component from the fat. Higher levels of aluminium were found in outer regions than inner regions of the breast tissue (but not the breast fat). The reasons for the disproportionate deposition of aluminium could relate to physiological mechanisms not yet understood, it would also be consistent with local absorption of aluminium from long-term antiperspirant use in that region of the body.

Ref.: Exley et al., 2007

In another study from Darbre team, aluminium was measured at very high levels in breast cyst fluid On the basis that antiperspirant is designed to block sweat ducts under the arm and breast cysts arise from blocked breast ducts in the adjacent region of the body, it is possible that antiperspirant use could be a cause of breast cysts if sufficient aluminium is absorbed into breast tissue over long-term usage of underarm aluminium salts. For the authors, finding of high levels of aluminium in breast cyst fluid is relevant to this issue.

Ref.: Mannello et al., 2009

Aluminium was also measured in nipple aspirate fluid in 2011 and was found in higher levels in nipple aspirate fluids from women with breast cancer than from those without.

Ref.: Mannello et al., 2011

Using a sensitive quantification technique Rodrigues-Peres et al. (2013) detected similar aluminium concentrations in the central and peripheral regions of breast tumors, and in normal tissues. In addition, they did not detect significant differences in aluminium concentrations as related to the location of the breast tumor within the breast, or to other relevant tumor features such as stage, size and steroid receptor status. This was also the conclusion of House et al. (2013) who did not observe any statistically significant differences in aluminium content across the whole breast tissue from women with breast cancer.

The known genotoxic effects of aluminium might play a role in the development of breast cancer. However, the data currently available on the subject are not sufficient to establish a causal relationship between aluminium exposure and the augmented risk of developing breast cancer.

Human studies

Few epidemiological studies have attempted to address the issue of exposure to antiperspirant and risk of breast cancer development.

Mirick et al. (2002) investigated a possible relationship between use of products applied for underarm perspiration and the risk for breast cancer in women aged 20–74 years (813 cases, 793 controls). The risk for breast cancer did not increase with any of the following activities: 1) antiperspirant (OR = 0.9; P = 0.23) or deodorant (OR = 1.2; P = 0.19) use; 2) product use among subjects who shaved with a blade razor; or 3) application of products within 1 hour of shaving (for antiperspirant, OR = 0.9; P = 0.40; for deodorant, OR = 1.2; P = 0.16). Fakri et al. (2006) interviewed 54 cases of breast cancer and 50 controls were interviewed. They found 82.0% of the controls used antiperspirants compared with 51.8% of cases (P < 0.05). These studies do not support the hypothesis that antiperspirant use increases the risk for breast cancer.

McGrath (2003) reported within a population of breast cancer patients (437 cases) that those who used antiperspirants/deodorants accompanied by axillary shaving were diagnosed at an earlier age with breast cancer (Non-users mean age at diagnoses 68 years, max-users 53 years [p<0.0001], users starting before age 16, mean age 57 years, users starting age 16 or after, mean age 67 year [p<0.0001]). Separately done, shaving alone and use of antiperspirants/deodorants alone were not associated with a significant earlier age of diagnosis.

SCCS comment
The latter study is a case study without any control group. It should be noted that of the 437 cancer patients only 40 patients had not shaved or used antiperspirants/deodorants and of the 349 patients that shaved only 23 patients did not use antiperspirants/deodorants. Moreover, it would have been of interest to know if the age when having their first child differed in the groups. Only 32.5% of the breast cancer patients replied. Thus, the risk of self-selection, information bias is high.

In a review from 2008 (Namer et al., 2008), a group of clinical experts in oncology have analysed published data concerning the link between the use of deodorants/antiperspirants and an increased risk of breast cancer. Fifty-nine studies resulting from the literature search were reviewed and nineteen articles with various methodologies were selected for in-depth analysis. Among these nineteen articles, many are methodologically unsound, do not answer to the questions posed or deal with the question of parabens and were therefore discarded by the reflection group. The expert group's conclusion coincides with those of the French, European and American health authorities. After analysis of the available literature on the subject, no scientific evidence to support the hypothesis was identified and no validated hypothesis appears likely to open the way to interesting avenues of research.

The EFSA noted that the 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. In addition, the animal studies did not show any carcinogenic potential. Moreover, epidemiological data do not establish any conclusive link between dermal aluminium exposure and development of cancer. In conclusion, there are insufficient data to establish a clear relationship between the use of underarm aluminium-based antiperspirants and breast cancer (Afssaps, 2011).

In a recent study, Sappino et al. (2012) have shown that aluminium chloride promotes anchorage-independent growth in human mammary epithelial cells. Their results suggest that aluminium is not generally mutagenic, but it induces proliferation stress, DSBs and senescence in normal mammary epithelial cells; and that long-term exposure to AlCl(3) generates and selects for cells able to bypass p53/p21(Waf1)-mediated cellular senescence.

The authors conclude that these observations do not formally identify aluminium as a breast carcinogen, but challenge the safety ascribed to its widespread use in underarm cosmetics.

Darbre et al. (2013a) point out that in addition to the rising incidence of breast cancer, there are also other characteristics of breast cancer which remain unexplained such as the relative increase in ductal carcinomas and of breast tumours which contain oestrogen receptors (ERs) and that breast cancer has been rising faster among affluent women. They argue that the largest unexplained clinical observation in breast cancer is the disproportionate incidence in the upper outer quadrant of the breast which has risen from 47.9% in 1979 to 53.3% in 2006 in England/Wales and from 38.3% in 1980 to 57.0% in 2006 in Scotland.

SCCS comment
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.

Aluminium compounds have been studied in three mice studies and two rat studies (see Annex 1). Two of the mice studies and one of the rat studies with aluminium potassium sulfate were performed with experimental methods generally accepted for evaluation of carcinogenicity. In the mice drinking water study leukemia lymphoma was increased in the female mice, but not in the male mice while in the mice feed study no toxic effects were found. In the rat drinking water study the tumour frequencies were increased among male rats but not among the females. All three 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 intrachtracheal instillations. It is not possible to draw conclusions in relation to potential carcinogenicity from the two latter studies.

The SCCS is of the opinion that the available information does not support concerns regarding potential carcinogenicity of aluminium compounds.

3.6.2. Aluminium and neurodegenerative diseases

Neurodegenerative disorders are featured by a variety of pathological conditions that share similar critical processes, such as oxidative stress, free radical activity, proteinaceous aggregations, mitochondrial dysfunctions, and energy failure. They are mediated or triggered by an imbalance of metal ions leading to changes of critical biological systems and initiating a cascade of events finally leading to neurodegeneration and cell death. Their causes are multifactorial, and although the source of the shift in oxidative homeostasis is still unclear, current evidence points to changes in the balance of redox transition metals, especially iron, copper, and other trace metals. They are present at elevated levels in Alzheimer disease, Parkinson disease, multisystem atrophy, etc.

Following the observation that high levels of aluminium in dialysis fluid could cause a form of dementia in dialysis patients, a number of studies were carried out to determine if aluminium could cause dementia or cognitive impairment as a consequence of environmental exposure over long periods. Aluminium was identified, along with other elements, in the amyloid plaques that are one of the diagnostic lesions in the brain for Alzheimer disease, a common form of senile and pre-senile dementia (EFSA, 2008).

Numerous epidemiological studies have been carried out to try to determine the validity of this hypothesis. These have been reviewed in detail by several authorities, including JECFA (FAO/WHO, 2007; WHO, 2007), the United Kingdom Committee on Toxicity of Chemicals in

Food (2013), Consumer Products and the Environment (COT, 2005), the United States Agency for Toxic Substances and Disease Registry (ATSDR, 2008) and Environment Canada & Health Canada (2010). Investigators have identified a number of difficulties in carrying out such studies on conditions for which the causes are multifactorial. In addition, there are questions regarding the levels of exposure to aluminium from different sources and the relative bioavailability from these sources. Most of the studies have focused on aluminium in drinking water—although this is a very minor source of exposure—and Alzheimer disease. Most of the studies do not consider the speciation of aluminium, and the assessment of exposure from both drinking-water and food is usually not well characterized. In particular, there are difficulties in determining recollected exposure when the subject has a degenerative neural condition affecting cognitive performance.

The conclusion of the recent JECFA evaluation (FAO/WHO, 2007, 2012) was that "some of the epidemiology studies suggest the possibility of an association of Alzheimer disease with aluminium in water, but other studies do not confirm this association…. All studies lack information on ingestion of aluminium from food and how concentrations of aluminium in food affect the association between aluminium in water and Alzheimer disease." There are suggestions that persons with some genetic variants may absorb more aluminium than others, but there is a need for more analytical research to determine whether aluminium from various sources has a significant causal association with Alzheimer disease and other neurodegenerative diseases (WHO, 2013).

Both EFSA and JECFA concluded that the information available was inconsistent and did not support a causal association between aluminium exposure and Alzheimer's disease or other chronic neurological diseases.

Aluminium is a neurotoxicant in experimental animals. However, most of the animal studies performed have several limitations and therefore cannot be used for quantitative risk assessment (see Annex 2).

In conclusion, SCCS considers that Aluminium (Al) is a known neurotoxicant 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 diseases (Oyanagi, 2005) and other chronic neurodegenerative diseases (Bondy, 2010) but no causal relationship has yet been proven.

3.7. Aggregate exposure to aluminium

- **Food and drinking water**

Aluminium may occur naturally in food and drinking water or as a contaminant. Other sources of aluminium in food are the use of food additives containing aluminium and migration of aluminium from food contact materials to food.
In the Norwegian opinion, the estimated dietary exposure to aluminium is based on data from the national food consumption surveys for infants, children, adolescents and adults. The estimated weekly exposure to aluminium through food for infants, children, adolescents and adults are shown in the following table (taken from VKM opinion).

Table 7: Aluminium exposure through food for 1-year-old infants (n=1635), 2-year-old-children (n=1674), 4-year-old children (n=391), 9-year-old children (n=310), 13-year-old adolescents (n=1005) and adults (n=1787) given as mg Al/kg bw/week.

Age groups	Mean exposure (mg Al kg bw/week)	High exposure (95-percentile) (mg Al kg bw/week)
1-year-old infants	0.89	1.9
2-year-old children	0.88	1.7
4-year-old children	0.53	0.90
9-year-old children	0.35	0.66
13-year-old adolescent	0.22	0.49
Adults	0.29	0.67

In adults, based on the VKM report, the mean dietary exposure to aluminium was 0.29 and 0.67 mg Al/kg bw/week for mean and high (95-percentile) exposures, respectively, corresponding to systemic exposures of 0.29 and 0.67 µg Al/kg bw/week, respectively.
In the Afssaps report, aggregated exposure was not calculated and the risk from aluminium exposure via food or water was not assessed. Exposure data from food and water were provided for comparison, based on the EFSA report (2008). In Europe, total exposure to aluminium via food was estimated between 0.2 and 1.5 mg Al/kg pc/week for an adult. In France the 97.5 percentile for children from 3 to 15 years old was 0.7 mg Al/kg bw/week and 0.4 mg Al/kg bw/week for adults. Corrected by an oral bioavailability factor of 0.1%, systemic exposure to aluminium by food exposure in France is 0.06 µg/kg bw/d (corresponding to 0.42 µg Al/kg bw/week).

- **Cosmetic**

In the Afssaps report (Afssaps, 2011), the estimated quantities of aluminium absorbed via daily exposure to an antiperspirant containing 20% of aluminium chlorohydrate (5% aluminium) were obtained using two scenarios:

- The first scenario corresponds to the exposure of intact skin, based on a dermal absorption rate of 0.5% leads to 2.1 µg Al/kg bw/d (equivalent to 14.7 µg Al/kg bw/week)

- The second scenario corresponds to the exposure of damaged skin, and assumes an absorption rate of 18% which leads to 75 µg Al/kg bw/d (equivalent to 525 µg Al/kg bw/week)

In light of these estimates, the report recommends that the concentration of aluminium in cosmetic products should be restricted to 0.6% and that aluminium-containing cosmetics should not be used on impaired skin.

In the Norwegian report (Norwegian Scientific Committee for food safety, 2013), the use of lipstick and lip gloss, antiperspirants and whitening toothpaste were considered relevant for adults.
With the additional contribution from the use of lipstick/lip gloss the total exposure, in a standard scenario, was 0.51 and 0.89 µg Al/kg bw/week for mean and high exposures, respectively. In a worst case the mean and high exposures were 4.5 and 4.9 µg Al/kg bw/week, respectively. With the additional contribution from the use of antiperspirants the total exposure, in a standard scenario, was 31 and 32 µg Al/kg bw/week for mean and high exposures, respectively. In a worst case scenario, both the mean and high exposures were

600 µg Al/kg bw/week. Adding the contribution from the use of toothpaste in a worst case scenario did not change the total exposure.

- **Infants**

Infants may be exposed to aluminium compounds through inhalation of dust, ingestion of soil and from the diet. Use of aluminium-containing cosmetic products is unlikely in this age group. The diet is likely to be the main source (the United Kingdom Committee on Toxicity of Chemicals in Food (2013)).

3.8. Discussion

Risk assessments linked to the use of Aluminium in cosmetic products have recently been performed by the French Agency in charge of cosmetic products (Afssaps, 2011), by the Norwegian Scientific Committee for food safety (2013) and by the German institute in charge of cosmetic products (BfR, 2014).These reports concluded that based on the current knowledge, aluminium in cosmetic products cannot be considered safe.

The 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 are considered by the SCCS to be the main contributing sources of exposure via cosmetic products.

Aluminium compounds used as deodorants or antiperspirants are soluble at very low pH in the formulation, however once applied on the skin they form chemically inert polymeric complexes with basic components of sweat and skin. This limits the bioaccessibility of aluminium on living skin. In addition the high molecular weight, low 'Log Pow' and high positive charge would limit the potential for skin penetration.

There are limited human data on the dermal absorption of aluminium. Using [26]Al labelled aluminium chlorohydrate applied to the left axilla surface of two subjects, Flarend et al. (2001) estimated that 0.0082% (male subject) and 0.016% (female subject) of the applied aluminium was eliminated in urine. The results indicate that 3.6 µg aluminium is absorbed from one single application of aluminium chlorydrate to both underarms. SCCS considers that the study from Flarend *et al*. (2001) is associated with too high uncertainties and that Tthe results of this study cannot be used to estimate dermal absorption following repeated exposure to aluminium.

The available experimental *in vitro* studies are also of poor quality and have not been carried out according to current requirements.

A study by Anane et al. (1995) found increased levels of aluminium in the urine of mice exposed to 0.1 or 0.4 µg/day aluminium chloride (0.01– 0.04 µg Al/day) applied daily to a 4 cm[2] shaved area for 130 days. Interpretation of this study is limited due to the lack of control measures to prevent the animals from licking their fur and thus ingesting aluminium.

In a recently published study (Pineau et al., 2012), dermal absorption of aluminium from three cosmetic formulations of antiperspirant (aerosol, roll-on emulsion and stick) was studied by using human full skin (intact and stripped) biopsies mounted in Franz[TM] diffusion cell. This study showed only insignificant transdermal absorption of aluminium (<0.07% of the quantity of aluminium deposited). On stripped skin, for which only the stick formulation was tested, the measured uptake was significantly higher. The SCCS considers that there

are many shortcomings in this absorption study and aluminium absorption after dermal administration is still very poorly understood.

In the absence of any better data to estimate skin penetration of aluminium, the SCCS is of the opinion that no firm conclusion on internal exposure to aluminium following use of aluminium containing cosmetics can be drawn.

Concerning the toxicity of aluminium, many reports have been published which include extensive review of the effects of aluminium, mainly by the oral route, on health (EFSA, 2008, 2011, ATSDR, 2008, JECFA, 2008, 2011). It is generally well acknowledged that the biochemical and toxicological behaviors of aluminium depend on the chemical form of aluminium. Furthermore, it has been shown that aluminium absorption, tissue retention and deposition, and excretion depend on the properties of the aluminium complexes formed with biological ligands. Both EFSA (2008) and JECFA (2011) commented on the lack of specific toxicological data for food additives containing aluminium and on the limitations of the available animal studies. The more recent evaluation, the 2011 JECFA evaluation was based on new data which included a multigenerational study and a developmental toxicity study specifically evaluating neurobehavioural endpoints. The LOAELs identified in these studies were consistent with the body of data reviewed previously by the other committees; however, the developmental study 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, the JECFA considered it appropriate to revise the PTWI upward to 2 mg/kg bw/week.

The SCCS agrees on the NOAEL of 30 mg/kg bw/day used by JECFA for risk assessment.

Aluminium is a low oral bioavailable compound. 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. However, considering the available human and animal data as discussed above, it is likely that the oral absorption of aluminium can vary 10-fold based on chemical form alone. Although bioavailability appears to generally parallel water solubility, insufficient data are available to directly extrapolate from solubility in water to bioavailability. Additionally, due to available dietary ligands such as citrate, lactate, and other organic carboxylic acid complexing agents, the bioavailability of any particular aluminium compound can differ markedly in the presence of food from that under empty stomach conditions.

Aluminium is a known neurotoxicant in animals and in patients previously undergoing dialysis. 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.

Due to the potential toxicity of Aluminium after systemic exposure and the lack of proper data to estimate internal exposure to aluminium following cosmetic uses, the SCCS considers that a proper risk assessment from dermal exposure cannot be performed based on the current knowledge. Therefore internal exposure to aluminium after skin application should be determined using a human exposure study under real-life conditions.

4. CONCLUSION

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.

Confusion exists with respect to the correct terminology for underarm deodorants that are actually present on the market since they often contain both, typical deodorant as well as typical antiperspirant ingredients.

5. MINORITY OPINION

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Annex 1: Carcinogenicity of Aluminium in Animal

Mice

Drinking water study

Guideline/method	/
Species:	Random-bred white Swiss mice
Age at start of study:	19 – 20 days
Groups:	54 males and 54 females
Test substances:	Aluminium potassium sulfate
Batch:	/
Conc a.i.:	/
Purity:	/
Dose applied:	5 ppm Al in drinking water
Route:	Drinking water
Exposure time:	Lifetime
GLP:	/
Date of report:	1975
Published:	Yes

Procedure
Groups of 54 mice of each sex received different soluble salts (methyl mercury, mercury, beryllium, barium, aluminium, boron, tungsten, titanium, lead, nickel, and vanadium) in the drinking water from days 19 – 20 and for the rest of their lives. The basal drinking water contained soluble salts as simple complexes (in ppm): zinc, 50; manganese, 10; copper, 5; chromium, 5; cobalt, 1; and molybdenum. Animals dying a natural death were weighed and dissected, gross tumors were detected, and some sections were made of heart, lung, liver, kidney, and spleen for microscopic examination. Tumours were considered malignant when they were multiple, but the study authors wrote that in their experience most tumours in mice were malignant.

Results
The aluminium potassium sulfate (5 ppm Al), did not affect the weight of the mice or their mean survival (Male control 540 days, male exposed to Al 568 days, female control 533 days, female exposed to Al 533 days). The tumour frequencies are given in Table X.

Table X: Tumour frequencies in mice after administration of aluminium potassium sulfate in the drinking water.

Group	No aut-opsied	Tumours				
		No	Multiple	Lymphoma leukemia	Lung	% of mice with tumours
Male control	38	11	2	3	5	28.9
Al exposed	41	15	9	9	9	36.6
Female control	47	14	4	3	9	29.8
Al exposed	41	19	12[a]	10[b]	11	46.3

[a]$P<0.025$, [b]$P<0.05$

Conclusion
The study authors concluded that leukemia lymphoma was found most frequently in the female aluminium group and that aluminium had slight tumorigenic effect (P<0.05) in females mice.

Ref.: Schroeder and Mitchener, 1975a

SCCS comment
The study is very old and insufficiently reported. Thus, it is difficult to draw any conclusion from the study.

Feed study

Procedure
The tumorigenic potential of aluminium potassium sulfate (APS) was investigated in B6C3F1 mice. APS was administered in the diet for 20 months at dose levels of 1.0, 2.5, 5.0 and 10.0% (w/w). One group receiving basal diet served as the control.

Results
Body weight gain in both sexes was decreased in the 10.0% APS treated group, and increased in the 1.0 and 2.5% APS treated groups. The survival rates at the end of the dosing period were 73.3% (male) and 78.3% (female) in the control group, and 86.7-95.0% (male) and 86.7-91.7% (female) in the APS treated groups. The survival rate showed a tendency to increase in both sexes in all the APS treated groups.

The incidence of hepatocellular carcinoma was significantly decreased in the males in the 10% APS treated group. The incidence of hepatocellular carcinoma was significantly decreased in females in all groups.

Conclusion
The study authors concluded that the results of the present study indicate that long-term administration of aluminium potassium sulfate does not exert tumorigenic or any other toxic actions in B6C3F1 mice.

Ref.: Oneda et al., 1994

SCCS comment
Only the abstract was available.
It is unclear whether this was a guideline study and which tissues have been examined

Intraperitoneally injections

Procedure
Aluminium oxide (97.3% pure, impurities 1.5% SiO_2, 0.8% CaO, 0.1% Fe, 0.3% TiO_2), 10 mg in 0.5 ml saline was injected intraperitoneally into non-inbred albino mice twice at intervals of one month. The first injection was given to the mice at the age of one month. Each group contained 50 males and 50 females. Observation continued until the end of the animals' life and the animals were subjected to standard histological examination.

Results
Mesotheliomas were found in 8 of 68 mice (11.7%) treated with aluminium oxide. Another group was treated with crysotile asbestos. In this group 21 of 60 mice (35%) developed mesotheliomas. The authors wrote that no mesotheliomas were observed in 280 untreated mice. In is stated that the number of mesotheliomas in the mice receiving aluminium oxide was statistically higher than the background level (p<0.001).

Ref.: Frash et al., 1992

SCCS comment
The study is difficult to draw conclusions from the study because it is incompletely described.

Rats

Drinking water study
Guideline/method   /
Species: Random-bred Long-Evans (BLU:LE) rats
Age at start of study: At weaning time
Groups: 52 males and 52 females
Test substances: Aluminium potassium sulfate
Batch: /
Conc a.i.:   /
Purity: /
Dose applied: 5 ppm Al in drinking water
Route: Drinking water
Exposure time: Lifetime
GLP: /
Date of report: 1975
Published: Yes

Procedure
Groups of 52 rats of each sex received different soluble salts (aluminium, barium, beryllium, and tungsten) in the drinking water from weaning time and for the rest of their lives. The water also contained 5 ppm chromium acetate, 50 ppm zinc acetate, 5 ppm copper acetate, 10 ppm manganese chloride, 1 ppm cobalt chloride, and 1 ppm sodium molybdate. Animals dying a natural death were weighed and dissected, gross tumors were detected, and some sections were made of heart, lung, liver, kidney, and spleen for microscopic examination.

Results
Compared to the controls, aluminium did not significantly affect growth rates in females, but males were heavier after a year of age. The lifetime was not affected by aluminium.

Aluminium caused a slightly elevated incidence of gross tumors in male rats but not in females (Table Z). The tumour frequencies were not affected in the groups treated with barium, beryllium, and tungsten.

Table Z: Tumour frequencies in rats after administration of aluminium potassium sulfate in the drinking water.

Group	No autopsied	Tumours			
		No	Percentage	Malignant No	Malignant percentage
Male control	26	4	15	2	50
Al exposed	25	13[a]	52	6	46
Female control	24	17	70	8	47
Al exposed	19	14	73	6	42

[a]$P<0.005$

Conclusion
The study authors concluded that male rats given aluminium had more gross tumours than their controls.

Ref.: Schroeder and Mitchener, 1975b

SCCS comment
The study is very old and insufficiently reported. No information is available in relation to the type and localization of the tumours. Thus, it is difficult to draw any conclusion from the study.

Intratracheal instillations

Guideline/method	/
Species:	Female Wistar rats
Age at start of study:	8 – 9 weeks
Groups:	48 females
Test substances:	Aluminium oxide, Sigma-Aldrich /Degussa
	Aluminium silicate, Sigma-Aldrich /Degussa
	Kaolin, Sigma-Aldrich
Batch:	/
Organic content:	/
Conc a.i.:	/
Particle size:	Al-oxide: Particle size 13 nm. Density 3.2 g/ml Specific surface area 124 m^2/g
	Al-silicate: Particle size 15 nm. Density 2.1 g/ml Specific surface area 62.9 m^2/g
	Kaolin: Particle size ~ 2000 nm. Density 2.5 g/ml Specific surface area 19 m^2/g
Purity:	Aluminium oxide; purity > 99.6% Al_2O_3
	Aluminium silicate P 820, 9.6% Al_2O_3 82% SiO_2, 8% Na_2O
	Kaolin ~ $Al_2Si_2O_5(OH)_4$, K7
Dose applied:	See Table Y
Route:	Intratracheal instillations
Exposure time:	Once a week (number of instillations given in Table X
GLP:	/
Date of report:	2005
Published:	Yes

Procedure
Groups of 48 female Wistar rats, 8–9 weeks of age, received intratracheal instillations at weekly intervals of one of three Al-compounds, respectively. The dusts had been suspended in 0.4 ml 0.9% phosphate buffered saline solution and 0.5% Tween 80 was added to improve the homogeneity of the suspensions. A control group of 48 rats was maintained untreated. Rats were inspected for mortality and clinical signs of morbidity twice per weekday and once a day on the weekends.

The experiment was terminated after 30 months unless rats were killed when moribund or diagnosed with a growing subcutaneous tumour. After death of the animals and before necropsy of the thoracic and abdominal cavity, lungs were insufflated via the trachea in situ with 6% neutral buffered formalin. In particular, the surface of the lung was inspected and lesions were recorded. The lungs were fixed and embedded in paraffin and sections were strained with haematoxylin–eosin. All tissues suspected of having tumours that were taken from other sites were examined for histopathological lesions.

Results
The lung tumour incidence in each group is summarized in Table Y.

Table Y: Dose schedules and incidence of lung tumours in female
Wistar rats administered aluminium compounds by intratracheal instillation.

Aluminium	Dose instilled	Rats at risk[a]	50% survival (weeks)[b]	Malignant lung tumours (%)[c]	Total lung tumours (%)[c]
Al-oxide	5x6 mg	44	111	65.9	81.8
	10x6 mg	47	97	46.8	72.3
Al-silicate	5x6 mg	47	107	38.3	59.6
	10x6 mg	45	108	42.2	75.6
Kaolin	10x6mg	48	115	25.0	41.7
	20x6 mg	47	121	59.6	74.5
Control	--	46	124	0.0	2.2

Conclusion
The study authors conclude that statistically significant increases in benign and/or malignant lung tumours were observed with the types of aluminium compounds studied.

Ref.: Pott and Roller 2005

SCCS general comments
Aluminium compounds have been studied in three mouse studies and two rat studies. Two of the mouse studies and one of the rat studies with aluminium potassium sulfate were performed with experimental methods generally accepted for evaluation of carcinogenicity. In the mouse drinking water study leukemia lymphoma was increased in female mice, but not in male mice, while in the mouse feed study no toxic effects were found. In the rat drinking water study, the tumour frequencies were increased among male rats but not among the females. All three 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 intrachtracheal instillations. It is not possible to draw conclusions in relation to potential carcinogenicity from the two latter studies.

Conclusion: SCCS is of the opinion that no conclusions can be drawn concerning the potential carcinogenicity of aluminium compounds from the available animal studies.

Annex 2: Neurotoxicity of Aluminium: new publications (copy of abstracts)

Double-blind, vehicle-controlled randomized twelve-month neurodevelopmental toxicity study of common aluminium salts in the rat.

Poirier J, Semple H, Davies J, Lapointe R, Dziwenka M, Hiltz M, Mujibi D.

This good laboratory practice (GLP) study of aluminium salts in Sprague-Dawley rats was conducted according to double-blind, vehicle-controlled randomized design by exposing offspring to aluminium citrate in-utero, through lactation, and then in drinking water post-weaning. 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). Endpoints were assessed in both female and male pups: behavioral (motor activity, T-maze, auditory startle, the Functional Observational Battery (FOB) with domains targeting autonomic function, activity, neuromuscular function, sensimotor function, and physiological function), cognitive function (Morris swim maze), brain weight, clinical chemistry, hematology, tissue/blood levels of aluminium and neuropathology. The most notable treatment-related effect observed in the offspring was renal pathology, most prominently in the male pups. Higher mortality and significant morbidity were observed in the male pups in the high Al-citrate dose group; leading to euthanization of this group at day 89. There was evidence for dose-response relationships between neuromuscular measurements-hind-limb and fore-limb grip strength-and Al-treatment in both males and females, although some of the effects may be secondary to body weight changes. No consistent treatment-related effects were observed in ambulatory counts (motor activity) in the different cohorts. No significant effects were observed for the auditory startle response, T-maze tests (pre-weaning day 23 cohort) or the Morris water maze test (day 120 cohort). None of the lesions seen on histopathological examination of brain tissues of the day 364 group was reported as treatment-related and, as these were also seen in the control group, were likely due to aging. In conclusion, these results indicate that concentrations of aluminium in the drinking water that are required to produce minimally detectable neurobiological effects in the rat are about 10,000 times higher than what is typically found in potable drinking water.

This study was used by JECFA as key study to derive the PTWI. The SCCS agrees on the NOAEL of 30 mg/kg bw/day used by JECFA for risk assessment

Prolonged exposure to low levels of aluminium leads to changes associated with brain aging and neurodegeneration.

Bondy SC.

Aluminium is one of the most common metal elements in the earth's crust. It is not an essential element for life and has commonly been thought of as a rather inert and insoluble mineral. Therefore, it has often been regarded as not posing a significant health hazard. In consequence, aluminium-containing agents been used in many food processing steps and also in removal by flocculation of particulate organic matter from water. In recent years, acid rain has tended to mobilize aluminium-containing minerals into a more soluble form,

ionic Al3+, which has found their way into many reservoirs that constitute residential drinking water resources. As a result, the human body burden of aluminium has increased. Epidemiological studies suggest that aluminium may not be as innocuous as was previously thought and that aluminium may actively promote the onset and progression of Alzheimer's disease. Epidemiological data is strengthened by experimental evidence of aluminium exposure leading to excess inflammatory activity within the brain. Such apparently irrelevant immune activity unprovoked by an exogenous infectious agent characterizes the aging brain and is even more pronounced in several neurodegenerative diseases. The causation of most of these age-related neurological disorders is not understood but since they are generally not genetic, one must assume that their development is underlain by unknown environmental factors. There is an increasing and coherent body of evidence that implicates aluminium as being one such significant factor. Evidence is outlined supporting the concept of aluminium's involvement in hastening brain aging. This acceleration would then inevitably lead to increased incidence of specific age-related neurological diseases.

3. Int Rev Neurobiol. 2013;110:1-47. doi: 10.1016/B978-0-12-410502-7.00002-8.

 The relevance of metals in the pathophysiology of neurodegeneration, pathological considerations.

Jellinger KA.

Neurodegenerative disorders are featured by a variety of pathological conditions that share similar critical processes, such as oxidative stress, free radical activity, proteinaceous aggregations, mitochondrial dysfunctions, and energy failure. They are mediated or triggered by an imbalance of metal ions leading to changes of critical biological systems and initiating a cascade of events finally leading to neurodegeneration and cell death. Their causes are multifactorial, and although the source of the shift in oxidative homeostasis is still unclear, current evidence points to changes in the balance of redox transition metals, especially iron, copper, and other trace metals. They are present at elevated levels in Alzheimer disease, Parkinson disease, multisystem atrophy, etc., while in other neurodegenerative disorders, copper, zinc, aluminium, and manganese are involved. This chapter will review the recent advances of the role of metals in the pathogenesis and pathophysiology of major neurodegenerative diseases and discuss the use of chelating agents as potential therapies for metal-related disorders.

4. J Toxicol Sci. 2013;38(2):255-68.

Effects of subchronic aluminium exposure on spatial memory, ultrastructure and L-LTP of hippocampus in rats.

Zhang L, Jin C, Liu Q, Lu X, Wu S, Yang J, Du Y, Zheng L, Cai Y.

See above: citation from abstract
Epidemiological investigations have indicated that aluminium (Al), as an important environmental neurotoxicant, could cause damage to the cognitive function which was closely related with neurodegenerative diseases. Long-term potentiation (LTP) is one form of synaptic plasticity in association with cognitive function. Previous studies have demonstrated that Al impaired early phase long-term potentiation (E-LTP) in vivo and in vitro. However, Al-induced damage to late phase long-term potentiation (L-LTP) has poorly been studied. The present study was designed to observe the effects of subchronic Al exposure on the spatial memory, hippocampus ultrastructure and L-LTP in rats. Pregnant Wistar rats were assigned to four groups. Neonatal rats were exposed to Al by parental lactation from parturition to weaning for 3 weeks and then fed with the distilled water containing 0, 0.2%, 0.4% and 0.6% aluminium chloride (AlCl3) respectively from weaning

to postnatal 3 months. The levels of Al in blood and hippocampus were quantitated by atomic absorption spectrophotometer. Morris water maze test was performed to study spatial memory. The induction and maintenance of L-LTP in area of Schaffer collateral- CA1 synapse was recorded by extracellular microelectrode recording technology in hippocampus of experimental rats. Hippocampus was collected for transmission electron microscopy observation. The results showed that the Al concentrations in blood and hippocampus of Al-exposed rats were higher than those of the control rats. Al could impair spatial memory ability of rats. Neuronal and synaptic ultrastructure from Al-exposed rats presented pathological changes; the incidence of L-LTP has a decrease trend while population spike (PS) amplitude was much smaller significantly stimulated by high-frequency stimulation (HFS) in Al-exposed rats. Our findings showed that Al exposure caused spatial memory damage, under which the neuronal and synaptic ultrastructure changes maybe were their morphological basis and the impaired L-LTP of hippocampus could be their electrophysiological basis.

SCCS comments
The results of this study indicated that rats orally exposed to AlCl3 from parturition to postnatal 3 months had weaker spatial memory and memory retention than the control rats. Dose related effects of aluminium on the ultrastructure of neurons and synapses as well as on the morphology of nerve cells in hippocampus were also observed.

5. Industrial Health Vol. 50 (2012) No. 5 p. 428-436

Aluminium-Maltolate-induced Impairment of Learning, Memory and Hippocampal Long-term Potentiation in Rats

Rui-feng LIANG, Wei-qing LI, Xiao-hui WANG, Hui-fang ZHANG, Hong WANG, Jun-xia WANG, Yu ZHANG, Ming-tao WAN, Bao-long PAN, Qiao NIU

See avove, citation from abstract
Recently, aluminium (Al) has been proposed to be one of the environmental factors responsible to cause Alzheimer's disease (AD). However, the relationship between Al and AD is controversial. To investigate the effects of subchronic Aluminium-maltolate (Al $(mal)_3$) exposure on the behavioral, electrophysiological functions. Forty Sprague-Dawley (SD) rats were randomly distributed into five groups. Over two months, rats in the saline group received daily intraperitoneal (i.p.) injections of 0.9% saline, rats in the maltolate group received 7.56 mg/kg maltolate, and rats in the 0.27, 0.54, 1.08 mg/kg Al $(mal)_3$ groups received i.p. administrations of these three doses, respectively. Neural behavior was assessed in Morris water maze. Long-term potentiation (LTP) in hippocampus was recorded. Al content in the neocortex was determined using a graphite furnace atomic absorption spectrophotometer. Our studies indicate that subchronic Al $(mal)_3$ exposure significantly impaired spatial learning and memory abilities, suppressed the LTP in the CA1 hippocampal area, and elevated Al levels in cerebral cortex in a dose-dependent fashion. In conclusion, low doses of Al $(mal)_3$ can still lead to dramatic Al accumulation in the brain, severely impair learning and memory capacities, and hippocampal LTP.

SCCS comments
This study evaluated the effects of subchronic i.p. injections of aluminium-maltolate. Due to the route of exposure which is not representative of human exposure via cosmetic products, this study cannot be used as a key study for RA.

6. Med Hypotheses. 2013 Mar;80(3):326-7. doi: 10.1016/j.mehy.2012.11.036. Epub 2012 Dec 20.

Aluminium may mediate Alzheimer's disease through liver toxicity, with aberrant hepatic synthesis of ceruloplasmin and ATPase7B, the resultant excess free copper causing brain oxidation, beta-amyloid aggregation and Alzheimer disease.

Brenner S.