化粧品產品資訊檔案(範例)

<清新止汗爽身露>

＜PIF **無特定之格式**，本範例**僅提供參考用**＞

中華民國 112 年 10 月

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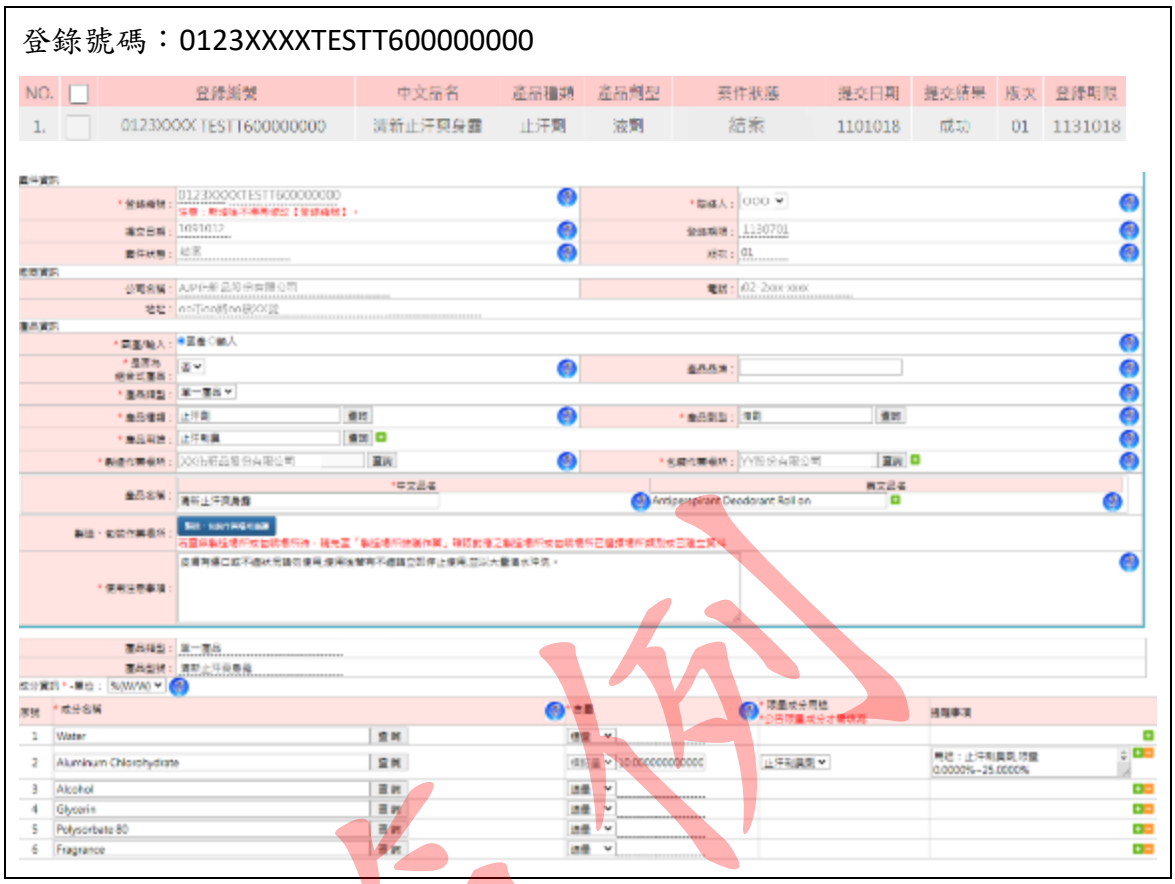
I. 產品敘述

(1) 產品基本資料

項目	內容描述
產品名稱(中文/英文)	清新止汗爽身露 (Antiperspirant Deodorant Roll on)
產品類別	止汗劑
產品劑型	液劑
用途	止汗制臭
製造作業場所資訊	製造廠名稱：XX 化粧品股份有限公司 廠址：○○市○○區○○路○○號 國別：台灣
包裝作業場所資訊	包裝廠名稱：YY 股份有限公司 廠址：○○市○○區○○路○○號 國別：台灣
產品製造業者資訊	製造業者：AJP 化粧品股份有限公司 地址：○○市○○路○○段 XX 號 公司負責人：李o基 聯絡電話：02-2xxx-xxxx 統一編號：0123XXXX

(2) 完成產品登錄之證明文件

登錄號碼：0123XXXXTESTT600000000

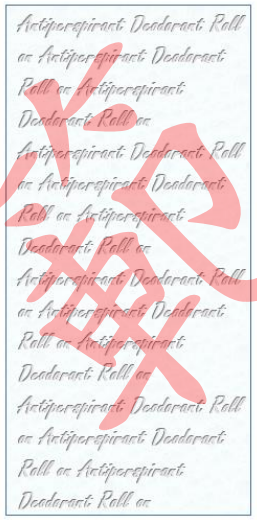


(3) 全成分名稱及其各別含量

INCI Name	Cas No.	w/w%	功能
Aqua	7732-18-5	70.5	溶劑
Aluminum Chlorohydrate	12042-91-0	10.0	止汗制臭
Alcohol	64-17-5	10.0	溶劑
Glycerin	56-81-5	5.0	保濕劑
Polysorbate 80	9005-65-6	4.0	助乳化劑
Fragrance*	-	0.5	香精
TOTAL		100	

*供應商：ABC Company

(4) 產品標籤、仿單、外包裝或容器

項目	資料
內包裝/容器 (正反面)	 正面  反面  內包裝
標籤/仿單	正面  背面  品名：清新止汗爽身露 用途：止汗制臭 用法：打開瓶蓋稍微倒置使滾珠沾滿爽身露，再以滾珠端接觸腋下肌膚，並來回均勻塗抹，使用後緊閉瓶蓋。 保存方法：避免高溫及日光直射，置於孩童伸手不及之場所。 製造業者名稱/地址/電話號碼： AJP 化粧品股份有限公司 / oo 市 oo 路 oo 段 XX 號 / 02-2xxx-xxxx 製造日期及有效期間：製造日期 2022.05.03、有效期間 3 年

	批號：IT22050A 容量：10 ml 全成分(W/W)：Aqua、Aluminum Chlorohydrate (10%)、Alcohol、Glycerin、Polysorbate 80、Fragrance。 使用注意事項：皮膚有傷口或不適狀況請勿使用；使用後若有不適請立即停止使用，並以大量清水沖洗。

(5) 製造場所符合化粧品優良製造準則之證明文件或聲明書

衛 生 福 利 部

化 粧 品 優 良 製 造 證 明 書

證號：(C)GMPOOOO-OOO

製造廠（場所）名稱： XX化粧品股份有限公司

製造廠（場所）地址： ○○市○○區○○路○○號

核定劑型及作業項目： 液劑
製造作業
包裝作業(充填、分裝、標示)

本證明書依據化粧品衛生安全管理法第 29 條規定發給。
本部係依據「化粧品優良製造準則」之規定進行查核，該優良製造準則之要求符合國際標準化組織(ISO)發布之 ISO 22716：2007。

衛生福利部

發 證 日 期： 年 月 日
有 效 日 期： 年 月 日

XXXX(流水號)

衛生福利部

化粧品優良製造證明書

證號：(C)GMPOOOO-OOO

製造廠（場所）名稱： YY化粧品股份有限公司

製造廠（場所）地址： ○○市○○區○○路○○號

核定劑型及作業項目： 液劑
製造作業
包裝作業(充填、分裝、標示)

本證明書依據化粧品衛生安全管理法第 29 條規定發給。
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衛生福利部

發 證 日 期： 年 月 日
有 效 日 期： 年 月 日

XXXX(流水號)

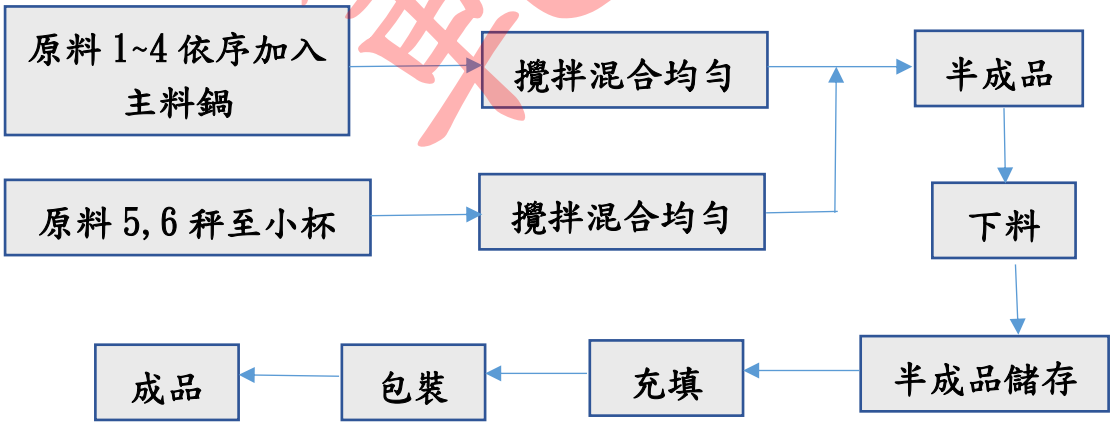
(6) 製造方法、流程

	INCI Name	Cas No.	w/w%	功能
1	Aqua	7732-18-5	70.5	溶劑
2	Aluminum Chlorohydrate	12042-91-0	10.0	止汗制臭
3	Alcohol	64-17-5	10.0	溶劑
4	Glycerin	56-81-5	5.0	保濕劑
5	Polysorbate 80	9005-65-6	4.0	助乳化劑
6	Fragrance		0.5	香精
TOTAL			100	

製程簡述：

1. 依序將第 1、2、3、4 加入主料鍋中，攪拌混合均勻。
2. 將第 5、6 項秤入小杯中攪拌均勻，再加入步驟 1 攪拌混合均勻。

製程流程圖：



(7) 使用方法、部位、用量、頻率及族群

使用方法及用量：打開瓶蓋稍微倒置使滾珠沾滿爽身露，再以滾珠端接觸腋下肌膚，並來回均勻塗抹，使用後緊閉瓶蓋。

使用族群：青少年、成年人。

使用頻率：每日最多兩次。

(8) 產品使用不良反應資料

目前本產品尚未有任何不良反應事件報告。如有不良影響和嚴重不良影響的資料時會及時提供給安全資料簽署人員進行確認與評估，並更新於本產品資訊檔案中。

II. 品質資料

(9) 產品及各別成分之物理及化學特性

成品規格檢驗報告

清新止汗爽身露成品 CoA			
檢測項目	**規格**	**實際檢驗結果**	**檢驗方法**
外觀	流動液體	流動液體	目視
顏色	無色透明	無色透明	目視
氣味	綠茶氣味	綠茶氣味	嗅覺
pH (at 25 °C)	4.1±0.2	4. 00	使用已校正之 pH meter 依 pH meter 檢測方法測定
黏度(at 25 °C)	100 ~200 mPa·s	120 mPa·s	使用已校正之黏度計依黏度計檢測方法測定
密度(at 25 °C)	1.0 ± 0.05 g/cm^3	1.00 g/cm^3	定量瓶
微生物規格	生菌數 < 1000 cfu/g 不得檢出： 大腸桿菌 金黃色葡萄球菌 綠膿桿菌 白色念珠菌	生菌數 未檢出 (<10 cfu/g)； 大腸桿菌 陰性； 金黃色葡萄球菌 陰性； 綠膿桿菌陰性； 白色念珠菌 陰性	參考衛生福利部食品藥物管理署 109.07.28 及 111.04.21 公告建議檢驗方法-化粧品中微生物檢驗方法及化粧品中白色念珠菌之檢驗方法。
檢測人員/日期		(請簽名並加上日期)	
複核人員/日期		(請簽名並加上日期)	

各成分物理化學特性

- 由 AJP 化粧品股份有限公司及安全資料簽署人員彙整各成分之安全資料表、檢驗成績書或技術資料表，另存放於成分物理化學特性檔案夾(附錄 1)。
- 安全資料簽署人員依據上述資料內容摘錄各成分物理化學特性如下：

Aqua CoA			
檢測項目	**規格**	**實際檢驗結果**	**檢驗方法**
pH (at 25 °C)	6.0~8.5	7.35	使用已校正之線上(on line) pH meter 測定
導電度(at 25 °C)	<10 µS/cm	5.0 µS/cm	使用已校正之線上(on line)導電度計測定
微生物規格	生菌數 < 100 cfu/ml	生菌數 未檢出 (<10 cfu/ml)；	參考環境保護署環境檢驗所公告之水中總菌落數檢測方法測定
檢測人員/日期		(請簽名並加上日期)	
複核人員/日期		(請簽名並加上日期)	

INCI name：Aluminum Chlorohydrate

Parameter	Specifications
Aluminum/Chloride Atomic Ratio	1.91: 1-2.01: 1
Assay (Anhydrous Basis)	72.3 - 88.3 %
pH of a 15% Solution	3.0 - 5.0
Chloride (Cl)	As reported
Aluminum	As reported
Arsenic (As)	Max 2 µg/ g
Heavy Metals	Max 0.002 %
Iron (Fe)	Max 150 µg/ g
Identification	To pass test

Certificate of Analysis

(Representative Sample Certificate)

Product Name: Aluminum Chlorohydrate
INCI Name: Aluminum Chlorohydrate
CAS Number: 12042-91-0
Lot Number: Not available (data may vary slightly with different lots or batches)
Expiration Date: 36 months from production date

Analytical Tests	Specifications	Results
Aluminum/Chloride Atomic Ratio	1.91: 1-2.01: 1	1.95
Assay (Anhydrous Basis)	72.3 - 88.3 %	79.0 %
pH of a 15% Solution	3.0 - 5.0	4.3
Chloride (Cl)	As reported	16.5 %
Aluminum	As reported	24.5 %
Arsenic (As)	Max 2 ug/ g	< 2 ug/ g
Heavy Metals	Max 0.002 %	< 0.002 %
Iron (Fe)	Max 150 ug/ g	72 ug/ g
Identification	To pass test	Passes Test

The above data were obtained using the test indicated and is subject to the deviation inherent in the test method. Results may vary under other test methods or conditions.

This report is not to be signed.

INCI name：Alcohol

Product Name	ethanol/ethanol absolute
CAS NO	64-17-5
EINECS No.:	200-578-6
Chemical formula:	C2H6O
Molecular weight:	46.07
Viscosity:	1.074 mPa.s,20℃
Melting point:	-114℃
Flashing point:	13℃
Density:	0.789g/cm³
PH:	7.0 (10g/l, H2O, 20℃)
Boiling point:	78.4℃
Vapor pressure:	5.8 kpa,20℃
Explosive limit:	3.1-27.7%(V)

Characteristics	Specifications	Results
Specific Gravity @ 60°F (15.56°C)	NMT 0.7962	0.7959
Proof	NLT 199.0	199.12
Ethyl Alcohol, % volume	NLT 99.5	99.3
Appearance	Bright and clear, free from suspended matter	Pass
Order	Characteristic ethanol	Pass
Water, wt. %	0.7 max	0.6
Color, Pt-Co	0.0	Pass
Chloride (mg/L)	1 max	0.02
Inorganic Sulfate (mg/kg)	1 max	0.0

INCI name：Glycerin

Certificate of Analysis

GLYCERIN

Glycerin 99.7% USP / Kosher Grade

Test	Result	Specification
Assay % by wt.	99.7	99.7 Min.
Color, APHA	9.0	< 10
Specific Gravity 25°C	1.2613	1.2612 Min.
Residue on Ignition (%)	0.001	< 0.005
Chlorides (ppm)	< 1.0	< 10
Sulfates (ppm)	< 1.0	< 20
Chlorinated Compounds (ppm)	< 1.0	< 5
Moisture (%)	0.3	0.30 max.
Fatty Acids & Esters (titrant: 0.5N NaOH)	NMT 0.3	< NMT 1.0 ml
Arsenic (ppm)	< 1.0	< 1.5
Heavy Metals (ppm)	< 1.0	< 5
Ethylene Glycol Content(%)	< 0.001	< 0.1
Diethylene Glycol Content (%)	< 0.001	< 0.1
Identification By IR	PASS	Match to Standard
Identification By GC	PASS	Match to Standard
USP Monogram	PASS	Match to Standard

INCI name：Polysorbate 80

Certificate of Analysis

Product Name:

TWEEN® 80

CAS Number:

9005-65-6

TEST

SPECIFICATION

hydroxyl value

74.7

Parameters	Unit	Standard Value
Acid value	mg KOH/g	≤2.0
Saponification value	mg KOH/g	45-55
Hydroxyl value	Mg KOH/g	65-80
Moisture	w/%	≤3.0
Residue on ignition	w/%	≤0.25
Arsenic	mg/kg	≤3.0
Pb	mg/kg	≤2.0
Oxyethylene	w/%	65.0-69.5

INCI name：Fragrance

Parameter	Specifications
Appearance	Yellow to Olive Green, liquid
Flash point	170 °F (76.67 °C)
Vapor Pressure (mmHg@20 °C)	0.1497
%VOC	0.15
Specific Gravity@25 °C	1.0430
Density @25 °C	1.0400
Refractive Index @ 20 °C	1.5010

(10) 成分之毒理資料

- 由 AJP 化粧品股份有限公司及安全資料簽署人員查詢蒐集各成分之毒理資料，另存放於成分毒理資料檔案夾(附錄 2)。
- 安全資料簽署人員依據上述資料內容摘錄各成分相關毒理資料如下：

1. INCI name：Aluminum Chlorohydrate

- 毒理代謝動力學：幾項小規模人體研究給予含放射性 ^{26}Al 飲用水後測量尿液中的鋁所估計出的鋁吸收效率為 0.07-0.39%，[1] 其可能低估胃腸道吸收，因為保存於組織中或經非腎臟途徑排泄的鋁未列入吸收計算。而在大鼠研究以 ^{26}Al 估計飲用水中鋁的生物利用率，考量尿液和骨骼中的鋁含量，吸收率為 0.04-0.06%。[1] 依 EFSA 報告指出，人類和實驗動物飲用水中鋁離子的口服生物利用率在 0.3% 的範圍內，而食品和飲料中鋁的生物利用率通常較低，約為 0.1%。[2]
- 急性毒性：鋁化合物(溴化物、硝酸鹽、氯化物和硫酸鹽)的急性口服毒性為低至中等毒性，LD_{50} 範圍: 大鼠為 162~ 750 mg Al/kg bw，小鼠為 164 ~ 980 mg Al/kg bw。[2]
- 皮膚腐蝕性/刺激性：鋁化合物廣泛用於止汗劑，有報告指出少數人對局部應用的鋁化合物異常敏感。據報導，在使用以乙醇溶解高劑量六水氯化鋁的製品(20%)治療腋窩或手掌多汗症或使用含有明礬的除臭劑後，受試者出現皮膚刺激狀況。[1]
- 皮膚致敏性：非皮膚致敏物質。[1]
- 重複劑量毒性：在 Sprague-Dawley 大鼠的 12 個月口服長期試驗，給予檸檬酸鋁 30、100 與 300 mg Al/kg bw/day，結果顯示 NOAEL 為 30 mg Al/kg bw/day。檸檬酸鋁是最易溶解和生物利用率最高的鋁鹽。[3]
- 致突變性/遺傳毒性：鋁化合物在細菌和哺乳動物細胞系統中無致突變與遺傳毒性，但有一些鋁化合物在體外試驗中會造成 DNA 損傷並影響染色體完整性。[1]
- 致癌性：鋁化合物致癌性的資料有限，未有流行病學證據證明用於治療的鋁化合物具有致癌性。SCCS 經審查動物致癌性研究，沒有顯示口服高劑量(850 mg Al/kg bw/day)具有致癌性跡象。[1]
- 生殖毒性：為期 12 個月的神經發育毒性研究，檸檬酸鋁通過飲用水給予 Sprague-Dawley 大鼠，高劑量組(300 mg Al/kg bw/day)和較中等劑量組(100 mg Al/kg bw/day)具有毒性，在高劑量組中主要影響是腎損害，導致雄性後代的死亡率很高。結果顯示 LOAEL 為 100 mg Al/kg

bw/day，NOAEL 為 30 mg Al/kg bw/day。[3]

- 光毒性：無數據。
- 人體數據：止汗劑中 ^{26}Al 經皮吸收的初步研究中，腋窩封閉反覆暴露於含 Aluminum Chlorohydrate 21 %(約 13 mg)的止汗劑，6 天後研究結果估計鋁的吸收比例平均為 0.012%。但此研究沒有依 GCP 完成，且僅有 2 名志願者。[1]
- 其他安全資料：德國 BfR 關於含鋁止汗劑的研究，參考 2019 年一項人體試驗，於 6 位女性受試者腋窩塗抹含 6.25% 放射性標記 ACH 的止汗劑，經計算出經皮膚吸收之鋁生物利用率(Bioavailability)為 0.00192%；並在根據大鼠試驗得到 NOAEL 並考量口服之鋁生物利用率為 0.3%[2]，轉換為體內 NOAEL 值 90μg Al/kg bw/day；BfR 推導出使用含鋁止汗劑之 MoS 為 3396 (90/0.026496)，其數值遠大於 100。SCCS 安全報告引述 Poirier 等人的神經發育大鼠研究得知 NOAEL 為 30 mg Aluminium citrate/kg bw/day，並以 Aluminium citrate 的大鼠口服生物利用率 0.6%進行調整，將調整後的 NOAEL 估算值 180 μg Al/kg bw/day 用作安全評估的 PoD。[5]
- 參考資料：

1. SCCS/1525/14- OPINION ON the safety of Aluminium in cosmetic products, 2014.
2. European Food Safety Authority. Safety of Aluminium from dietary intake - Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC). EFSA Journal 6:754, 2008.
3. Poirier, J., Semple, H., Davies, J., Lapointe, R., Dziwenka, M., Hiltz, M., Mujibi, D. Double-blind, vehicle-controlled randomized twelve-month neurodevelopmental toxicity study of common aluminum salts in the rat. Neuroscience 193:338-362, 2011.
4. BfR. New studies on antiperspirants containing aluminium: impairments to health unlikely as a result of aluminium uptake via the skin, 2020.
5. SCCS/1613/19- OPINION ON the safety of aluminium in cosmetic products Submission II, 2020.

2. INCI name：Alcohol

- 毒理動力學：乙醇(Alcohol)很容易經由口服和吸入途徑吸收，隨後在人體中代謝和排泄。在製造和使用含乙醇產品期間及消費者相關的接觸中，肝臟中的乙醇脫氫酶(Alcohol dehydrogenase, ADH)為主要代謝途徑且不會飽和。代謝路徑的第一步是速率決定步驟；中間代謝產物乙醛(Acetaldehyde)的濃度非常低。Alcohol 不會在體內積聚，皮膚吸收非常低。[1]
- 經皮吸收：在對非人類靈長類動物和人類皮膚樣本進行的一項研究中，Scott 等人(1991)發現皮膚結構和對快速滲透劑、水及 Alcohol 的滲透性之間沒有明顯的關係。Schaefer 和 Redelmeier (1996)提出，將 1000cm^3 的皮膚暴露在 70% Alcohol 中不到 1 小時會產生大約 100 mg Alcohol 吸收，這相當於含有 10% (v/v) Alcohol 的 1.5 ml 酒精。Pendlington (2001)等人在 16 名成年志願者進行人體實驗，將氣溶膠的乙醇製劑噴灑在身體上 10 秒，然後等待 15 分鐘。在氣相色譜中使用兩種不同的色譜柱測定血液酒精濃度。96 個樣品中只有 22 個顯示 Alcohol 的存在，記錄到最大濃度為 1.3 mg/100 ml。然而，使用兩種色譜柱都沒有偵測到血液樣本對酒精的存在呈現陽性。結論是使用含 Alcohol 的噴霧劑不會導致血液中的酒精濃度達到顯著的毒理學水平。[2]
- 急性毒性：在所有暴露途徑下均具有較低的急性毒性。報告中小鼠 1 小時吸入最低的 LC_{50} 值>60000 ppm (114000 mg/m^3)，小鼠口服的 LD_{50} 是 8300 mg/kg bw。[1]
- 皮膚刺激性：不具皮膚刺激性。[1]
- 眼睛刺激性：中度眼睛刺激性。[1]
- 皮膚致敏性：非致敏性物質。[1]
- 重複劑量毒性：對大鼠每日飲食研究報告的未觀察到不良反應劑量(No Observed Adverse Effect Level, NOAEL)為約 2400 mg /kg bw/day。高劑量時，雄性大鼠的器官重量和血液學/血清生化學變化較小。雌性大鼠的血清生化學變化較小，可能延長發情週期的長度以及增加肝結節；在每天≥3600 mg/kg bw/day 濃度下觀察到不利的肝臟作用。[1]
- 遺傳毒性：沒有遺傳毒性。[1]
- 致突變性：細菌突變檢測結果陰性，非致突變性。在對大鼠和中國倉鼠體內染色體突變進行測試的結果均為陰性。[1]

- 發育/生殖毒性：吸入暴露量高達 16000 ppm (30400 mg/m^3)時未見對生育力或發育影響。[1]
- 人體數據：Alcohol 會對人類健康構成危害的是在飲用含酒精飲料下才能呈現出來。[1]Alcohol 的大部分全身毒性與長期濫用酒精有關。儘管 Alcohol 已變性使其不適合食用，但據報導指出仍在有意或無意食用含有變性酒精產品的情況下發生。Alcohol 在一些測試系統中具有遺傳毒性，並且已提出 Alcohol 的遺傳毒性作用是通過其代謝物 Acetaldehyde 所導致的。綜上，長期攝入 Alcohol 的影響，包括中毒、肝損傷、腦損傷和可能的致癌性。由於皮膚塗抹或吸入含有這些成分的化粧品不會產生明顯的 Alcohol 全身暴露，因此 CIR 專家小組得出結論，成分的安全性應以所使用之變性劑的安全性為基礎。[2]

- 參考資料：

1. SIDS Initial Assessment Report For SIAM 19, ETHANOL. OECD SIDS 2004.
2. Final report of the safety assessment of Alcohol Denat., including SD Alcohol 3-A, SD Alcohol 30, SD Alcohol 39, SD Alcohol 39-B, SD Alcohol 39-C, SD Alcohol 40, SD Alcohol 40-B, and SD Alcohol 40-C, and the denaturants, Quassin, Brucine sulfate/Brucine, and Denatonium Benzoate., CIR, 2008.

3. INCI name：Glycerin

- 不純物：美國藥典國民處方集(USP-NF)標準規定甘油中任何單體雜質的含量不得超過 0.1%，所有雜質（包括二甘醇 Diethylene Glycol 和乙二醇 Ethylene Glycol）的總量不得超過 1%。[1]
- 急性毒性：大鼠口服 LD_{50} 2530~58400 mg/kg。大鼠皮膚 LD_{50} >21900 mg/kg bw。據研究顯示，對人類甘油的口服 LD_{50} 為 1428 mg/kg。當人類口服 30 ml 甘油時，沒有毒性跡象。當作為藥物口服給藥時，對人類的不良反應包括輕度頭痛、頭暈、噁心、嘔吐、口渴和腹瀉。[1]
- 腐蝕性和刺激性：刺激眼睛和皮膚的可能性極小。[1]
- 皮膚致敏性：非皮膚致敏物。[1]
- 重複給藥毒性：當雜種犬口服給藥 3 天時的 NOAEL 為 950 mg/kg bw/day，在劑量 3800 mg/kg bw/day 時，胃粘膜嚴重充血並伴有點狀出血。當雜種狗在飼料中加入 35%甘油時，在 36 週後體重減輕。 天竺鼠口服 6300 mg/kg bw/day 甘油 30 至 40 天未見病理變化。當人類患者口服大約 1300 至 2200 mg/kg bw/day 甘油 50 天時，沒有出現毒性或對血液或尿液產生影響的跡象，NOAEL 為 2200 mg/kg bw/day。當 100%甘油每天局部施用於兔子 30%的體表 45 週時，沒有任何效應。[1]
- 致突變性/遺傳毒性：既沒有致突變性也沒有遺傳毒性。[1]
- 致癌性：非致癌性物質。[1]
- 生殖毒性：非生殖毒性物質。[1]
- 毒理代謝動力學：來自人類和動物研究的數據顯示，甘油在腸道和胃中迅速被吸收，並分佈在細胞外。由於甘油的 Log Pow(-2.66 至-1.76)較低且缺乏其他研究數據，甘油的皮膚吸收率設定為 80%。[2]
- 人體案例報導：一名 29 歲女性因眼瞼、面部、頸部、頭皮和腋窩出現斑片狀濕疹 7 個月就診。根據歐洲化粧品和美髮系列標準，對她自己的化粧品和洗漱用品進行了 Patch Test，她在第 4 天對二甲氨基丙胺（1%水溶液）和她自己的手部保濕霜有 a+陽性反應。對該保濕霜成分的進一步測試在第 4 天對甘油（1%水溶液）有 a+陽性反應，當停用含甘油的化粧品後，濕疹得以緩解。[1]
- 其他安全性資料：2014 年化粧品成分審查專家小組對支持用於化粧品和個人護理產品的甘油安全性科學數據進行了徹底審查，並根據現有文獻和數據，專家小組得出結論：甘油在目前的使用和濃度做法上是安全的（例如在免沖洗類產品中高達 79%，在沖洗類產品中高達

99%）。美國食品和藥物管理局承認甘油在食品包裝中的使用是一般公認安全的(GRAS)，並且在按照優良製造規範使用時，它是一種多用途的 GRAS 食品物質。此外，甘油已獲得美國食品和藥物管理局批准用於 OTC 藥物，例如肛門直腸藥物產品、皮膚保護劑、眼科藥物和口腔保健產品。可用的甘油科學數據顯示，單次和重複劑量使用後，口服和皮膚不良反應較低。此外，數據顯示在人體臨床研究中沒有報告過敏性皮膚反應。在多項實驗室繁殖和發育安全性研究中，甘油不會對親代繁殖能力或其後代的生長發育、生育力或繁殖性能產生任何不利影響。在對製造合成甘油的男性員工進行的一項人類生育研究中，與使用化粧品的消費者相比，他們預期會接觸到更高暴露量，與使用化粧品的組別相比，在精子數量或正常形狀精子的百分比方面沒有觀察到差異。此外，多項實驗室研究顯示，在口服天然和合成甘油長達兩年的情況下，甘油不會導致基因突變，也沒有證據顯示腫瘤發生率會增加（即甘油不會導致癌症）。[3]

◆ 參考資料：

1. Safety Assessment of Glycerin as Used in Cosmetics, International Journal of Toxicology, Vol.38(Supplement 3), 6S-22S, CIR, 2019.
2. SIDS Initial Assessment Report For SIAM 14 . Glycerol CAS N°: 56-81-5, 2002.
3. Cosmetics Info 網站：https://cosmeticsinfo.org/ingredient/glycerin-0

4. INCI name：Polysorbate 80

- 暴露途徑：經皮膚吸收、眼睛接觸吸收、吸入。[2]
- 不純物：製造過程中，需將聚山梨酯(Polysorbate)進行蒸餾以去除不需要的水溶性副產物，例如：1,4-二噁烷(1,4-Dioxane)。由於聚乙二醇(Polyethylene glycol, PEG)是環氧乙烷(ethylene oxide)與水的縮合產物，其鍊長取決於聚合的環氧乙烷之摩爾數，因此它們可能含有 1,4-Dioxane 不純物（乙氧基化的副產物）。1,4-Dioxane 是已知的動物致癌物，美國食品藥物管理局(U.S. Food and Drug Administration, FDA) 一直在定期監測化粧品中 1,4-Dioxane 的含量，根據化粧品行業報告顯示已知 1,4-Dioxane 可能是 PEG 製程中生成之不純物，因此，在摻入化粧品配方前須另進行純化步驟以降低其殘留量。[1]

- 急性毒性：無 Polysorbate 80 之研究數據，而類似的聚山梨酯類成分 Polysorbate 81 的口服 LD_{50} 對大鼠> 20000 mg/kg；乙氧基化脫水山梨糖醇單硬脂酸酯(sorbitan monostearate, ethoxylated)在大鼠中的急性皮膚 LD_{50}> 2000 mg/kg；乙氧基化脫水山梨糖醇單硬脂酸酯(sorbitan monostearate, ethoxylated)給藥 4 小時，吸入 LC_{50} 為 5.1 mg/L；Polysorbate 20 對小鼠的靜脈注射 LD_{50} 為 1420 mg/kg。[1]

- 重複劑量毒性：90 天以狗為試驗對象對於 Polysorbate 80 最高口服 NOAEL 為 5 mL/kg bw/day，大鼠 4 週試驗中對於 Polysorbate 80 的最高口服 NOAEL 為 5 mL/kg bw/day。鼻腔給藥方式給予小鼠 0.2% Polysorbate 80 的 NOAEL 為 10 µL /鼻腔/day。在對 Sprague-Dawley 大鼠(n = 6 /性別)高脂餵食 28 天後，口服 28 天的 Polysorbate 80 (148、740 或 3700 mg/kg bw/day)，無不良反應或致命的報導，但尚不清楚大鼠在施用 Polysorbate 80 期間是否繼續高脂飲食。對大鼠使用 Polysorbate 80 進行的亞慢性毒性研究(NTP, 1992a)顯示，無觀察到的不良反應，其 NOAEL 相當於 4500mg/kg bw/day。在大鼠膳食亞慢性毒性研究(BIBRA, 1981)中，確定的 NOAEL 相當於 1460 mg/kg bw/day。[1]

- 生殖毒性：在一項生殖和發育研究中，在妊娠第 6 天，透過管飼法對 25 隻 Crl：CD BR VAF/Plus TM 大鼠餵食 Polysorbate80（在蒸餾水中濃度為 500 和 5000 mg/kg bw/day；5 mL），對照組接受 5 mL/kg 蒸餾水。據實驗結果顯示母親和發育中胎兒的 NOAEL >5000 mg/kg bw/day。未觀察到產婦死亡或與治療有關的毒性中毒臨床症狀，對體重增加、器

官重量(非不利的相對肝臟重量增加)以及飼料和水的消耗沒有影響，在實驗組和對照組之間沒有觀察到致畸胎的差異。[1]

- 致癌性：在已發表的文獻中未發現有關聚山梨酯的致癌性數據。[1]
- 遺傳毒性：Polysorbate 80 對鼠傷寒沙門氏菌(菌株 TA1535、TA1537、TA98 和 TA100)和大腸桿菌(菌株 WP2 uvr A)遺傳毒性試驗，濃度高達 5000 μg/plate（在 Alcohol 中），無論在有或沒有代謝活化的情況下，均無遺傳毒性，對照組均達到預期的結果。[1]
- 皮膚刺激性：無 Polysorbate 80 之數據，在人體皮膚刺激性研究中，類似的聚山梨酯類成分乙氧基化的 Polysorbate 60 (1%)，Polysorbate 80 (100%)和脫水山梨糖醇單硬脂酸酯(25%)對皮膚無刺激性。[1]
- 眼睛刺激性：無 Polysorbate 80 之數據，而類似的聚山梨酯類成分 Polysorbate 20 (10%)和 Polysorbate 81 (100%)的測試顯示對兔子的眼部沒有刺激性。[1]
- 毒理代謝動力學：使用 Franz 體外穿透試驗發現 Polysorbate 80 增強硫酸鹽穿過大鼠皮膚，提高皮膚滲透率。[1]
- 其他安全資料：Polysorbate 20、Polysorbate 21、Polysorbate 40、Polysorbate 60、Polysorbate 61、Polysorbate 65、Polysorbate 80、Polysorbate 81 和 Polysorbate 85 的安全性，經 CIR 專家小組評估科學數據並得出結論，Polysorbate 20、21、40、60、61、65、80、81 和 85 作為化粧品成分是安全的。Polysorbate 80 已獲得 FDA 批准作為眼科緩和劑，可用於非處方藥(Over The Counter, OTC)眼科藥物產品。Polysorbate 是一系列聚氧乙烯化脫水山梨糖醇酯，它們的不同之處在於聚合氧乙烯亞單元的數量以及存在的脂肪酸基團的數量和類型。CIR 專家小組表示 Polysorbate 不是誘變劑或完全致癌物。現有數據顯示，這些成分被用於許多製劑中，但沒有出現明顯不良反應的臨床報告。[3,4]
- 參考資料：

1. Safety Assessment of Polysorbates as Used in Cosmetics. CIR, March 31, 2015.
2. Scientific Opinion on the re-evaluation of polyoxyethylene sorbitan monolaurate (E432), polyoxyethylene sorbitan monooleate (E433), polyoxyethylene sorbitan monopalmitate (E 434), polyoxyethylene sorbitan monostearate (E435) and polyoxyethylene sorbitan tristearate (E436) as food additives. EFSA Journal 2015;13(7):4152.

3. Food Safety Commission, Evaluation report of food Additives. Polysorbates (Polysorbates 20, 60, 65 and 80), 2007. Original: Japanese- Available. from: https://www.fsc.go.jp/english/evaluationreports/foodadditive/polysorbate_report.pdf
4. Cosmetics Info 網站：https://cosmeticsinfo.org/ingredient/polysorbate-80

5. INCI name：Fragrance

IFRA Certificate

IFRA Certificate 49th - ALL LIMITS

Product: **Green Tea**
Product#:
SKU#: **gre**

2020-06-05

xxxxxxxxxx certifies that the above mentioned fragrance product is in compliance with the standards of the International Fragrance Association [IFRA 49th Amendment (January '20)], provided the fragrance is used in the following application(s) at the following maximum concentration level(s):

Application	Maximum Usage Level
1 - Lip Products of all Types (Solid & Liquid) lipsticks, Balms & Wax (Clear or Colored)	NOT Allowed
1 - Toys	NOT Allowed
2 - Deodorant & Antiperspirant of all Types (Spray, Stick, Roll-On, Deo-Cologne & Body Spray)	1.3%
3 - Bodypaint (for children & adults)	22.2%
3 - Eye products of all types	22.2%
3 - Facial make up and foundation	22.2%
3 - Facial masks for face, lip & around the eyes	22.2%
3 - Make-up remover for face, eyes and lips	22.2%
3 - Nose pore strips	22.2%
3 - Wipes or refreshing tissues for face, neck, hands, body	22.2%
4 - Fine fragrance of all types (eau de toilette, parfum, cologne, solid perfume, fragrancing cream, etc.	24.7%
4 - Fragranced bracelets	24.7%
4 - Perfume kit fragrance ingredients/mixtures	24.7%
4 - Scent pads, foil packs	24.7%
4 - Scent strips for hydroalcoholic products	24.7%
5A - All powders and talcs (excluding baby powders and talcs)	6.5%
5A - Body creams, oils, lotions of all types	6.5%
5A - Foot care products (creams & powders)	6.5%
5A - Insect repellent (intended to be applied to the skin)	6.5%
5B - Face Toner	6.5%
5B - Facial moisturizer and creams	6.5%
5C - Hand Cream	6.5%
5C - Hand sanitizers	6.5%
5C - Nail care products including cuticle creams, etc.	6.5%
5D - Baby cream/lotion, baby oil, baby powders and talcs	5.0%
6 - Mouthwash, including breath sprays	NOT Allowed
6 - Toothpaste	NOT Allowed
7A - Hair permanent or other hair chemical treatments (Rinse-off) (e.g. relaxers), including rinse-off hair dyes	29.3%
7B - Hair Deodorizer	24.7%
7B - Hair permanent or other hair chemical treatments (Leave-on) (e.g. relaxers), including Leave-On hair dyes	24.7%

(11) 產品安定性試驗報告

試驗結果評估：針對外觀、顏色、氣味、pH、黏度、微生物、包材外觀項目進行 6 個月產品安定性試驗，結果判定均合格，將持續執行達宣稱效期之長期安定性試驗。

產品名稱	清新止汗爽身露			
包裝材質	瓶身:玻璃、瓶蓋:PP、滾珠:PE			
試驗時間 / 試驗項目	第 0 個月	第 1 個月	第 3 個月	第 6 個月
	40 ℃ 75 %RH	40 ℃ 75 %RH	40 ℃ 75 %RH	40 ℃ 75 %RH
外觀	流動液體	流動液體	流動液體	流動液體
顏色	無色透明	無色透明	無色透明	無色透明
氣味	綠茶氣味	綠茶氣味	綠茶氣味	綠茶氣味
pH (at 25 °C)	4.00	4.15	4.12	4.06
黏度(at 25 °C)	120 mPa·s	135 mPa·s	140 mPa·s	136 mPa·s
密度(at 25 °C)	1.00 g/cm^3	1.02 g/cm^3	0.99 g/cm^3	1.01 g/cm^3
微生物檢測結果	未檢出	未檢出	未檢出	未檢出
包材外觀	無膨脹、變色、腐蝕及脆裂之現象	無膨脹、變色、腐蝕及脆裂之現象	無膨脹、變色、腐蝕及脆裂之現象	無膨脹、變色、腐蝕及脆裂之現象
結果判定	■合格 □不合格	■合格 □不合格	■合格 □不合格	■合格 □不合格
參考試驗方法	ISO/TR 18811 Cosmetics-Guidelines on the stability testing of cosmetics products,2018. 參考 5.3.2 建議之溫度及濕度進行加速安定性試驗			
檢測人員/日期	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)
複核人員/日期	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)

(12) 微生物檢測報告

產品名稱	清新止汗爽身露		
產品批號	IT22050A		
產品製造日期	2022.05.03		
包裝材質	瓶身:玻璃、瓶蓋:PP、滾珠:PE	試驗日期	2022.05.06
檢測項目	規 格	檢測結果	參考測試方法
生菌數	<1000 cfu/g	未檢出 (<10 cfu/g)	參考衛生福利部食品藥物管理署 109.07.28 及 111.04.21 公告建議檢驗方法-化粧品中微生物檢驗方法及化粧品中白色念珠菌之檢驗方法。
大腸桿菌	不得檢出	未檢出	
綠膿桿菌	不得檢出	未檢出	
金黃色葡萄球菌	不得檢出	未檢出	
白色念珠菌	不得檢出	未檢出	
結果判定	■合格 □不合格		
檢測人員/日期	(請簽名並加上日期)		
複核人員/日期	(請簽名並加上日期)		

(13) 防腐效能試驗報告

清新止汗爽身露雖然含10% Aluminum Chlorohydrate，但未符合ISO 29621: 2017微生物低風險性含氯化鋁鹽≥25%之條件，判斷非屬於低微生物風險產品，此類產品仍須進行防腐效能試驗及微生物檢測。

樣品名稱 (Sample Name)	**清新止汗爽身露**
測試日期(Date Tested): 111.04.06~111.05.11	
試驗參考方法(Method Code): 參考衛生福利部食品藥物管理署 110.05.13 公告「化粧品防腐效能試驗指引」	

測試菌種 (Microbial strains)					
分析時間點 (Assay Time)	**大腸桿菌 *Escherichia coli* (ATCC 8739)** **(CFU/g or ml)**	**金黃色葡萄球菌 *Staphylococcus aureus* (ATCC 6538)** **(CFU/g or ml)**	**綠膿桿菌 *Pseudomonas aeruginosa* (ATCC 9027)** **(CFU/g or ml)**	**白色念珠菌 *Candida albicans* (ATCC 10231)** **(CFU/g or ml)**	**黑麴菌 *Aspergillus brasiliensis* (ATCC 16404)** **(CFU/g or ml)**
第 0 天	1.2×10^6	1.0×10^6	1.5×10^6	2.3×10^5	2.0×10^5
第 7 天	<10	<10	<10	3.0×10^3	3.2×10^3
第 14 天	<10	<10	<10	<10	2.2×10^2
第 28 天	<10	<10	<10	<10	<10

檢測人員/日期	(請簽名並加上日期)
複核人員/日期	(請簽名並加上日期)

(14) 功能評估佐證資料

清新止汗爽身露相關功能性測定，如止汗功效及制臭功效試驗等。

(15) 與產品接觸之包裝材質資料

產品容量 ：10 ml

包裝材料	材質
清新止汗爽身露-瓶身	玻璃
清新止汗爽身露-瓶蓋	聚丙烯 (Polypropylene, PP)
清新止汗爽身露-滾珠	聚乙烯 (Polyethylene, PE)

III. 安全評估資料

(16) 產品安全資料

清新止汗爽身露每日皮膚暴露量計算

參考 2023 年 5 月發布之歐盟消費者安全科學委員會(Scientific Committee on Consumer Safety, SCCS)化粧品成分測試及其安全性評估指引第 12 版(SCCS/1647/22)，並依其用途、部位、頻率進行皮膚暴露量計算。

基本數據	
平均體重	60 kg
接觸部位	腋下皮膚
接觸種類	駐留產品
每日使用頻率	2/day
使用表面積(cm^2)	200
駐留因子	1

皮膚每日暴露量參考 SCCS 指南表 3A，得知相對每日暴露量($E_{product}$)為 **22.08 mg/kg bw/day**。

Product type	*Estimated daily amount applied* q_x *(g/d)*	*Relative daily amount applied*[1] q_x/bw *(mg/kg bw/d)*	*Retention factor*[2] f_{ret}	*Calculated daily exposure* $E_{product}$ *(g/d)*	*Calculated relative daily exposure*[1] $E_{product}/bw$ *(mg/kg bw/d)*
Deodorant					
Deodorant non-spray	1.50	22.08	1.00	**1.50**	**22.08**
Deodorant spray	0.69	10.00	1.00	**0.69**	**10.00**

清新止汗爽身露各成分 MoS 值計算

計算各個成分之 Margin of Safety (MoS) 安全邊際值如下表：

SED= $E_{product}$ (每日皮膚暴露量)×C/100(配方百分比)×DAp/100(皮膚吸收率)

MoS= PoD_{sys}/SED

SED (mg /kg bw/day)為全身暴露劑量；$E_{product}$ (mg /kg bw/day)為每日皮膚暴露量；C(%)為配方百分比；DAp(%)為皮膚吸收率；PoD_{sys} 以 NOAEL 或 LOAEL 估算。

SCCS 化粧品成分測試及其安全性評估指引第 12 版(SCCS/1647/22)提及 90 天口服毒性試驗是化粧品成分最常用的重複劑量毒性試驗，當有科學合理的 90 天研究確認明確的劑量反應點(Point of Departure, PoD)時，SCCS 會考慮以該研究計算 MoS，當對亞慢性毒性研究的品質存疑或缺乏支持 90 天研究的 PoD 時，則建議應用不確定性因子來推估，為了保守嚴謹評估，故亦將各成分之 NOAEL 在考慮各別的毒理試驗條件後將不確定因子進行校正。以校正後之 NOAEL 值計算結果如下:

INCI name	配方百分比 C(%)	皮膚吸收率 DA_P(%)	NOAEL (mg /kg bw/day)	SED (mg /kg bw/day)	MoS
Water	70.5	-	-	-	>100
Aluminum Chlorohydrate*	10.0	0.00192	0.18	0.000042	4286
Alcohol	10.0	100	1200	2.21	543
Glycerin	5.0	100	611	1.11	550
Polysorbate 80	4.0	100	730	0.88	830
Fragrance	0.5	-	-	-	符合 IFRA

* Aluminum Chlorohydrate 參考德國 BfR 2019 年人體試驗，於 6 位女性受試者腋窩塗抹含 6.25% 放射性標記 ACH 的止汗劑，計算出經皮膚吸收之鋁生物利用率(Bioavailability)為 0.00192%。

INCI name	NOAEL 校正說明
Aluminum Chlorohydrate	由 12 個月大鼠口服試驗得出 NOAEL 為 30 mg/kg bw/day，考慮口服之鋁生物利用率(Bioavailability)為 0.6%之不確定因子，將 30*0.6% =0.18 mg/kg bw/day (180 μg/kg bw/day)。
Alcohol	對大鼠每日飲食研究報告的最低 NOAEL 為約 2400 mg /kg bw/day (未說明天數)，考慮口服生物可用率 50%等不確定因子， 將 2400*50% =1200 mg/kg bw/day。
Glycerin	人類患者口服甘油 50 天時，NOAEL 為 2200 mg/kg bw/day，考慮口服生物可用率 50%及試驗天數等不確定因子，將 2200*50%

	*50/90 =611.1 mg/kg bw/day。
Polysorbate 80	大鼠膳食亞慢性毒性研究(BIBRA, 1981)中，確定的 NOAEL 相當於 1460 mg/kg bw/day(未說明天數)，考慮口服生物可用率 50%之不確定因子，將 1460*50% =730 mg/kg bw/day。

清新止汗爽身露安全評估結論

安全評估結論簡述

經分析所有可取得之安全性資料，根據上述評估計算結果並根據當前科學知識，推定清新止汗爽身露在預期正常合理使用條件下，本產品為可安全使用之產品，對人體健康造成傷害風險低。

標籤警語和使用說明

清新止汗爽身露的包裝材料/標籤上提到了以下警告和使用說明：

使用方式：打開瓶蓋稍微倒置使滾珠沾滿爽身露，再以滾珠端接觸腋下肌膚，並來回均勻塗抹，使用後緊閉瓶蓋。

使用注意事項：皮膚若有傷口請勿使用；使用後若有不適請立即停止使用，並以大量清水沖洗，症狀若未改善，建議就醫。

安全評估理由

清新止汗爽身露的安全性評估基於每種成分的毒理學特徵並評估所收集之產品數據。

1. 該產品在符合化粧品優良製造規範之場所和生產設施中生產，並進行微生物品質管理以及倉儲管理作業。
2. 本產品添加之止汗成分 10% Aluminum chlorohydrate，符合我國之規定(限量標準 25%)。
3. 根據本產品「清新止汗爽身露」之化粧品的物理/化學特性、安定性試驗報告、微生物檢測報告及防腐效能試驗報告，結果由數據顯示產品符合規格特性，證實了「清新止汗爽身露」產品配方具有足夠安定性及微生物安全性。由六個月之加速安定性試驗推測本產品於架儲期間品質穩定，上市後將同時進行長期安定性試驗。
4. 微生物檢測報告結果符合我國化粧品微生物容許量基準之要求。防腐效能試驗報告顯示符合衛福部食藥署 110.05.13 公告之化粧品防腐效能試驗指引標準 A，表示產品微生物汙染風險受到管控，可保護產品避免受到潛在微生物汙染之風險。
5. 根據包材材質使用和本產品成分使用經驗分析，本產品使用之包裝材料材質與產品成分間可能之交互作用，對產品產生安全性影響的不純物殘留風險低，評估包裝材料合適且安全。
6. 根據 SCCS 化粧品成分測試及其安全性評估指引第 12 版，計算化粧品中產品和每種成分的暴露程度。對於產品使用暴露量，採用國際間常用 SCCS 用

於非噴霧型止汗產品之標準暴露值以計算安全邊際值(MoS)。

7. 使用之香精符合國際香料協會標準(IFRA 49th Amendment)，應用止汗致臭劑之最大濃度為 1.3%，此清新止汗爽身露添加 0.5%香精，推測不具致敏性。
8. 此清新止汗爽身露中的所有原材料和成分均可使用於化粧品中，而針對所有成分計算的安全邊際值(MoS)皆高於 100，這支持此產品的安全性。
9. 目前此產品尚未出現不良反應和嚴重不良反應，如有不良反應和嚴重不良反應的相關資料時，會及時提供給安全資料簽署人員重新評估此產品之安全性，並更新於本產品資訊檔案。

（請簽名並加上日期）

_____

安全資料簽署人員簽名及日期

附錄 1 產品及各別成分之物理及化學特性資料

註：本範例僅提供其中一成分之物理化學特性資料為示範，實際執行時應包含所有蒐集到之產品及內含各成分之品質規格或各成分(亦須包含 Fragrance 內含成分)之檢驗報告(Certificate of Analysis, COA)、安全資料表(Safety Data Sheet, SDS)、檢驗標準或試驗方法等分析規格書，且內容如有變更應隨時更新。

INCI name：Aluminum Chlorohydrate

SAFETY DATA SHEET

Revision date 2021-Jan-06 **Revision number** 1.03

1. IDENTIFICATION

Product identifier

Product name Aluminum Chlorohydrate Solution

Other means of identification

Product code
Synonyms

Recommended use of the chemical and restrictions on use

Recommended use [RU] No information available
Uses advised against None known

Details of the supplier of the safety data sheet

Supplier

Contact Point

Emergency telephone number

24 Hour Emergency Phone Number

2. HAZARDS IDENTIFICATION

Classification

OSHA Regulatory Status
This chemical is considered hazardous by the 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200).

Skin corrosion/irritation	Category 2
Serious eye damage/eye irritation	Category 2
Corrosive to metals	Category 1

EMERGENCY OVERVIEW

Physical state	Color	Appearance	Odor
liquid	colorless to yellow	clear	no appreciable odor

GHS Label elements, including precautionary statements

WARNING

Hazard statements
Causes skin irritation
Causes serious eye irritation
May be corrosive to metals

Precautionary Statements - Prevention
Wash face, hands and any exposed skin thoroughly after handling. Wear protective gloves/protective clothing/eye protection/face protection. Keep only in original container.

Precautionary Statements - Response
IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. If eye irritation persists: Get medical advice/attention.
IF ON SKIN: Wash with plenty of soap and water. If skin irritation occurs: Get medical advice/attention. Take off contaminated clothing and wash before reuse.
Absorb spillage to prevent material damage.

Precautionary Statements - Storage
Store in corrosive resistant container with a resistant inner liner.

Other information
• May be harmful in contact with skin

3. COMPOSITION/INFORMATION ON INGREDIENTS

Component	CAS-No	weight-%	TRADE SECRET
Aluminum Chlorohydrate	12042-91-0	50%	--
Water	7732-18-5	50%	--

If CAS number is "proprietary", the specific chemical identity and percentage of composition has been withheld as a trade secret.

4. FIRST AID MEASURES

First Aid Measures

Eye contact
Immediately flush with plenty of water for at least 20 minutes, holding eyelids apart to ensure flushing of the entire surface. Washing within one minute is essential to achieve maximum effectiveness. Seek immediate medical attention.

Skin contact
Immediately wash thoroughly with soap and water, remove contaminated clothing and footwear. Wash clothing before reuse. Get medical attention if irritation should develop.

Ingestion
Seek medical attention immediately. Give large amounts of water to drink. If vomiting should occur spontaneously, keep airway clear. Never give anything by mouth to an unconscious person.

Inhalation
Remove to fresh air.

Most important symptoms and effects, both acute and delayed

Acute effects
Possible eye, skin and respiratory tract irritation.

Chronic effects
May aggravate existing skin, eye, and lung conditions. Persons with kidney disorders have an increased risk from exposure based on general information found on aluminum salts.

Indication of any immediate medical attention and special treatment needed

Note to physicians
Aluminum soluble salts may cause gastroenteritis if ingested. Treatment includes the use of demulcents. Note: Consideration should be given to the possibility that overexposure to materials other than this product may have occurred.

5. FIRE-FIGHTING MEASURES

Extinguishing media

Suitable extinguishing media
Water Spray, Carbon Dioxide, Foam, Dry Chemical.

Extinguishing media which must not be used for safety reasons
No information available.

Special hazards arising from the substance or mixture

Special Hazard
May produce hazardous fumes or hazardous decomposition products.

Advice for firefighters

Firefighting measures
Product is a water solution and nonflammable. In a fire, this product may build up pressure and rupture a sealed container; cool exposed containers with water spray. Use self-contained breathing apparatus in confined areas; avoid breathing mist or spray.

Special protective equipment for firefighters
Not determined

Explosion data

Sensitivity to Mechanical Impact
None.

Sensitivity to Static Discharge
None.

6. ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures

Personal precautions
Wear suitable protective clothing and gloves.

Environmental precautions

Environmental precautions
Do not permit run-off to get into sewers or surface waterways.

Methods and material for containment and cleaning up

Methods for containment
Prevent further leakage or spillage if safe to do so. Dike to collect large liquid spills.

Methods for cleaning up
Clear spills immediately. Contain large spill and remove using a vacuum truck. Soak up small spills with inert absorbent material and place in a labeled waste container for disposal. Ventilate area of leak or spill. Spills of solution are extremely slippery so all residue must be removed promptly.

7. HANDLING AND STORAGE

Precautions for safe handling

Advice on safe handling
Keep container closed when not in use
Keep away from heat and open flame.
Avoid contact with eyes, skin and clothing
Wash thoroughly after handling
Wear chemical splash goggles, gloves, and protective clothing when handling.
Avoid breathing vapors or mists
Use with adequate ventilation and employ respiratory protection where mist or vapors may be generated.
FOR INDUSTRIAL USE ONLY.

Conditions for safe storage, including any incompatibilities

Technical measures and storage conditions
Do not store in unlined metal containers.
Product may slowly corrode iron, brass, copper, aluminum, mild steel, and stainless steel.
Store in a cool, dry place away from direct heat.
Keep in tightly closed container.

Incompatible products
Oxidizing agents.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Control parameters

Exposure Guidelines

Component	weight-%	ACGIH TLV	OSHA PEL	NIOSH IDLH
Aluminum Chlorohydrate 12042-91-0	50%	1 mg/m³ TWA (respirable particulate matter)	--	--

Appropriate engineering controls

Engineering controls
Local exhaust ventilation as necessary to maintain exposures to within applicable limits. Please refer to the ACGIH document, "Industrial Ventilation, A Manual of Recommended Practices", most recent edition, for details. If there are no applicable or established exposure limit requirements or guidelines, general ventilation should be sufficient.

Individual protection measures, such as personal protective equipment

Eye/face Protection
Wear chemical splash goggles and face shield (when eye and face contact is possible due to splashing or spraying of material).

Hand Protection
Appropriate chemical resistant gloves should be worn

Skin and body protection
Standard work clothing and work shoes.

Respiratory protection
If exposures exceed the PEL or TLV, use NIOSH/MSHA approved respirator in accordance with OSHA Respiratory Protection Requirements under 29 CFR 1910.134.

Other personal protection data
Eyewash fountains and safety showers must be easily accessible.

Hygiene measures
Handle in accordance with good industrial hygiene and safety practice.

9. PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Physical state	liquid
Color	colorless to yellow
Appearance	clear
Odor	no appreciable odor
Odor threshold	No information available

Property	Values	Remarks / Method
pH	3.5	as is
Melting / freezing point	-7 °C / 19 °F	No information available
Boiling point / boiling range	No information available	No information available
Flash point	Not applicable	No information available
Evaporation rate	No information available	No information available
Flammability (solid, gas)	Not applicable	No information available
Flammability Limit in Air		
Upper flammability limit	Not applicable	No information available
Lower flammability limit	Not applicable	No information available
Vapor pressure	No information available	No information available
Vapor density	No information available	No information available
Specific gravity	1.33 - 1.35	No information available
Solubility (water)	Soluble	No information available
Solubility in other solvents	No information available	No information available
Partition coefficient: n-octanol/water	No information available	No information available
Autoignition temperature	Not applicable	No information available

Decomposition temperature	No information available	No information available
Kinematic viscosity	No information available	No information available
Dynamic viscosity	< 100 cps @ 20 °C	No information available

Other information

Density	11.0 - 11.3 lb/gal
Bulk Density	No information available
Explosive properties	No information available
Oxidizing properties	No information available
Softening point	No information available
Molecular weight	No information available
Volatile Organic Compound (VOC) content, wt.%	No information available
Percent Volatile, wt.%	40 - 50%

10. STABILITY AND REACTIVITY

Reactivity

Reactivity
No data available.

Chemical stability

Chemical stability
Stable.

Possibility of hazardous reactions

Possibility of hazardous reactions
None under normal processing.

Hazardous polymerization
No.

Conditions to avoid

Conditions to avoid
None.

Incompatible materials

Materials to avoid
Oxidizing agents.

Hazardous decomposition products

Hazardous decomposition products
Thermal decomposition may release toxic and/or hazardous gases such as Cl_2 and HCl.

11. TOXICOLOGICAL INFORMATION

Information on likely routes of exposure

Eye contact
May cause moderate eye irritation that can become severe with prolonged contact. Prolonged exposure to Aluminum salts may cause conjunctivitis.

Skin contact
May be harmful in contact with skin. Prolonged and/or repeated contact may cause skin irritation.

Ingestion
May cause irritation of the mouth, throat and stomach. Ingestion may cause gastrointestinal irritation, nausea, vomiting and diarrhea.

Inhalation
Inhalation of mist or vapor may cause respiratory tract irritation.

Acute toxicity - Product Information

Oral LD50	No information available
Dermal LD50	No information available
Inhalation LC50	No information available

Acute toxicity - Component Information

Component	weight-%	Oral LD50	Dermal LD50	Inhalation LC50
Aluminum Chlorohydrate 12042-91-0	50%	= 9187 mg/kg (Rat)	> 2000 mg/kg (Rat)	--

Information on toxicological effects

Symptoms
No information available.

Delayed and immediate effects as well as chronic effects from short and long-term exposure

Skin corrosion/irritation
Irritating to skin

Serious eye damage/eye irritation
Causes serious eye irritation

Sensitization
No information available

Germ cell mutagenicity
No information available

Carcinogenicity
This product does not contain any components in concentrations greater than or equal to 0.1% that are listed as known or suspected carcinogens by NTP, IARC, ACGIH, or OSHA.

Reproductive toxicity
No information available

Specific target organ toxicity - Single exposure
No information available.

Specific target organ toxicity - Repeated exposure
No information available

Aspiration hazard
No information available.

Numerical measures of toxicity - Product Information

The following values are calculated based on chapter 3.1 of the GHS document

ATEmix (oral) 18374 mg/kg
ATEmix (dermal) 4004 mg/kg

Other information
Conclusions are drawn from sources other than direct testing.

12. ECOLOGICAL INFORMATION

Ecotoxicity

Acute aquatic toxicity - Product Information

Fish
LC_{50} (48 hour, 3-brood, static, renewal) 400 mg/L *Pimephales promelas* (Fathead Minnow) [1]
IC_{25} (48 hour, 3-brood, static, renewal) 29.57 mg/L *Pimephales promelas* (Fathead Minnow) [1]
IC_{50} (48 hour, 3-brood, static, renewal) 39.10 mg/L *Pimephales promelas* (Fathead Minnow) [1]

Crustacea
LC_{50} (96 hour, static, renewal) > 400 mg/L *Ceriodaphnia dubia* (Water Flea) [1]
IC_{25} (96 hour, static, renewal) 8.61 mg/L *Ceriodaphnia dubia* (Water Flea) [1]
IC_{50} (96 hour, static, renewal) 17.22 mg/L *Ceriodaphnia dubia* (Water Flea) [1]

Algae/aquatic plants No information available

Acute aquatic toxicity - Component Information

Component	weight-%	Algae/aquatic plants	Fish	Toxicity to daphnia and other aquatic invertebrates
Aluminum Chlorohydrate 12042-91-0	50%	--	LC50 (96 h static) 100 - 500 mg/L (Brachydanio rerio)	--

Chronic aquatic toxicity - Product Information

Fish
$NOEC_S$ (48 hour, 3-brood, static, renewal, survival) 200 mg/L *Pimephales promelas* (Fathead Minnow) [1]
$NOEC_R$ (48 hour, 3-brood, static, renewal, reproduction) 25 mg/L *Pimephales promelas* (Fathead Minnow) [1]

Crustacea
$NOEC_S$ (96 hour, static, renewal, survival) > 25 mg/L *Ceriodaphnia dubia* (Water Flea) [1]
$NOEC_G$ (96 hour, static, renewal, growth) > 25 mg/L *Ceriodaphnia dubia* (Water Flea) [1]

Persistence and degradability

Persistence and degradability
No information available

Bioaccumulative potential

Bioaccumulative potential
No information available

Mobility

Mobility
No information available

Results of PBT and vPvB assessment

PBT and vPvB assessment
No information available

Other adverse effects

Other information
[1] Tests conducted by EnviroScience, Inc. using Standard Operating Procedures (SOP's) derived from EPA methods EPA-821-R-02-012 and EPA-821-R-02-013. Report dated 3-2-2018.

13. DISPOSAL CONSIDERATIONS

Waste treatment methods

Disposal of wastes
Do NOT mix with other chemical wastes. Do not put solutions containing this product into sewer systems. Dispose of product in an approved chemical waste landfill or incinerate in accordance with applicable Federal, state and local regulations. Do not re-use empty containers.

Contaminated packaging
Since empty containers retain product residue, follow label warnings even after container is emptied.

14. TRANSPORT INFORMATION

DOT	NOT REGULATED FOR TRANSPORTATION This product is excepted from DOT regulations under 49 CFR 173.154(d) when shipped by road or railway. The product exception is referenced in 49 CFR 172.101 Table. Packaging material must not be aluminum, steel or be degraded by this product
ICAO/IATA	Regulated
UN number	UN3264
Proper shipping name	Corrosive Liquid, Acidic, Inorganic, N.O.S. (Polyaluminum Chloride Solution)
Hazard class	8
Packing group	III
ERG Code	8L
IMDG	Regulated
UN number	UN3264
Proper shipping name	Corrosive Liquid, Acidic, Inorganic, N.O.S. (Polyaluminum Chloride Solution)
Hazard class	8
Packing group	III
EmS	F-A, S-B

15. REGULATORY INFORMATION

International Inventories

United States (TSCA)
All ingredients are on the inventory or exempt from listing

Australia (AICS)
All ingredients are on the inventory or exempt from listing

Canada (DSL)
All ingredients are on the inventory or exempt from listing

Canada (NDSL)
None of the ingredients are on the inventory.

China (IECSC)
All ingredients are on the inventory or exempt from listing

European Union (EINECS)
All ingredients are on the inventory or exempt from listing

European Union (ELINCS)
None of the ingredients are on the inventory.

Japan (ENCS)
All ingredients are on the inventory or exempt from listing

South Korea (KECL)
All ingredients are on the inventory or exempt from listing

Philippines (PICCS)
All ingredients are on the inventory or exempt from listing

Legend

TSCA - United States Toxic Substances Control Act Section 8(b) Inventory
AICS - Australian Inventory of Chemical Substances
DSL/NDSL - Canadian Domestic Substances List/Non-Domestic Substances List
IECSC - China Inventory of Existing Chemical Substances
EINECS/ELINCS - European Inventory of Existing Commercial Chemical Substances/EU List of Notified Chemical Substances
ENCS - Japan Existing and New Chemical Substances
KECL - Korean Existing and Evaluated Chemical Substances
PICCS - Philippines Inventory of Chemicals and Chemical Substances

U.S. Federal Regulations

CERCLA
This material, as supplied, does not contain any substances regulated as hazardous substances under the Comprehensive Environmental Response Compensation and Liability Act (CERCLA) (40 CFR 302) or the Superfund Amendments and Reauthorization Act (SARA) (40 CFR 355). There may be specific reporting requirements at the local, regional, or state level pertaining to releases of this material.

CWA (Clean Water Act)
This product does not contain any substances regulated as pollutants pursuant to the Clean Water Act (40 CFR 122.21 and 40 CFR 122.42).

SARA 313
Section 313 of Title III of the Superfund Amendments and Reauthorization Act of 1986 (SARA). This product does not contain any chemicals which are subject to the reporting requirements of the Act and Title 40 of the Code of Federal Regulations, Part 372.

U.S. State Regulations

California Proposition 65
This product does not contain any Proposition 65 chemicals.

U.S. State Right-to-Know Regulations
This product does not contain any substances regulated under applicable state right-to-know regulations

16. OTHER INFORMATION

NFPA Rating	Health - 1	Flammability - 0	Instability - 0	Special Hazard -
HMIS Rating	Health - 1	Flammability - 0	Physical hazards - 0	Personal protection - B
Product code	3204H			
Revision date	2021-Jan-06			

Revision number 1.03

Disclaimer
The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text.

End of Safety Data Sheet

附錄 2 各成分之毒理相關資料

註：本範例僅提供其中一成分之毒理資料為示範，實際執行時應包含所有蒐集之各個成分之毒理資料，且內容如有變更應隨時更新。

INCI name：Aluminum Chlorohydrate

SCCS/1613/19
Final Opinion

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

Members of the Working Group are acknowledged for their valuable contribution to this Opinion. The members of the Working Group are:

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http://ec.europa.eu/health/scientific_committees/experts/declarations/sccs_en.htm

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.

/

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

/

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

/

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 cm^2, 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

Blood Data
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.

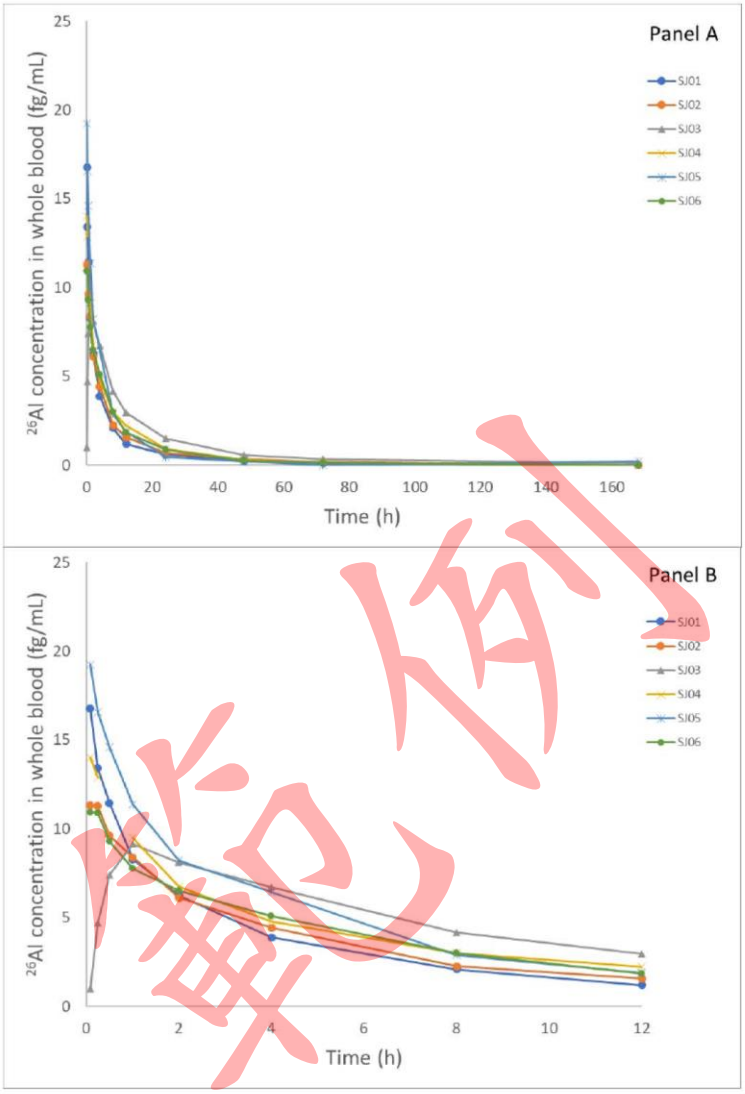

Figure 1 Study 2A: ^{26}Al concentrations in whole blood after IV injection: (A) 0-168h and (B) 0-12h (Panel B).

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.

Urine data

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.

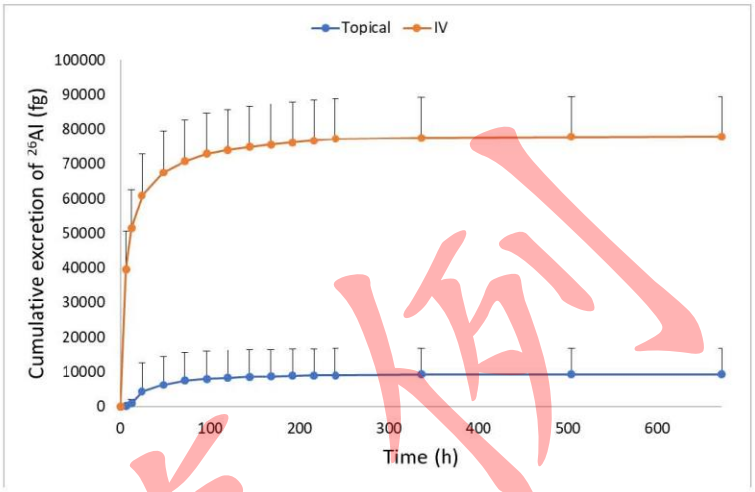

Figure 2 Study 2A: Cumulative urinary excretion of ^{26}Al after topical application or IV injection of ^{26}Al.

	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.

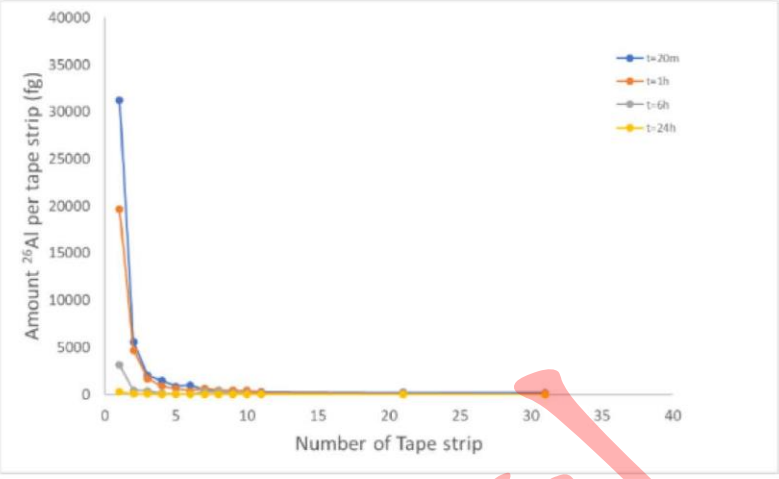

Figure 3 Study 2B: Representation of the amount ^{26}Al (in fg) recovered from tape strips (Reproduced from Figure 4 of the TNO study report).

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	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).

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

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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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	$(NH_4^+)_5[Al_3(H_2Cit)_3(OH)(H_2O)[NO_3^-]\bullet 6H_2O$	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	-	$Al_2(OH)_xCl_z$ 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)	-	-	-	$(Na,Ca)Al_{1-2}Si_{3-2}O_8$	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:

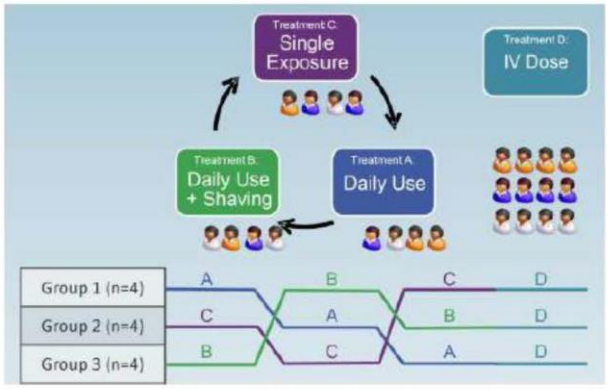
7µg ^{26}Al-HCl (obtained from Los Alamos Laboratory) was used to prepare ^{26}Al-citrate for the intravenous dose. A lab scale batch of ^{26}Al-ACH was prepared meeting commercial specifications for pH, density, Al:Cl ratio and molecular weight profile. The proportion of ^{26}Al:^{27}Al in the ACH test 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)

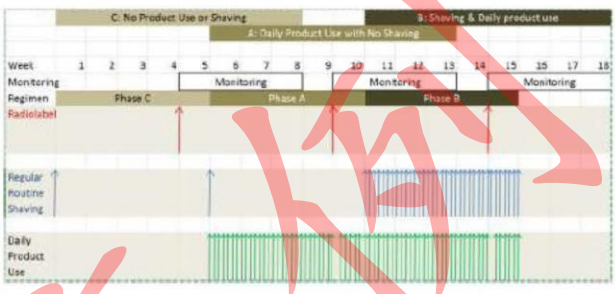


Figure 1 (i) The basic cross-over study design for three groups of n =4 human volunteers and (ii) an example of the detailed study regimen for Group 2 (n =4) - C, A, B, D (not showing the intravenous stage (D).

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).

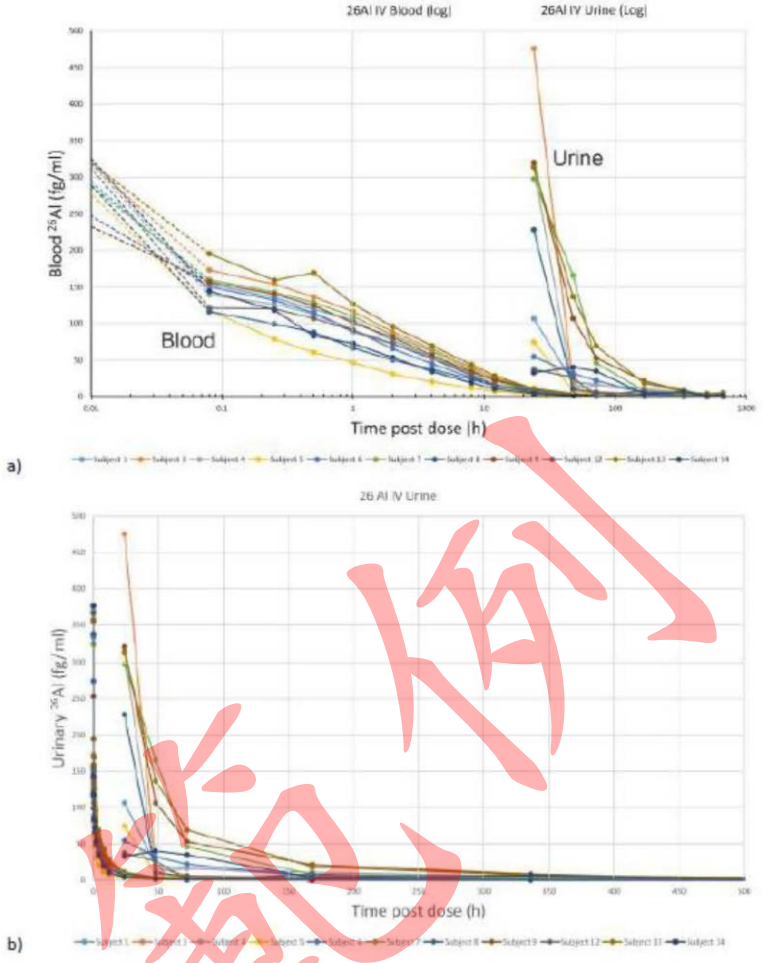


Figure 2 Blood and urine measurement (fg/ml) of ^{26}Al following intravenous dosing in 11 human volunteers a) on a logarithmic scale and b) on a linear scale.

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.
