化粧品產品資訊檔案(範例)

<清爽型防曬乳>

＜PIF **無特定之格式**，本範例**僅提供參考用**＞

中華民國 111 年 7 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	清爽型防曬乳
產品類別	化粧水/油/面霜/乳液類
產品劑型	乳劑
用途	防曬
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：0123XXXXTEST3000000000

(3) 全成分名稱及其各別含量

INCI Name	Cas No.	w/w%	功能
Aqua	7732-18-5	73.57	溶劑
Decyl Oleate	3687-46-5	15.0	潤膚劑
Ethylhexyl Methoxycinnamate	5466-77-3	3.0	防曬劑
Phenylbenzimidazole Sulfonic Acid	27503-81-7	2.78	防曬劑
Cetearyl Alcohol	67762-27-0 / 8005-44-5	2.205	乳化劑
Sodium Hydroxide (45 % solution)	1310-73-2	1.2	pH 調節劑
PEG-40 Hydrogenated Castor Oil	61788-85-0	0.63	乳化劑
Butyl Methoxydibenzoylmethane	70356-09-1	0.5	防曬劑
Sodium Cetearyl Sulfate	59186-41-3	0.315	乳化劑
Carbomer	9007-20-9 / 9003-01-4 / 76050-42-5 / 9062-04-8 / 9007-16-3 / 9007-17-4	0.3	增稠劑
Disodium EDTA	139-33-3/ 6381-92-6	0.1	螯合劑
Methylparaben	99-76-3	0.3	防腐劑
Propylparaben	94-13-3	0.1	防腐劑
Total		100.00	

(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)	 
外盒	

標籤/仿單	品名：清爽型防曬乳 用途：防曬 用法：曝曬前 15 分鐘取適量均勻塗抹於臉部或身體。 保存方法：使用後將瓶口緊閉、置於室溫陰涼處避免陽光直射。 全成分： 特定用途成分：Ethylhexyl Methoxycinnamate 3.0%、Phenylbenzimidazole Sulfonic Acid 2.78%、Butyl Methoxydibenzoylmethane 0.5% 其他成分：Aqua、Decyl Oleate、Cetearyl Alcohol、PEG-40 Hydrogenated Castor Oil、Sodium Hydroxide、Sodium Cetearyl Sulfate、Carbomer、Methylparaben、Propylparaben、Disodium EDTA 使用注意事項：塗抹時避免接觸眼睛，若不慎接觸請以大量清水沖洗。使用後若有不適，請立即停止使用並以大量清水沖洗。不得使用於三歲以下孩童之尿布部位。 製造業者/地址/連絡電話： 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 2021.07.05、 保存期限 2024.07.04 批號：IT0803CY 容量：40 mL

(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：

製造廠（場所）地址：

核定劑型及作業項目：

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)

符合化粧品優良製造準則聲明書(範例)

符合化粧品優良製造準則聲明書

Declaration of Conformity

本業者／本人(製造或輸入)之化粧品符合中華民國之化粧品優良製造準則，產品資料如下：

I hereby declare that the products described below manufactured in conformity with Cosmetic Good Manufacturing Practice

一、製造廠名稱：
Manufacturer's Name

二、製造廠地址：
Manufacturer's Address

三、產品劑型：
Product forms

四、作業項目：
The process of operations

以上聲明書所保證之內容，如有造假不實或違背相關法規等情事，本業者／本人願自行負擔法律上一切責任。

Where violations of this declaration occur, I agree to take the legal responsibilities.

立聲明書人：　(Signature)　申請廠商蓋公司章
Applicant

負責人/代表人：　(Signature)　負責人或代表人章
Person in charge

統一編號或身分證字號：
Company Tax ID No. / ID Number

地址：
Address:

中 華 民 國　　年　　月　　日
Date　year　month　day

(6) 製造方法、流程

Phase	INCI Name	w/w%
A	Cetearyl Alcohol	2.205
	PEG-40 Hydrogenated Castor Oil	0.63
	Sodium Cetearyl Sulfate	0.315
	Decyl Oleate	15.0
	Ethylhexyl Methoxycinnamate	3.0
	Butyl Methoxydibenzoylmethane	0.5
	Propylparaben	0.1
B	Aqua	53.57
	Phenylbenzimidazole Sulfonic Acid	2.78
	Sodium Hydroxide (45 % solution)	0.9
	Methylparaben	0.3
	Disodium EDTA	0.1
C	Aqua	20.0
	Carbomer	0.3
	Sodium Hydroxide (45 % solution)	0.3

製程簡述：

1.將 A 相加熱 75~80°C。將 B 相加熱至 80°C (必要時可煮沸至溶液呈透明後，再降溫至 75~80°C)。

2.再將 A 相混合物加入攪拌中的 B 相混合物。

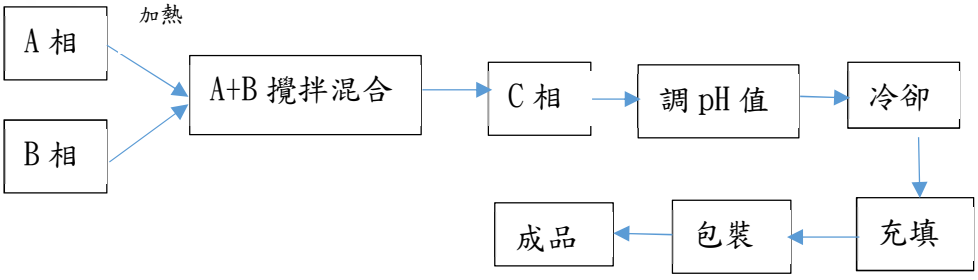
3.將 C 相的 Carbomer 加入水中，以攪拌器攪拌使其分散，再以氫氧化鈉中和。

4.將 C 相加入攪拌中的 A 相與 B 相後，均質 3 分鐘。

5.以氫氧化鈉調整其 pH 值，持續攪拌至完全冷卻。

6.補足散失的水量，並均質之。

製程流程圖：



(7) 使用方法、部位、用量、頻率及族群

使用方法、部位及用量：曝曬前 15 分鐘取適量均勻塗抹於臉部或身體。

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立即更新於本產品資訊檔案，並及時提供給安全資料簽署人員。

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

成品 CoA			
檢測項目	規格	實際檢驗結果	檢驗方法
外觀	乳狀	乳狀	目視
顏色	白色至淡黃色	白色至淡黃色	目視
氣味	無	無添加香精	嗅覺
pH	7.5 ± 0.5	7.30	使用已校正之 pH meter 依 pH meter 檢測方法測定
黏度	2000 ~ 4000 mPas	3050 mPas	使用已校正之黏度計依黏度計檢測方法測定
密度	0.970 ± 0.05 g/cm^3	1.01 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； 綠膿桿菌 陰性； 金黃色葡萄球菌 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	6.0~8.5	7.35	使用已校正之線上(on line) pH meter 測定
導電度	<20 µS/cm	15.0 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：Decyl Oleate

decyl oleate

Modify Date: 2021-02-13 22:11:03

Common Name	decyl oleate		
CAS Number	3687-46-5	Molecular Weight	422.72700
Density	0.866g/cm3	Boiling Point	494.8℃ at 760 mmHg
Molecular Formula	$C_{28}H_{54}O_2$	Melting Point	N/A
MSDS	N/A	Flash Point	77.1℃

Chemical & Physical Properties

Density	0.866g/cm3
Boiling Point	494.8℃ at 760mmHg
Molecular Formula	$C_{28}H_{54}O_2$
Molecular Weight	422.72700
Flash Point	77.1℃
Exact Mass	422.41200
PSA	26.30000
LogP	9.70780
Index of Refraction	1.459
Water Solubility	Practically insoluble in water, miscible with ethanol (96 per cent), with methylene chloride and with light petroleum (bp: 40-60 °C).

INCI name：Ethylhexyl Methoxycinnamate

Appearance	:	liquid
Physical state	:	liquid
Colour	:	light yellow
Odour	:	mild
Odour Threshold	:	No data available
pH	:	No data available
Melting point/freezing point	:	-13 °F / -25 °C
Boiling point/boiling range	:	387.9 - 392 °F / 197.7 - 200 °C (4 hPa)
Flash point	:	192.7 °C
Evaporation rate	:	not determined
Upper explosion limit	:	Upper explosion limit not determined
Lower explosion limit	:	Lower explosion limit not determined
Vapour pressure	:	not determined
Relative vapour density	:	not determined
Relative density	:	No data available
Density	:	1.005 - 1.013 g/cm3 (20 °C)
Solubility(ies)		
Water solubility	:	insoluble

INCI name：Phenylbenzimidazole Sulfonic Acid

PHYSICAL AND CHEMICAL PROPERTIES

Physical state: Solid	**Appearance:** Crystalline powder.	**Color:** White.
Odor: None.	**Taste** No information available.	**Formula** C13H10N2O3S
Molecular/Formula weight (g/mole): 274.28	**Flammability (solid, gas)** no data available	**Flashpoint (°C/°F):** No information available
Flash Point Tested according to: Not available	**Autoignition Temperature (°C/°F):** No information available	**Lower Explosion Limit (%):** No information available
Upper Explosion Limit (%): No information available	**Melting point/range(°C/°F):** >300 °C/572 °F	**Decomposition temperature(°C/°F):** No information available
Boiling point/range(°C/°F): No information available	**Bulk density:** No information available	**Density (g/cm3):** No information available
Specific gravity: No information available	**pH** No information available	**Vapor pressure @ 20°C (kPa):** No information available
Evaporation rate: No information available	**Vapor density:** 9.46	**VOC content (g/L):** No information available
Odor threshold (ppm): No information available	**Partition coefficient (n-octanol/water):** No information available	**Viscosity:** No information available
Miscibility: No information available	**Solubility:** Soluble in Water	

INCI name：Cetearyl Alcohol

Certificate of Analysis

(Representative Sample Certificate)

Product Name:	Cetearyl Alcohol
INCI Name:	Cetearyl Alcohol
CAS Number:	67762-27-0
Lot Number:	Not available (data may vary slightly with different lots or batches)
Expiration Date:	24 months from production date

Analytical Tests	Specification	Actual Analysis
Appearance @ 25°C	White Flake/Pastille	White Pastilles
Hydroxyl Value, mg KOH/g	208.0 – 228.0	214.7
Saponification Value, mg KOH/g	3.0 Max	0.25
Iodine Value, cg 12/g	4.0 Max	0.15
Moisture, % w/w	0.10 Max	0.09
Color (APHA)	40 Max	5
C14 & Lower	2.0 Max	0.22
C16	22-32	29.30
C18	66-76	69.24
C20 & Higher	5.8 Max	0.61
Total Alcohol, %	96.8 Min	99.80

INCI name：Sodium Hydroxide

Physical and Chemical Properties

Appearance	Clear to slightly turbid, viscous liquid
Physical state	Liquid
Form	Viscous liquid
Colour	Clear water-white
Odor	Odorless
Odor threshold	Not Available
pH	> 14 (at high alkali concentration in water, pH scale is not applicable)
Melting point/freezing point	57.2 °F (14 °C) / 57.2 °F (14 °C) (approximately)
Initial boiling point and boiling range	284 °F (140 °C) @ 760 mmHg
Flash point	Not Applicable
Evaporation rate	Not Applicable (the only evaporation that occurs is water)
Flammability (solid, gas)	Not Available
Upper/lower flammability or explosive limits	
Flammability limit – lower (%)	Not Applicable
Flammability limit – upper (%)	Not Applicable
Explosive limit – lower (%)	Not Applicable
Explosive limit – upper (%)	Not Applicable
Vapor pressure	0.2 kPa 1.5 mm Hg
Vapor pressure temp.	77 °F (25 °C)
Vapor density	Not Available
Relative density	1.52 g/cm³
Solubility (ies)	
Solubility (water)	Soluble in all proportions
Solubility (other)	Soluble in absolute alcohol, methanol and glycerol. Moderately soluble in ethanol. Insoluble in acetone and diethyl ether.
Partition coefficient (n-octanol/water)	Not available
Auto-ignition temperature	Not Applicable
Decomposition temperature	Not Available
Viscosity	25.39 cSt (40% solution)
Viscosity temperature	68 °F (20 °C)
Other information	
Specific gravity	1.52 at 20 °C

INCI name：PEG-40 Hydrogenated Castor Oil

Appearance	
Physical state:	solid
Form:	Paste
Color:	White
Odor:	Slight characteristic odor
Odor Threshold:	No data available.
pH:	No data available.
Melting Point:	< 104 °F/40 °C
Boiling Point:	No data available.
Flash Point:	509 °F/265 °C (Cleveland open cup)
Evaporation Rate:	No data available.
Flammability:	No data available.
Explosive limit - upper:	No data available.
Explosive limit - lower:	No data available.
Vapor pressure:	No data available.
Vapor density (air=1):	No data available.
Density:	1.0333 g/ml (122 °F/50 °C) 1.0258 g/ml (140 °F/60 °C) 1.0183 g/ml (158 °F/70 °C)
Relative density:	No data available.
Solubility in Water:	Emulsion(1%,25C)
Solubility (other):	Soluble in lower alcohols
Partition coefficient (n-octanol/water):	No data available.
Self Ignition Temperature:	No data available.
Decomposition Temperature:	No data available.
Kinematic viscosity:	No data available.
Dynamic viscosity:	360 mPa.s (122 °F/50 °C) 255 mPa.s (140 °F/60 °C) 215 mPa.s (158 °F/70 °C)
Particle properties:	No data available.

INCI name：Butyl Methoxydibenzoylmethane

PHYSICAL AND CHEMICAL PROPERTIES

Appearance	Refer to Spec Sheet
Physical state	Powder\Crystal.
Form	Powder. Crystalline powder.
Color	Refer to Spec Sheet
Odor	Characteristic.
Odor threshold	Not available.
pH	Not available.
Melting point/freezing point	182.3 °F (83.5 °C)
Initial boiling point and boiling range	865.4 °F (463 °C)
Flash point	> 200.0 °F (> 93.3 °C) Closed Cup
Evaporation rate	Not available.
Flammability (solid, gas)	Not available.
Upper/lower flammability or explosive limits	
Flammability limit - lower (%)	Not available.
Flammability limit - upper (%)	Not available.
Explosive limit - lower (%)	Not available.
Explosive limit - upper (%)	Not available.
Vapor pressure	0.0000002 kPa (77 °F (25 °C))
Vapor density	10.8
Relative density	1.22 g/cm³ at 20 °C relation to density of water at 4°C
Solubility(ies)	
Solubility (water)	Insoluble
Partition coefficient (n-octanol/water)	Not available.
Auto-ignition temperature	Not available.
Decomposition temperature	Not available.
Viscosity	Not available.
Other information	
Explosive properties	Not explosive.
Flammability class	Combustible IIIB estimated
Molecular formula	C20H22O3
Molecular weight	310.39 g/mol 430.39 g/mol
Oxidizing properties	Not oxidizing.

INCI name：Sodium Cetearyl Sulfate

sodium,hexadecyl sulfate,octadecyl sulfate

Modify Date: 2021-01-23 13:42:39

Common Name	sodium,hexadecyl sulfate,octadecyl sulfate		
CAS Number	59186-41-3	**Molecular Weight**	694.03500
Density	N/A	**Boiling Point**	N/A
Molecular Formula	$C_{34}H_{70}NaO_8S_2$	**Melting Point**	N/A
MSDS	N/A	**Flash Point**	N/A

Properties

Names

Name	sodium,hexadecyl sulfate,octadecyl sulfate
Synonym	More Synonyms

Chemical & Physical Properties

Molecular Formula	$C_{34}H_{70}NaO_8S_2$
Molecular Weight	694.03500
Exact Mass	693.44100
PSA	149.62000
LogP	12.83080

INCI name：Carbomer

Product Name: Carbomer Batch : 2021xxxx

ITEM	SPECIFICATION	RESULT
Appearance	White powder	Complies
Aqueous solution viscosity (0.5%)	45000-65000 cp	57000 cp
Clarity, % transmittance（420 nm）	≥88%	90%
Moisture	≤2.0%	0.73%
Residual ethyl acetate and cyclohexane	≤0.45%	Complies
Heavy metals	≤10 ppm	Complies

Storage: Low temperature store，Keep away from strong light and heat.

Shelf life: 2 years when properly stored.

Conclusion: Meet the requirements

INCI name： Disodium EDTA

Information on basic physical and chemical properties:

- **Appearance:** White
- **Physical State:** Solid
- **Odor:** Odorless
- **pH:** 4-6 in5% aq. solution
- **Melting Point:** 252°C
- **Ignition Temperature:** No data available
- **Decomposition Temperature:** > 252°C
- **Vapor Pressure:** No data available
- **Relative Vapor Density:** No data available
- **Density:** No data available
- **Volatility:** No data available
- **Bulk Density:** ca.700 kg/m^3
- **Odor Threshold:** No data available
- **Viscosity, dynamic:** No data available
- **Water/Oil Dist. Co eff.:** No data available
- **Ionicity (in Water):** No data available
- **Partition Co-efficient: n-octanol/water:** No data available
- **Boiling Point/Range:** No data available
- **Flash Point:** No data available
- **Sublimation Point:** No data available
- **Specific Gravity:** No data available
- **Water Solubility:** 100 g/l at 20°C

9.2. Other information:

Molecular Formula: $C_{10}H_{14}N_2Na_2O_8 \cdot 2H_2O$

Molecular Weight: 372.23 g/mol

INCI name： Methylparaben

methylparaben

Modify Date: 2021-01-23 10:42:42

Common Name	methylparaben		
CAS Number	99-76-3	**Molecular Weight**	152.147
Density	1.2±0.1 g/cm3	**Boiling Point**	265.5±13.0 °C at 760 mmHg
Molecular Formula	$C_8H_8O_3$	**Melting Point**	125-128 °C(lit.)
MSDS	Chinese USA	**Flash Point**	116.4±12.6 °C

Chemical & Physical Properties

Density	1.2±0.1 g/cm3
Boiling Point	265.5±13.0 °C at 760 mmHg
Melting Point	125-128 °C(lit.)
Molecular Formula	$C_8H_8O_3$
Molecular Weight	152.147
Flash Point	116.4±12.6 °C
Exact Mass	152.047348
PSA	46.53000
LogP	1.87
Vapour Pressure	0.0±0.6 mmHg at 25°C
Index of Refraction	1.547
Stability	Stable. Incompatible with strong oxidizing agents, strong bases.
Freezing Point	131°C

INCI name： Propylparaben

Propyl 4-hydroxybenzoate

Modify Date: 2021-01-23 17:44:55

Common Name	Propyl 4-hydroxybenzoate		
CAS Number	94-13-3	**Molecular Weight**	180.201
Density	1.1±0.1 g/cm3	**Boiling Point**	294.3±13.0 °C at 760 mmHg
Molecular Formula	$C_{10}H_{12}O_3$	**Melting Point**	95-98 °C(lit.)
	Chinese		
MSDS	USA	**Flash Point**	124.6±12.6 °C

Chemical & Physical Properties

Density	1.1±0.1 g/cm3
Boiling Point	294.3±13.0 °C at 760 mmHg
Melting Point	95-98 °C(lit.)
Molecular Formula	$C_{10}H_{12}O_3$
Molecular Weight	180.201
Flash Point	124.6±12.6 °C
Exact Mass	180.078644
PSA	46.53000
LogP	2.93
Vapour Pressure	0.0±0.6 mmHg at 25°C
Index of Refraction	1.532
Stability	Stable. Incompatible with strong oxidizing agents, strong bases.
Water Solubility	<0.1 g/100 mL at 12 ºC

(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之各個成分毒理資料，另存放於清爽型防曬乳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：Decyl Oleate

- 急性毒性：大鼠急性口服毒性 LD_{50}> 5000 mg/kg bw。[1] 大鼠急性皮膚毒性 LD_{50}> 2000 mg/kg bw。[4]
- 腐蝕性和刺激性：在兔子初級皮膚刺激研究中，測試 10%玉米油溶液、20%礦物油溶液和未稀釋 Decyl Oleate 的主要刺激指數(Primary Irritation Index, PII)依序為 0.08、0.05 和 0.28，而在改良 Draize 試驗中，未稀釋的 Decyl Oleate 無刺激性。[1]。以改進 Draize 方法評估 100% Decyl Oleate 的兔眼刺激性。觀察 1 小時和 1、2、3、4 和 7 天結果顯示 Decyl Oleate 非常輕微的眼刺激性。[2]
- 皮膚致敏性：8 週的兔子研究中，每天使用 15%溶液會產生一些丘疹或水泡，但通常耐受性良好，未稀釋則導致 3 隻兔子(但未說明總數)和 1 隻兔子的皮膚增厚，並且耐受性差；在天竺鼠試驗結果顯示 15%溶液在玉米油無致敏性。[1]
- 重複給藥毒性：在 28 天大鼠灌食研究，每週 5 天給予 100、500 或 1000 mg/kg bw 之劑量，NOAEL 為 1000 mg/kg bw/day。[3,4]
- 致突變性/遺傳毒性：在鼠傷寒沙門氏菌 TA98、TA100、TA1535、TA1537 和 TA1538 菌株的沙門氏菌致突變性試驗中，濃度 4 至 2500 µg/plate 之間的 Decyl Oleate 不具致突變性。[3]
- 致癌性：無數據。[3]
- 生殖毒性：無數據。[3]
- 毒理代謝動力學：無數據。[3]
- 經皮吸收：無數據。不可進行模型計算，因為在水中的溶解度極差，尤其是由於極高的 log K_{OW}。在大鼠急性皮膚毒性研究中直至測試的最高劑量 2000 mg/kg 仍未觀察到全身毒性跡象，因此 Decyl Oleate 未被指定標示"H"(即可通過皮膚吸收毒理相關劑量的物質)，因此，在人體的皮膚吸收被認為非常有限，皮膚暴露對於危害評估來說可以忽略不計。[4,5]
- 光毒性：無數據。[3]
- 人體數據：在人類反覆刺激斑貼試驗(Human Repeat-Insult Patch Test,

HRIPT) 測試中，103 名受試者施用含 1%~5% Decyl Oleate 配方後及 402 名受試者中施用 4 種含 5.5% Decyl Oleate 的四個配方後無產生過敏現象。[1]

- 其他安全性資料：根據 CIR 評估報告使用 Decyl Oleate 在化粧品的濃度範圍為≤ 0.1%至 50% (CIR 1982)，而 2003 年報告則為 0.5%–88% (CIR 2003)。[3]
- 參考資料：

1. Safety Assessment of Alkyl Esters as Used in Cosmetics. IJT 34(Suppl.2):5-69, 2015.
2. Final Report on the Safety Assessment of Decyl and Isodecyl Oleates. JACT 1(2):85-95, 1982.
3. The MAK-Collection for Occupational Health and Safety: Annual Thresholds and Classifications for the Workplace, 2002.
4. ECHA 網站: https://echa.europa.eu/registration-dossier/-/registered-dossier/13270/7/1 .
5. Hartwig A, MAK Commission.n-Decyl oleate. MAK Value Documentation, supplement-Translation of the German version from 2019. MAK Collect Occup Health Saf. Sep;6(3), Doc056, 2021.

2. INCI name：Ethylhexyl Methoxycinnamate

- 急性毒性：小鼠急性口服毒性 LD_{50} >8 g/kg bw，大鼠急性口服毒性 LD_{50}>20 mL/kg bw。[1]
- 腐蝕性和刺激性：20 隻天竺鼠給予未稀釋之測試物質每天兩次共 16 天，間隔 3 天未施用後再以每天給予測試物質共 3 天，結果無致敏反應。另一項試驗分兩組每組 4 隻，一組每天注射未稀釋之測試物質 0.05 ml 共 5 天，在另一組中將 0.025 ml 含測試物質的 50% 丙酮溶液施用於 2 cm^2 的兩側剃毛皮膚區域，無證據顯示具有致敏性。[1]
- 皮膚致敏性：20 隻天竺鼠給予未稀釋之測試物質每天兩次，共 16 天，無致敏反應。[1]
- 重複給藥毒性：在大鼠 13 週的皮膚暴露毒性研究中，每週 5 天在剃毛皮膚上施用 0、55.5、277 和 555 mg/kg bw 的劑量。NOAEL 為 555 mg/kg bw/day。[1]

- 致突變性/遺傳毒性：常用沙門氏菌 TA1538 菌株突變試驗，無代謝活化下呈陽性被認為是批次效應，而另一實驗室結果則有非常微弱的陽性反應，但兩重複及再次的 Ames 測試則未發現。以酵母菌、人類淋巴球細胞的突變試驗及 BALB/c 3T3 細胞的細胞轉化試驗均為陰性，中國倉鼠 V79 細胞的突變菌落有輕微增加。果蠅試驗結果顯示性聯隱性的頻率增加，餵養測試則沒有證據顯示誘變情形，而異體細胞突變與重組試驗呈陰性。綜合上述多項致突變性研究結果未顯示致突變性。[1]
- 致癌性：無數據。[1]
- 生殖毒性：在兔子及大鼠的測試結果顯示，非生殖毒性物質。[1]
- 毒理代謝動力學：8 名健康志願者的測試結果除尿液中約 0.2%以外均為陰性，沒有說明所使用濃度。[1]
- 經皮吸收：在 7.5%濃度應用於不同載體中，在迷你豬皮膚的完整表面暴露 6 小時，結果發現低於 4%的 Ethylhexyl Methoxycinnamate 被豬皮吸收，而不同載體的滲透率值沒有顯著差異。[2] 另一份評估資料採用的經皮吸收率為 2%。[3]
- 光毒性：S.cerevisiae 的光致突變試驗為陰性，CHO 細胞體外光致致裂試驗呈陰性。[1]
- 人體數據：在 10 位受試者中，以貼片施用 24 小時，然後將區域暴露於紫外線照射下觀察紅斑產生情形，結果顯示不具光毒性。[1]
- 參考資料：

1. European Commission, Reports of the Scientific Committee on Cosmetology (Ninth Series): 2-Ethylhexyl-4-methoxycinnamate (5466-77-3), 1999.
2. ECHA 網站: https://echa.europa.eu/registration-dossier/-/registered-dossier/15876/7/2/3 .
3. UV-Filters in Sun Protection Products, Opinion of the Federal Institute for Risk Assessment, 6th August, 2003.

3. INCI name：Phenylbenzimidazole Sulfonic Acid

- 急性毒性：小鼠急性口服毒性 LD_{50} >5000 mg/kg bw，大鼠急性口服毒性 LD_{50} >1600 mg/kg bw，大鼠急性皮膚毒性 LD_{50} >3000 mg/kg bw，大鼠急性腹腔注射毒性 LD_{50} 介於 1000 ~ 1500 mg/kg bw。[1]

- 腐蝕性和刺激性：根據在兔子的研究被評估為對皮膚無刺激性，對於結膜亦不具刺激性。[1]
- 皮膚致敏性：現有研究顯示無證據顯示為皮膚致敏物質。[1] 兩項在白化天竺鼠的皮膚致敏研究，在遵循 OECD 指引 406 和 GLP 原則下進行，研究結果均為陰性，在測試動物中未顯示任何皮膚過敏反應。[2]
- 重覆給藥毒性：在大鼠中進行 13 週口服研究結果，NOAEL 為 1000 mg/kg bw /day。[1]
- 致突變性/遺傳毒性：兩項細菌基因突變測試中，測試物質均未顯示具有突變活性，而陽性對照樣品則出現預期的誘導突變效應。另一體外染色體畸變測試的結果顯示，與對照相比測試物質並不會導致結構染色體畸變數量的增加。[1]
- 致癌性：無數據。[1]
- 生殖毒性：Wistar 大鼠在交配後第 6 天到第 15 天，每天以灌食給予 1000 mg/kg bw /day 的劑量，除了用水量增加外，此劑量未顯示對母體的毒性作用，亦無胚胎毒性及致畸性。[2]
- 毒理代謝動力學：對懷孕大鼠的吸收、分佈和排泄研究顯示，任何器官（口服與靜脈注射兩種途徑）中均未發現累積的跡象。靜脈注射後在大腦和胎兒中發現微量放射性，口服暴露途徑中這些器官未發現放射性，顯示未通過血/腦和胎盤屏障。至 48 小時，可從體內完全排除。[1]
- 經皮吸收：在人體研究中，將 1 g 含有 80 mg 放射性標記測試物質 (1.86 MBq)的凝膠塗抹於 6 名健康男性志願者上臂，非封閉覆蓋物保護，6 小時後去除凝膠並在施用 120 小時候採集血樣。結果顯示皮膚吸收率約 0.2%。[2]
- 光毒性：天竺鼠試驗中，於照射組陽性對照的測試部位有表現出輕微的紅斑(24 小時-3/10；48 小時-7/10)；其他測試組別均不受影響。以 3T3-NRU 光毒性測試，計算出的光刺激係數(photo-irritation factor, PIF)為 1.4，根據標準判定無光毒性。[1]
- 人體數據：分別將濃度 5%和 10% Neo Heliopan (Phenylbenzimidazole Sulfonic Acid)施用於 50 名志願者的背部，並保持原位 48 小時，暴露終止後 48 小時和 72 小時評估均未觀察到皮膚反應。以 5%和 10%進行重複開放型應用測試，每天兩次將 0.1mL 擦拭 20 名志願者的肘前窩連續 14 天，均未觀察到皮膚反應。[1]

◆ 參考資料：

1. SCCP/1056/06- Opinion on phenylbenzimidazole sulfonic acid and its salts COLIPA S45, 2006.
2. ECHA 網站: https://echa.europa.eu/registration-dossier/-/registered-dossier/5464/7/5/1 .

4. INCI name：Cetearyl Alcohol

◆ 不純物：Cetearyl Alcohol 鯨蠟硬脂醇為脂肪醇混合物，主要由 20%~35%的 Cetyl Alcohol 鯨蠟醇和 65%~80%的 Stearyl Alcohol 硬脂醇組成。可能含有不純物有碳氫化合物(主要由正十六烷和正十八烷組成)約 0.1%~1.4%，奇數直鏈醇約 1%~3.5%，支鏈初級醇約 0.2%~2%。[1]

◆ 急性毒性：Cetyl Alcohol 鯨蠟醇之大鼠急性口服毒性 LD_{50} 大於 8.2 g/kg bw。[1]

◆ 腐蝕性和刺激性：將含有 3.0% Cetearyl Alcohol 的乳膏塗抹在紐西蘭白化兔的皮膚上時，觀察到輕度刺激。而 Cetyl Alcohol (含 50.0%凡士林)塗在白化兔磨損和完整的皮膚上，對皮膚的刺激很小至輕微。當注入白化兔眼睛時，Cetyl Alcohol 被視為無刺激性。[1]

◆ 皮膚致敏性：無數據。參考 Isostearyl Alcohol 異硬脂醇(5.0%在丙二醇中)和含 5.0%異硬脂醇的止汗劑在天竺鼠的試驗結果非致敏物。在人體皮膚塗抹 25%異硬脂醇後，沒有觀察到皮膚刺激或致敏的跡象。[1]

◆ 重複給藥毒性：無數據。參考 Behenyl alcohol 山嵛醇在 CD 大鼠中進行 26 週口服研究結果，NOAEL 為 1000 mg/kg bw /day。[2]

◆ 致突變性/遺傳毒性：無數據。參考 Isostearyl Alcohol 異硬脂醇以鼠傷寒沙門氏菌 LT2 突變測試結果無致突變性。[1]

◆ 致癌性：無數據。[1]

◆ 生殖毒性：無數據。[1]

◆ 毒理代謝動力學：無數據。大部分長鏈脂肪醇的吸收、代謝和排泄數據來自鯨蠟醇和硬脂醇。[1]

◆ 光毒性：無數據。參考 Cetyl Alcohol 在 52 名受試者中評估含有 4.0%鯨蠟醇的唇膏產品之光致敏潛力，所有受試者均未發現光敏感反應；在另一項研究含有 1.0%鯨蠟醇的護膚製劑在測試 407 名受試者中

未引起光敏反應。[1]

- 人體數據：在含有 3.0% Cetearyl Alcohol 面霜進行的人體皮膚致敏性研究中，未有受試者出現陽性反應。[1]
- 其他安全性資料：CIR 專家小組認為脂肪醇，包括鯨蠟硬脂醇在化粧品中使用是安全的[1]，經重新審查新的可用研究以及關於使用類型和濃度資訊更新，專家小組確認鯨蠟硬脂醇、鯨蠟醇、異硬脂醇的安全性，鯨蠟硬脂醇的使用濃度範圍為 0.0002%~15%。[3]鯨蠟硬脂醇包括在美國 FDA 的安全和允許食品添加劑清單中。[4]
- 參考資料：

1. Final Report on the Safety Assessment of Cetearyl Alcohol, Cetyl Alcohol, Isostearyl Alcohol,Myristyl Alcohol, and Behenyl Alcohol. JACT 7(3):359-413, 1988.
2. Iglesias G, Hlywka J, Berg JE, Khalil MH, Pope LE and Tamarkin D. The toxicity of behenyl alcohol. I. Genotoxicity and subchronic toxicity in rats and dogs. Regul Toxicol Pharmacol. 36(1):69-79, 2002.
3. Annual Review of Cosmetic Ingredient Safety Assessments: 2005/2006, IJT 27(Suppl. 1):77-142, 2008.
4. CFR-code of federal regulations title 21: Part 172 - food additives permitted for direct addition to food for human consumption, 2020.

5. INCI name：Sodium Hydroxide

- 不純物：雜質為氯化鈉±2%、碳酸鈉≤1.0%、硫酸鹽≤0.2%，而其他雜質小於 0.1%。[1]
- 急性毒性：在口服毒性研究中，氫氧化鈉的口服會導致受測動物胃部廣泛受損；而在皮膚暴露毒性研究中，經 50%氫氧化鈉處理的小鼠在一小時內將試驗物沖洗掉，其存活率更高。大鼠的急性吸入毒性 LC_{50}> 0.75 mg/L(暴露 2 小時)。[2]
- 腐蝕性及刺激性：氫氧化鈉對所有組織都有腐蝕性，濃蒸氣會嚴重損害眼睛和呼吸系統。根據法規(EC)1272/2008，該物質被歸類為危險物質：皮膚腐蝕 1A，濃度≥5%引起嚴重的皮膚灼傷和眼損傷。毒性與 pH 相關，隨著 pH 值的增加，毒性更大。0.05% w/w 溶液的 pH 值約為 12，0.5%溶液約 13，5%溶液約 14。[3]
- 皮膚致敏性：人類反覆刺激斑貼試驗顯示，氫氧化鈉以高達 1.0%的

濃度誘導並以 0.125%的濃度激發時不致敏，但有觀察到皮膚刺激反應。[2]

- 重複給藥毒性：無氫氧化鈉局部作用的重複皮膚劑量數據。[2]
- 致突變性/遺傳毒性：在幾種不同的體外測定中，氫氧化鈉沒有遺傳毒性。[2]
- 致癌性：未發現有關無機氫氧化物的相關已公開致癌性數據。[2]
- 生殖毒性：無數據。[2]
- 毒理代謝動力學：無數據。[2]當人體皮膚接觸低(無刺激性)濃度時，由於離子吸收率低，NaOH 的攝取相對較低，通過暴露 NaOH 而攝入的 OH^- 估計不會改變血液 pH 值，而通過暴露 NaOH 而攝入的鈉遠低於通過食物攝取鈉。預計 NaOH 一般狀況下身體無法利用。[2]
- 光毒性：無數據。[2]
- 人體數據：利用四種不同的貼片系統在進行之人類皮膚斑貼測試，分別是 Finn 貼片、Hill Top 貼片、Van der Bend 貼片和 Webril 貼片，確定 1% NaOH 對皮膚的刺激反應。[1]
- 參考資料：

1. European Union Risk Assessment Report - Sodium Hydroxide, 2007.
2. CIR Final report. Safety assessment of inorganic hydroxides as used in cosmetics. 2016. IJT 40(Suppl. 2):16-35, 2021.
3. PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/14798

6. INCI name：PEG-40 Hydrogenated Castor Oil

- 不純物：PEG 是環氧乙烷和水的縮合產物，其鏈長由聚合的環氧乙烷的摩爾數控制。PEG 可能微量的乙氧基化的副產物 1,4-二噁烷，而 1,4-二噁烷已知是致癌物，應使用額外的純化步驟將其從成分中去除。[1]
- 急性毒性：含 0.25% PEG-40 Hydrogenated Castor Oil 之配方在大鼠急性口服毒性 LD_{50} 大於 15.0 g/kg bw。[2]
- 皮膚刺激性：未稀釋的 PEG-40 Hydrogenated Castor Oil 塗在白化兔子的背部 20 小時後會引起皮膚發紅和結痂，當在兔子的外耳上施用 20 小時，只有輕微的短暫變紅。[2]
- 眼睛刺激性：未稀釋及 50%的 PEG-40 Hydrogenated Castor Oil 水溶液為在兔結膜囊中滴入 0.05 mL，並在 24 和 48h 觀察。兩種濃度下

結膜均出現短暫變紅。[2]

- 皮膚致敏性：大多臨床數據顯示不具致敏性。[2]
- 重複給藥毒性：在 90 天的大鼠餵食研究中，每組 15 隻 Sherman-Wistar 大鼠飲食中分別添加含有 0.01%、0.04%、0.16%、0.64%、2.5%或 5.0% PEG-40 Hydrogenated Castor Oil。結果未發現明顯的肉眼或微觀病變，無毒理作用的劑量 5%相當於 2500 mg/kg bw。[2]
- 致突變性/遺傳毒性：無數據。參考 PEG- 35 Castor Oil 在小鼠試驗的結果顯示不具致突變性。[2]
- 致癌性：無數據。參考 PEG-30 Castor Oil 在大鼠試驗及其他 PEG Castor Oil 在小鼠試驗的結果顯示不具致癌性。[2]
- 生殖毒性：在小鼠和大鼠的灌食研究中，100,000 ppm 劑量下未發現發育毒性。[2]
- 毒理代謝動力學：無數據。參考 PEG-35 Castor Oil (87.8 mg PEG-35 castor oil/mg drug)用於癌症患者治療的結果，PEG-35 Castor Oil 的半衰期和清除率分別為 35.7+18.9 小時和 0.216+0.075 L/h，PEG-35Castor Oil 作為製劑載體可能會導致藥物相互作用和賦形劑相關毒副作用。[1]
- 光毒性：無數據。
- 人體數據：24 小時單次封閉型皮膚斑貼試驗測試含有 0.25% PEG-40 Hydrogenated Castor Oil 的配方，20 個受測者中只有 1 個有輕微的致敏。[2]
- 其他安全性資料：CIR 專家小組認為 PEG-30、-33、-35、-36 和-40 Castor Oil 可安全用於化粧品濃度高達 50%，PEG-30 及-40 Hydrogenated Castor Oil 是在濃度高達 100%可安全使用。[1]
- 參考資料：

1. Safety Assessment of PEGylated oils as used in cosmetics. IJT 33(Suppl 4):13-39, 2014.
2. Final report on the safety assessment of PEG-30, -35, -36, and -40 castor oil and PEG-30 and -40 hydrogenated castor oil. IJT 16(Suppl.3):269-306, 1997.

7. INCI name：Butyl Methoxydibenzoylmethane

- 急性毒性：大鼠急性口服毒性 LD_{50} 大於 16 g/kg bw，給藥組的附睪沒有精子或精子量少。小鼠(口服和腹腔投藥)在 8 mg/kg bw 劑量下觀察異常體徵，但並未引起死亡。大鼠覆蓋 24 小時之急性皮膚暴露試驗結果最高至 1000 mg/kg bw 未造成任何死亡，未發現與化合物相關之皮膚損傷，LD_{50} 估計大於 1 g/kg bw。[1]
- 皮膚刺激性：兔子研究分為 5 組(3 個實驗組、溶劑對照組及程序對照組)，每組包括 10 隻雄性和 10 隻雌性動物，每組有 5 隻動物的皮膚受傷，而另 5 隻則無。每天將 30、60 和 360 mg/kg bw/day 的實驗組覆蓋 6 個小時，連續 21 天，而使用的成分在卡必醇(Carbitol)中濃度分別為 1.5%、5%及 18%。在溶劑對照組中發現了輕微刺激，在實驗組中出現紅斑嚴重度具劑量依存性，30 mg/kg bw/day 時輕微，擦傷並無影響。除施用部位外，體重、食物或水的消耗量或血液學檢查均未發現因成分引起的變化。另一兔子試驗分兩組，每組 6 隻兔子，一組進行測試物質測試，一組進行溶劑對照組。將成分以 10%濃度溶於乙醇/2-苯乙醇(50/50)中；在 4 cm^2 的面積上，將 0.5 mL 塗抹在每隻動物的擦傷處和非擦傷處，覆蓋 4 小時。載體的原始刺激指數為 1.17，而成分溶液的刺激指數為 1.39。[1]
- 眼睛刺激性：將 Butyl Methoxydibenzoylmethane 溶於鄰苯二甲酸二乙酯，以兔子進行 Draize 眼睛刺激性測試。直至溶解度極限 20%時對眼睛無不良反應。[1]
- 皮膚致敏性：使用 Magnusson 及 Kligman 最大化方法以天竺鼠研究，以皮下注射 0.1ml 5%於完全弗氏佐劑(Freund's Complete Adjuvant, FCA)、5%於 FCA 生理食鹽水中及單獨 FCA 進行誘導。7 天後，表皮給予 20%懸浮液覆蓋 2 天，在第 21 天進行激發；分別給予 20%和 6% 24 小時，結果無致敏證據。[1]
- 重複給藥毒性：在 13 週大鼠研究中，以 4 組 12 隻雄性及 12 隻雌性大鼠分別在食物中給予 200、450 和 1000 mg/kg bw，結果無與投藥相關的死亡情形。中劑量組和最高劑量組的食物消耗減少且雌性的紅血球細胞下降。所有劑量組的動物血漿蛋白平均較高，但似乎與劑量無關。而中劑量和最高劑量的雌性動物的相對肝臟重量均增加。以最高劑量增加給予 6 隻大鼠之後 4 週恢復，犧牲後觀察大鼠的肝臟重量與對照大鼠相似。根據對肝臟重量增加的看法，無影響劑量 NOAEL 可能為 200 或 450 mg/kg bw/day。[1]

- 致突變性/遺傳毒性：非致癌物質。最高 500 µg 溶於 DMSO 進行 Ames 試驗，無論是否存在代謝酵素激活，測試均為陰性。[1]
- 生殖毒性：非生殖毒性物質。大鼠研究中劑量 1000 mg/kg bw/day 下既不具有胚胎毒性也不致畸，也不損害大鼠後代出生後發育。[2]
- 毒理代謝動力學：大鼠體內試驗標記化合物 1%溶液，將溶解在卡必醇(Carbitol)中的溶解劑以 120 mg/cm^2 的劑量施用 6 小時，在角質層和更深層中發現的量分別為 1.4%和 2.3%。[1]
- 經皮吸收：BfR 風險評資料採用的經皮吸收率為 0.56%。[3]
- 光毒性：在 25 名志願者研究中，將 2%成分摻入凡士林，其中添加 2% DMSO 作為最大化試劑，通過 UVA + UVB 285~400 nm 產生紅斑所需要時間來確定每個受試者的最小紅斑劑量(Minimal Erythemal Dose, MED)。誘導完成後約 10 天進行激發，施用於 2 個新部位並封閉 24 小時，這些部位暴露於 10 J/cm^2 的 UVA，320~400 nm，結果無光致敏證據。[1]
- 人體數據：一項含 11 名男性和 40 名女性受試者的人類反覆刺激斑貼試驗，其中 8 人未完成研究。在閉塞情況下，約 10 次將約 0.2 mL 的 10%溶液施用 24 小時，休息間隔為 24 或 48 小時。完成後休息 10 天然後在原始測試點和新測試點激發，結果沒有觀察到不良反應。[1]
- 參考資料：

1. European Commission, Reports of the Scientific Committee on Cosmetology (Ninth Series): Butyl Methoxydibenzoylmethane (70356-09-1), 1999.
2. ECHA 網站: https://echa.europa.eu/registration-dossier/-/registered-dossier/14835/7/9/3 .
3. BfR, UV-Filters in Sun Protection Products. Opinion of the Federal Institute for Risk Assessment, 6th August, 2003.

8. INCI name：Sodium Cetearyl Sulfate

- 不純物：Sodium Cetearyl Sulfate 鯨蠟硬脂基硫酸鈉是 cetyl sulfate 鯨蠟硫酸鈉和 stearyl sulfate 硬脂基硫酸鈉的混合物鈉鹽，硬脂基硫酸鈉中存在以下雜質：無機氯化物(最大值為 2.2%)鯨蠟硬脂基硫酸鈉中存在雜質：無機氯化物(最大值為 2.2%)，非硫化物(最大值為

4%)和無機硫酸鹽(最大值為 5.5%)。[1]

- 急性毒性：10 隻雄性 Wistar 大鼠(平均體重 150 g)通過胃管以 10 g/kg bw 劑量施用測試物質，觀察動物 8 天，結果給藥劑量未達到 LD_{50}。[1]
- 皮膚刺激性：20.0%的鯨蠟硬脂酸鈉水溶液對兔子的皮膚沒有刺激性，但是 10%未稀釋溶液為輕度刺激性物質。與 sodium lauryl sulfate 月桂基硫酸鈉相比，鯨蠟硬脂基硫酸鈉對皮膚的刺激性小。[1]
- 眼睛刺激性：以 Draize 眼睛刺激性試驗，20.0%的鯨蠟硬脂酸鈉水溶液不會刺激兔子眼睛。[1]
- 皮膚致敏性：在 Pirbright 雌性天竺鼠(平均體重 463 g)的皮膚致敏研究中，分別在誘導階段和激發階段分別以 25.0%和 1.0%濃度進行，在研究過程中實驗組或對照組都沒有觀察到反應。[1]
- 重複給藥毒性：無數據。[1]由於鯨蠟硬脂基硫酸鈉與 Sodium Lauryl Sulfate 十二烷基硫酸鈉這兩種成分的化學相似性，因此十二烷基硫酸鈉的安全性測試數據被認為可用於該成分的安全性評估。大鼠 90 天口服毒性 NOAEL 為 100 mg/kg/day，LOAEL 為 500 mg/kg/day。[2]
- 致突變性/遺傳毒性：無數據。[1]參考 90 天飼餵 1.13%和 0.56%十二烷基硫酸鈉的大鼠試驗，大鼠骨髓中染色體畸變的發生率與對照組無顯著差異。[3]
- 致癌性：無數據。[1]參考十二烷基硫酸鈉的一年長期研究，給米格魯餵食飼料中十二烷基硫酸鈉濃度最高 2.0%下亦未發現致癌作用。[3]
- 生殖毒性：無數據。[1]使用懷孕的 JCL/ACR 小鼠評估十二烷基硫酸鈉的致畸潛力。在妊娠第 6 天至第 13 天，每天(劑量 1.5 ml/kg)0.4、4.0 和 6.0%的水溶液分別用於三組小鼠的背部。在 0.4%受測組後代中觀察到腦疝、腭裂、眼瞼張開、多指畸形和馬蹄內翻足，在 4.0%和 6.0%受測組中也觀察到腭裂和眼瞼張開，在 4.0%和 6.0%受測組中分別觀察到數目異常和彎曲的尾巴。此外，隨著十二烷基硫酸鈉濃度的增加，骨化顯著延遲，未經治療的小鼠後代的異常包括睜開眼瞼、多指、彎曲的尾巴和畸形足。在水處理對照的後代中僅觀察到腹疝和眼瞼張開。睜眼和腭裂被認為是 JCL/ACR 小鼠中日益嚴重的現象。因此，這些異常在實驗和對照小鼠中的發生可能顯著也可能不顯著。[3]

- 毒理代謝動力學：無數據。[1] 參考十二烷基硫酸鈉以天竺鼠進行的經皮吸收評估，將測試物質在蒸餾水中在側面擦拭 10 分鐘，用水沖洗部位，並用非阻塞性貼劑覆蓋 24 小時。在糞便、腎臟或屍體中未檢測到放射性，而在呼出的 CO_2 和尿液中檢測到 0.1%的實驗劑量。大多數放射性在測試部位、測試部位沖洗處或貼布上被檢測到。而在大鼠腹腔內或皮下注射十二烷基硫酸鈉後，排泄的主要途徑是通過尿液。[3]
- 光毒性：無數據。[1] 而含有 2.5%十二烷基硫酸鈉的粉底產品不會造成 599 名受試者中的任何一位誘發光敏反應。[3]
- 人體數據：無數據。[1] 參考十二烷基硫酸鈉人類反覆刺激斑貼試驗，當受測者使用含 1.26%十二烷基硫酸鈉時，於誘導和激發階段會觀察到反應；而鯨蠟硬脂基硫酸鈉的動物測試，在 25.0%誘導和 1.0%激發階段後並不會對動物產生任何反應。基於數據，CIR 專家認為鯨蠟硬脂基硫酸鈉對人的皮膚刺激性和致敏潛力低於十二烷基硫酸鈉，因此認為無需要求鯨蠟硬脂基硫酸鈉的人體致敏試驗數據。[3]
- 參考資料：

1. Final report on the safety assessment of sodium cetearyl sulfate and related alkyl sulfates as used in cosmetics. IJT 29 (Suppl. 2):115-132, 2010.
2. SIDS Initial Assessment Report For SIAM 5. Sodium dodecyl sulphate (CAS No: 151-21-3):17, 2005.
3. Final Report on the Safety Assessment of Sodium Cetearyl Sulfate. JACT 11(1):145-155, 1992.

9. INCI name：Carbomer

- 不純物：Carbomer 的雜質可能包括水、苯、丙酸、乙酸、丙烯酸、重金屬、鐵、砷和鉛，CIR 專家小組提醒應注意可能作為雜質存在的苯，並建議應盡可能降低雜質含量。[1]
- 急性毒性：對大鼠、天竺鼠、小鼠和狗進行的急性口服研究表示，Carbomer 經攝入後毒性低，大鼠的口服急性 LD_{50}= 2500 mg/kg bw，大鼠的皮膚暴露 LD_{50} >3000 mg/kg bw。[1]
- 皮膚刺激性：0.5% Carbomer 水溶液對皮膚有輕微刺激性。[1]
- 眼睛刺激性：100% Carbomer 對眼睛有刺激性。以 Draize 眼睛刺激

性測試，兩個 Carbomer-934 100%溶液樣品結果主要刺激指數為 0.2，表示有很低的刺激性。由於 Carbomer 是吸濕性的凝膠形成聚合物，因此預期它們會因從眼組織中吸出水分而引起某種刺激性。[1]

- 皮膚致敏性：無動物數據。人類反覆刺激斑貼試驗數據顯示低致敏化能力。[1]
- 重複給藥毒性：雄性和雌性大鼠分為四組(每組每性別 30 隻)，飲食接受 0 (對照組)、300、1000 或 3000 mg PA (high-molecular-weight crosslinked polyacrylate)/kg bw/day，在 32 天或 93 天犧牲。結果顯示，最高 3000 mg/kg/day 組的大鼠並無組織病理學、血液學、體重或臨床化學變化。但是，PA 會導致尿中鈉和磷的排泄量增加，而鎂、鈣和鉀的排泄量降低。[2] 在大鼠飲食中以 0.1%、0.5%或 5.0%攝入 Carbomer 持續 6.5 個月，其器官重量發生了各種變化；而狗在餵食 0.5 或 1.0 g/kg/day Carbomer 6.5 個月，觀察到胃腸道刺激和肝臟 Kupffer 細胞內明顯的色素沉積，另一項狗餵食 1.0 g/kg /day Carbomer 連續 32 個月的研究結果則沒有明顯影響。[3] 在一項 13 週的飲食毒性研究中，Sprague-Dawley 大鼠給予 Carbopol 974(假定純度 100%)，四組(每組每性別 10 隻)分別接受 0、12,500、25,000 和 50,000 mg/kg 飲食 (相當於雄性每天 0、744、1,513 和 3,147 mg/kg bw 而雌性為 0、835、1,681 和 3,416 mg/kg bw)，另一項研究則在狗的飲食中給予 Carbopol 974(假定純度 100%)至少 13 週，三組(每組每性別 4 隻)分別接受 0、12,500、25,000 和 50,000 mg/kg bw(相當於雄性每天 0、420、802 和 1,657 mg/kg bw 而雌性為 0，394，784 和 1642 mg/kg bw)。在大鼠結果在高劑量觀察到對體重和體重增加的影響以及對臨床化學參數的一些輕微影響。專家組認為體重和體重增加的減少可能反映了營養素和 Carbomer 之間的相互作用，導致營養素吸收不良，這被認為是一種不良影響，因此專家群確定 NOAEL 為 1,513 mg/kg bw/day；狗的研究結果顯示劑量高達 50,000 mg/kg bw 飲食無任何毒性作用，NOAEL 為 1,642 mg/kg bw per day 即測試的最高劑量。[4]
- 致突變性/遺傳毒性：在 Ames 測試顯示，非致突變物質。[1]
- 生殖毒性：非生殖毒性物質。[1]
- 毒理代謝動力學：大鼠口服吸收率低 3.5%。[1]
- 光毒性：無光毒性。[1]
- 人體數據：人類反覆刺激斑貼試驗和其他研究顯示出較低的刺激性

和致敏能力。[1]

- 其他安全性資料：Carbomer 的安全性已經過化粧品成分審查(Cosmetic Ingredient Review, CIR)專家小組的評估。CIR 專家小組評估了科學數據並得出結論，Carbomer 聚合物作為化粧品和個人護理產品的成分是安全的。2001 年，作為計劃重新評估成分的一部分，CIR 專家小組考慮了有關 Carbomer 聚合物的現有新數據，並重申了上述結論。CIR 專家小組審查了急性口服研究，顯示 Carbomer 聚合物在攝入時具有低毒性。觀察到最小的皮膚刺激和無到中度的眼睛刺激。使用 Carbomer 聚合物進行的亞慢性餵食研究導致體重低於正常體重，但在器官中未觀察到異常變化。在 Carbomer 的研究中發現了一些胃腸道刺激和肝臟特定細胞(Kupffer cells)內的顯著色素沉積。Carbomer 的臨床研究顯示，這些聚合物在高達 100%的濃度下對皮膚的刺激和致敏的可能性很小。Carbomer 聚合物表現出低光毒性和光接觸致敏性的可能性。[5]
- 參考資料：

1. Final Amended Report. Amended Safety Assessment of Acrylates Copolymers as Used in Cosmetics, CIR, 2018.
2. Effects of oral administration of a high-molecular-weight crosslinked polyacrylate in rats. Fundam Appl Toxicol 17 (1): 128-35, 1991.
3. Final report on Carbomers -934, -910, -934P, -940, -941, and -962. JACT 1(2):109-141, CIR, 1982.
4. Safety evaluation of crosslinked polyacrylic acid polymers (carbomer) as a new food additive. EFSA Journal;19(8):6693, 2021.
5. Cosmetics Info 網站：https://cosmeticsinfo.org/ingredient/carbomer-0

10. INCI name：Disodium EDTA

- 不純物：預計無重大雜質，但應監測重金屬。CIR 指出化粧品使用的 Disodium EDTA，重金屬含量一般應低於 10 ppm，甲醛含量低於 100 ppm。[1]
- 急性毒性：大鼠急性口服毒性 LD_{50} 為 2800 mg/kg bw，急性吸入毒 LOAEL 為 30 mg/m³ air。[2]

- 刺激性：對皮膚沒有刺激性，對眼睛沒有刺激性。[1]
- 皮膚致敏性：無數據。參考 Na_3EDTA 類似化合物不具致敏性。[1]
- 重複給藥毒性：在一項為期兩年的研究中，33 隻大鼠分 5 組給予了 0、0.5、1 和 5% Disodium EDTA。5%實驗組比其他組的大鼠表現出腹瀉和少食，沒有觀察到對體重增加的顯著影響，凝血時間、紅細胞計數或骨頭也沒有受到不利影響。動物的死亡率與 Disodium EDTA 量無關。死亡率最高的是對照組。各種器官的肉眼和顯微鏡檢查顯示兩組之間無顯著差異[3]。在一項為期 13 週的重複給藥毒性研究中，餵食 Disodium EDTA（0%、1%、5%、10%）的大鼠在最高劑量下顯示出死亡率，此外，在 5%（約 4206 mg/kg bw/day）及以上的劑量下，食物消耗減少（消瘦 10%）和腹瀉。Disodium EDTA NOAEL 為 1%（約 692 mg/kg bw/day）。[5]
- 致突變性/遺傳毒性：高劑量的體外和體內研究具弱致突變性，不致引起人類致突變性。[4]
- 致癌性：無數據。參考 Na_3EDTA 類似化合物以 7500 ppm 劑量餵食大鼠及小鼠達 103 週，結果無致癌性。[1]
- 生殖毒性：口服 EDTA 劑量高於 1000 mg/kg bw/day 可能導致鋅消耗不足，使試驗動物產生生殖/發育毒性[1]。EDTA 使用濃度低和皮膚吸收差，皮膚給藥後不太可能產生生殖毒性。[4]
- 毒理代謝動力學：不太可能通過皮膚吸收，但可以用作滲透促進劑。[1] 口服的吸收率差<3%，低於 20%劑量被胃腸吸收，吸收的物質隨著尿液迅速排出體外。[4]
- 光毒性：無數據。[1]
- 人體數據：四個正常血鈣患者在 4 小時內靜脈滴注 4 g Sodium EDTA 或 Calcium EDTA，導致更多的鈣排泄率分別為 75%~88%和 57%~70%。服用 Disodium EDTA 4 小時內，約有 60%~80%的過量鈣排泄出。當給三個人服用放射性劑量(未指定劑量)的 Calcium EDTA 時，24 小時之內就會排泄 100%。而口服的 Sodium EDTA 及 Calcium EDTA(6 g/day，共 6 天)在人體的胃腸道中吸收差。然而，在接受 Calcium EDTA 的受試者糞便中鈣的含量有增加情況。[1]
- 其他安全資料：CIR 專家小組評估科學數據並得出結論，Sodium EDTA 和相關成分用於化粧品和個人護理產品是安全的。化粧品和個人護理產品中使用濃度下的 EDTA 和相關成分不是皮膚刺激物或致敏劑。研究顯示，這些成分不是致癌物質。由於這些成分結合正

常細胞分裂所需的金屬，一些研究顯示這些化合物具有弱致突變性。另研究資料顯示，口服暴露於大劑量金屬螯合劑後會對生殖和發育產生影響，這可能是正常生殖和發育所需的金屬結合的影響。CIR 專家小組審查了 EDTA 和相關成分，發現其不易透過皮膚吸收。因此，通過使用含有這些成分的化粧品和個人護理產品，皮膚接觸 EDTA 或 HEDTA 會導致非常少的皮膚滲透和全身暴露量，遠低於口服研究中顯示的產生不良影響的劑量。[6]

◆ 參考資料：

1. Final Report on the safety assessment of EDTA, Calcium Disodium EDTA, Diammonium EDTA, Dipotassium EDTA, Disodium EDTA, TEA-EDTA, Tetrasodium EDTA, Tripotassium EDTA, Trisodium EDTA, HEDTA, and Trisodium HEDTA. IJT 21(Suppl.2):95-142, 2002.
2. ECHA 網站: https://echa.europa.eu/registration-dossier/-/registered-dossier/14817/7/3/1 .
3. Seventeenth Report of the Joint FAO/WHO Expert Committee on Food Additives, Wld Hlth Org. techn. Rep. Ser., No. 539, 1974. FAO Nutrition Meetings Report Series, No. 53, 1974. ETHYLENEDIAMINETETRAACETATE, DISODIUM AND CALCIUM DISODIUMSALTS.(https://inchem.org/documents/jecfa/jecmono/v05je25.htm)
4. CSTEE, Opinion on the results of the Risk Assessment of: TETRASODIUM ETHYLENEDIAMINE TETRAACETATE (NA_4EDTA) and EDETIC ACID (EDTA) HUMAN HEALTH PART, 2003.
5. SIDS Initial Assessment Profile, COCAM 3, SIDS, 16-18 October 2012.
6. Cosmetics Info 網站：https://cosmeticsinfo.org/ingredient/disodium-edta

11. INCI name：Methylparaben

- 經皮吸收：測試濃度介於 0.1%-2%，Methylparaben 對羥基苯甲酸甲酯、對羥基苯甲酸丙酯和對羥基苯甲酸丁酯在人類屍體皮膚(0.37-0.91 cm/h×10^{-4})和小鼠皮膚(1.17-1.76 cm/h×10^{-4})中的滲透係數估計值相似。[1]
- 急性毒性：大鼠急性口服毒性 LD_{50} 大於 5600 mg/kg，在已發表文獻中沒有新的口服或皮膚急性毒性研究。[1,2] 小鼠皮下注射對羥基苯甲酸甲酯，劑量大於 165 mg/kg 會暫時引起疲勞、失調、和呼吸窘迫，急性致死皮下劑量大於 333 mg/kg，而大鼠皮下注射毒性大於 500 mg/kg bw。[1,2]
- 皮膚刺激性：未稀釋的 Methylparaben 對羥基苯甲酸甲酯以 Draize 測試，九隻兔子將 0.1 mL 的對羥基苯甲酸酯塗在剃毛之皮膚上並覆蓋 24 小時，最終的主要刺激指數為 0.67，顯示對皮膚有輕微刺激性。[1]
- 眼睛刺激性：將 0.1mL 0.20%的對羥基苯甲酸甲酯滴入兔眼，在此測試濃度下，對羥基苯甲酸甲酯誘導輕度短暫性結膜充血。在關於刺激性的調查各種眼科藥物成分，0.1%至 0.2%對羥基苯甲酸甲酯在等滲溶液中滴注到眼睛中不會引起兔子和天竺鼠的眼睛刺激性。[2]
- 皮膚致敏性：對羥基苯甲酸甲酯、對羥基苯甲酸乙酯、對羥基苯甲酸丙酯和對羥基苯甲酸丁酯(0.1%在生理鹽水中)皮下注射至未指定數量的天竺鼠，每週 3 次，共 3 週(10 次注射)。結果顯示對羥基苯甲酸酯未誘導任何過敏反應。含有 0.1%至 0.8%的一種或兩種對羥基苯甲酸酯的產品配方(包括對羥基苯甲酸甲酯，對羥基苯甲酸乙酯，對羥基苯甲酸丙酯和對羥基苯甲酸丁酯)的皮膚配方進行皮膚刺激和致敏測試，沒有證據顯示這些成分的刺激性或致敏性。[2,3]
- 重複給藥毒性：口服慢性毒性每劑量各 24 隻雄性和雌性大鼠餵食含有 0、2 或 8%的對羥基苯甲酸甲酯 96 週，試驗組動物攝入量分別為 1050 mg/kg bw 及 5500 mg/kg bw， NOAEL 為 5500 mg/kg bw/day。[1,2,3]
- 致突變性/遺傳毒性：對羥基苯甲酸甲酯確實在中國倉鼠卵巢細胞試驗中增加了染色體畸變。[1,2,3]
- 致癌性：當在小鼠或大鼠皮下注射或在大鼠陰道內給藥時，對羥基苯甲酸甲酯無致癌性。[1,2]

- 生殖毒性：非生殖毒性物質。小鼠的飲食添加 0.1%或 1.0%的對羥基苯甲酸甲酯的體內研究報告顯示沒有精子毒性作用。在暴露於 1,000 ppm 或 10,000 ppm 飲食 8 週的大鼠中，對羥基苯甲酸甲酯與異常精子發生率顯著升高有關，4% ~ 5%的精子中大部分為無頭精子，對照組則為 2.3%，荷爾蒙濃度大致並無變化；研究結果顯示未觀察到不良反應的濃度是測試最高濃度 10,000 ppm，對應於對羥基苯甲酸甲酯的 NOAEL 約為 1,140 mg/kg bw/day。[1]
- 毒理代謝動力學：大鼠的肝微粒體對於對羥基苯甲酸酯類的活性最高，其次是小腸和肺微粒體。其中對羥基苯甲酸丁酯被肝微粒體最有效地水解，而對具有較短和較長烷基側鏈的對羥基苯甲酸酯則顯示出較低的水解活性。相反於大鼠小腸微粒體對較長側鏈的對羥基苯甲酸酯表現出相對較高的活性，人肝微粒體對於對羥基苯甲酸酯的水解活性最高，其活性隨側鍊長度的增加而降低。人小腸微粒體的特異性模式與大鼠小腸微粒體相似。[1,2]
- 光毒性：對含有 0.1%至 0.8%的對羥基苯甲酸甲酯、對羥基苯甲酸丙酯和/或對羥基苯甲酸丁酯的產品配方進行光致敏化和光毒性測試，沒有發現明顯的光反應性證據。[1,2]
- 人體數據：對羥基苯甲酸酯施於 50 名受試者背部，其中 5、7、10、12 和 15%對羥基苯甲酸甲酯在丙二醇中。每天施用 5 天後被移除，並對施測部位評分。濃度為 5%的對羥基苯甲酸甲酯不會產生刺激，而較高的濃度會產生一些皮膚刺激。另一 50 位受試者的人類反覆刺激斑貼試驗，結果並無皮膚致敏反應。[3,4]
- 參考資料：

1. Amended Safety Assessment of Parabens as Used in Cosmetics. International Journal of Toxicology, Vol. 39 (Supplement 1) 5S-97S, CIR, 2020.
2. Safety Assessment of parabens as Used in Cosmetics. CIR, 2018.
3. Final Amended Report on the Safety Assessment of Methylparaben, Ethylparaben, Propylparaben, Isopropylparaben, Butylparaben, Isobutylparaben, and Benzylparaben as used in Cosmetic Products. International Journalof Toxicology, 27 (Suppl. 4): 1-82, 2008.
4. Final Report on the Safety Assessment of Methylparaben, Ethylparaben, Propylparaben, and Butylparaben.JACT 3(5):147-209, 1984.

12. INCI name：Propylparaben

- 經皮吸收：測試濃度介於 0.1%-2%，對羥基苯甲酸甲酯、Propylparaben 對羥基苯甲酸丙酯和對羥基苯甲酸丁酯在人類屍體皮膚(0.37-0.91 cm/h×10^{-4})和小鼠皮膚(1.17-1.76 cm/h×10^{-4})中的滲透係數估計值相似。[1]
- 急性毒性：小鼠急性口服毒性 LD_{50} 為 5600 mg/kg，在已發表文獻中沒有新的口服或皮膚急性毒性研究。[1,2] 小鼠皮下注射對羥基苯甲酸丙酯 LD_{50} 為 1.65 g/kg。[1,2]
- 皮膚刺激性：產品含有 0.2%的對羥基苯甲酸丙酯產生的刺激性最小，主要刺激指數為 0.5。[2]
- 眼睛刺激性：含有濃度為 0.1%至 0.8%的對羥基苯甲酸甲酯、對羥基苯甲酸乙酯、對羥基苯甲酸丙酯或對羥基苯甲酸丁酯的產品進行了許多兔眼睛刺激性研究，大多數產品都沒有眼睛刺激的症狀。[1]
- 皮膚致敏性：對羥基苯甲酸甲酯、對羥基苯甲酸乙酯、對羥基苯甲酸丙酯和對羥基苯甲酸丁酯(0.1%在生理鹽水中)皮下注射至未指定數量的天竺鼠，每週 3 次，共 3 週(10 次注射)。結果顯示對羥基苯甲酸酯未誘導任何過敏反應。含有 0.1%至 0.8%的一種或兩種對羥基苯甲酸酯的產品配方(包括對羥基苯甲酸甲酯，對羥基苯甲酸乙酯，對羥基苯甲酸丙酯和對羥基苯甲酸丁酯)的皮膚配方進行皮膚刺激和致敏測試，沒有證據顯示這些成分的皮膚刺激性或致敏性。[3]
- 重複給藥毒性：幼齡 Wistar 大鼠(每組 n = 20)口服對羥基苯甲酸丙酯，劑量為 3、10、100 或 1000 mg/kg bw /day。在 8 週試驗結束時測量青春期的成熟度、生殖器官重量、精子數量、運動能力和血漿激素含量並進行毒物代謝動力學分析。研究顯示沒有證據顯示對羥基苯甲酸丙酯對男性生殖有影響。此研究確定對羥基苯甲酸丙酯的 NOAEL 為 1000 mg/kg bw/day。[1,4]
- 致突變性/遺傳毒性：許多致突變性研究顯示對羥基苯甲酸丙酯是非致突變性。以 Ames 試驗研究對羥基苯甲酸丙酯的致突變潛力，以 10 到 2000 µg/plate 的劑量進行測試時，對羥基苯甲酸丙酯在有無代謝活化的情況下都是不具致突變性的。[1,3]
- 致癌性：對羥基苯甲酸丙酯胎盤測定和新生兒測定。給懷孕的嚙齒動物口服最大劑量，研究結果對羥基苯甲酸丙酯均無致癌性。[1,3]
- 生殖毒性：在一項體外研究中，精子在低至 3 mg/mL 對羥基苯甲酸

丙酯的濃度下無法存活。對羥基苯甲酸丙酯在 0.01%至 1.0%的濃度下會影響體內的精子數量。[2]

- 毒理代謝動力學：大鼠的肝微粒體對於對羥基苯甲酸酯類的活性最高，其次是小腸和肺微粒體。其中對羥基苯甲酸丁酯被肝微粒體最有效地水解，而對具有較短和較長烷基側鏈的對羥基苯甲酸酯則顯示出較低的水解活性。相反，大鼠小腸微粒體對較長的側鏈對羥基苯甲酸酯表現出相對較高的活性。人肝微粒體對於對羥基苯甲酸酯的水解活性最高，其活性隨側鍊長度的增加而降低。人小腸微粒體的特異性模式與大鼠小腸微粒體相似。[1]
- 光毒性：對含有 0.1%至 0.8%的對羥基苯甲酸甲酯、對羥基苯甲酸丙酯和/或對羥基苯甲酸丁酯的產品配方進行光致敏化和光毒性測試，沒有發現明顯的光反應性證據。[1]
- 人體數據：對羥基苯甲酸酯施於 50 名受試者背部，其中 5%、7%、10%、12%和 15%對羥基苯甲酸丙酯在丙二醇中。每天施用 5 天後被移除，並對施測部位評分。濃度為 12%的對羥基苯甲酸丙酯不會產生刺激，而較高的濃度會產生一些皮膚刺激。另一 50 位受試者的人類反覆刺激斑貼試驗，結果並無皮膚致敏反應。[2,3]
- 參考資料：

1. Amended Safety Assessment of Parabens as Used in Cosmetics. IJT 39(Suppl. 1):5-97, 2020.
2. Final Amended Report on the Safety Assessment of Methylparaben, Ethylparaben, Propylparaben, Isopropylparaben, Butylparaben, Isobutylparaben, and Benzylparaben as used in Cosmetic Products. International Journalof Toxicology, 27 (Suppl. 4): 1-82, 2008.
3. Final Report on the Safety Assessment of Methylparaben, Ethylparaben, Propylparaben, and Butylparaben.JACT 3(5):147-209, 1984.
4. RIVM Report 2017-0028.Exposure to and toxicity of methyl-, ethyl- and propylparaben, 2018.

(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、密度項目進行 6 個月產品加速安定性試驗，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	清爽型防曬乳			
包裝材質	LDPE			
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	乳狀	乳狀	乳狀	乳狀
顏色	白色至淡黃色	白色至淡黃色	白色至淡黃色	白色至淡黃色
氣味	無添加香精	無添加香精	無添加香精	無添加香精
pH	7.30	7.41	7.25	7.33
黏度	3050 mPas	2950 mPas	3100 mPas	3180 mPas
密度	1.01 g/cm^3	1.00 g/cm^3	0.98 g/cm^3	0.99 g/cm^3
微生物檢測結果	未檢出	未檢出	未檢出	未檢出
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	清爽型防曬乳		
產品批號	IT0803CY		
產品製造日期	110.07.05		
包裝材質	LDPE	試驗日期	110.07.08
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

樣品名稱 (Sample Name)	清爽型防曬乳
測試日期(Date Tested): 110.03.09~110.04.10	
試驗參考方法(Method Code): ISO 11930:2019	

測試菌種 (Organism)					
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	1.0×10^6	4.2×10^5	5.5×10^5	3.3×10^4	4.6×10^4
第 7 天	<10	<10	<10	1.3×10^3	2.2×10^3
第 14 天	<10	<10	<10	<10	1.2×10^2
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

清爽型防曬乳之防曬係數測試係以ISO 24444:2010 Cosmetics — Sun protection test methods - In vivo determination of the sun protection factor (SPF)方法進行。

SPF TEST Result Table									Laboratory： ABC Lab.						
Product：清爽型防曬乳 SPF 期望值：15 測試日期：110.05.01 UV source：Xe MP															
N°	TEST		SUBJECTS						RESULTS					CONCLUSION	COMMENTS
	Exposure date	Technician name	Subject code	Skin ITA°	Photo type	MEDu (mJ·cm⁻²)	MEDp (mJ·cm⁻²)	SPFi	$SPF_{n'}$	$S_{n'}$	$C_{n'}$	$Cl_{n'}$[%] ($100c_{n'}$ /$SPF_{n'}$)	n	$Cl_{n'}$[%]≤17 %	
1				56,4	I	19	290	15,3	-	-	-	-		-	
2				48,6	II	29	350	12,1	-	-	-	-		-	
3				58,1	I	19	290	15,3	-	-	-	-		-	
4				43.5	II	24	420	17,5	-	-	-	-		-	
5				44,0	II	20	440	22,0	-	-	-	-		-	
6				42,7	II	17	330	19,4	-	-	-	-		-	
7				34,9	III	29	460	15,9	-	-	-	-		-	
8				57,0	I	19	260	13,2	-	-	-	-		-	
9				54,8	II	27	370	13,7	-	-	-	-		-	
10				45,3	II	19	230	12,1	**15,6**	**3,2**	**2,31**	14,8%	8	Complies	
FINAL RESULT			**Mean SPF = 15,6**				**s = 3,2**		**c= 2,31**		**Cl[%] = 14,8 %**			**95 % Cl： 13,3 – 17,9 (n = 10)**	

(15) 與產品接觸之包裝材質資料

包裝材料	材質
清爽型防曬乳-瓶身	LDPE
清爽型防曬乳-瓶蓋	LDPE

III. 安全評估資料

(16) 產品安全資料

清爽型防曬乳每日皮膚暴露量計算

參考 2021 年 3 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 11 版(SCCS/1628/21)，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	全身皮膚
接觸種類	駐留產品
每日使用頻率	2/day
駐留因子	1
防曬乳/霜使用表面積(cm^2)	17500
每日皮膚暴露量($E_{product}$) 對於防曬產品，在 MoS 計算中使用的皮膚暴露量為 18.0 g/day，以成人平均體重估算即為 300 mg/kg bw/day。 備註: 此為 SCCS 進行安全評估時作為防曬產品之標準暴露值，但並不表示建議消費者依此用量使用(SCCNFP/0321/02)。	

清爽型防曬乳各成分 MoS 值計算

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

SED= Eproduct (每日皮膚暴露量)×C/100(配方百分比)×DAp/100(皮膚吸收率)

*M*oS= PODsys/*S*ED

SED (mg /kg bw/day)為全身暴露劑量；Eproduct (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；PoDsys 一般常用 NOAEL 估算。

SCCS 化粧品成分測試及其安全性評估指引第 11 版 (SCCS/1628/21) 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
Aqua	73.57	-	-	-	>100
Decyl Oleate	15.0	1	111.1	0.450	246.9
Ethylhexyl Methoxycinnamate	3.0	4	396.4	0.360	1101.1
Phenylbenzimidazole Sulfonic Acid	2.78	0.2	500	0.017	29976.0
Cetearyl Alcohol	2.205	10	1000	0.662	1511.7
Sodium Hydroxide (45 % solution)	1.2	not relevant	not relevant	not relevant	not relevant
PEG-40 Hydrogenated Castor Oil	0.63	10	1250	0.189	6613.8
Butyl Methoxydibenzoylmethane	0.5	0.56	100	0.008	11904.8
Sodium Cetearyl Sulfate	0.315	10	50	0.095	529.1
Carbomer	0.3	10	756.5	0.090	8405.6
Disodium EDTA	0.1	10	346	0.030	11533
Methylparaben	0.3	100	350.8	0.900	389.8
Propylparaben	0.1	100	307.7	0.300	1025.7

INCI name	NOAEL 校正說明
Decyl Oleate	28天每週5天的大鼠灌食毒性得知NOAEL為1000 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，1000*50%*5/7*28/90 =111.1 mg/kg bw/day。
Ethylhexyl Methoxycinnamate	13週每週5天的大鼠皮膚毒性得知NOAEL為555 mg/kg bw/day，考慮試驗天數之不確定因子，555*5/7 =396.4 mg/kg bw/day。
Phenylbenzimidazole Sulfonic Acid	13週大鼠口服毒性得知NOAEL為1,000 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，1000*50% =500 mg/kg bw/day。
Cetearyl Alcohol	交互參照Behenyl alcohol在26週大鼠口服毒性得知NOAEL為1000 mg/kg bw /day，此為更保守值故未以不確定因子進行校正。
Sodium Hydroxide	不相關，作為pH調節劑。
PEG-40 Hydrogenated Castor Oil	90天大鼠餵食毒性得知NOAEL為2,500 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，將2,500*50% =1,250 mg/kg bw/day。
Butyl Methoxydibenzoylmethane	13週大鼠口服毒性得知最低NOAEL為200 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，將200*50% =100 mg/kg bw/day。
Sodium Cetearyl Sulfate	90天大鼠口服毒性得知NOAEL為100 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，將100*50% =50 mg/kg bw/day。
Carbomer	90天大鼠口服毒性得知NOAEL為1,513 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，1513*50% =756.5 mg/kg bw/day。
Disodium EDTA	為期13週餵食大暑試驗中得知NOAEL為692 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，692*50% =346 mg/kg bw/day。
Methylparaben	8週小鼠口服生殖毒性得知NOAEL為1140 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1140*50% *8/13 =350.8 mg/kg bw/day。
Propylparaben	8週大鼠口服毒性得知NOAEL為1000 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，1000*50% *8/13 =307.7 mg/kg bw/day。

清爽型防曬乳安全評估結論

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據以結論，推定清爽型防曬乳在預期正常合理使用條件下，本產品為可安全使用之產品，不致對人體健康造成傷害。

標籤警語和使用說明

清爽型防曬乳的包裝材料/標籤上提到了以下警告和使用說明：

使用方式：曝曬前 15 分鐘取適量均勻塗抹於臉部或身體。

使用注意事項：塗抹時避免接觸眼睛，若不慎接觸請以大量清水沖洗。使用後若有不適，請立即停止使用並以大量清水沖洗。不得使用於三歲以下孩童之尿布部位。

內含 Propylparaben 及 Methylparaben，已依我國化粧品防腐劑成分名稱及使用限制表應刊載之注意事項進行標示。

安全評估理由

清爽型防曬乳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. 本產品所含之三種防曬成分 Ethylhexyl Methoxycinnamate(限量 10%)、Phenylbenzimidazole sulfonic acid(限量 8%)及 Butyl methoxydibenzoylmethane(限量 5%)符合我國特定用途化粧品成分名稱及使用限制表之規定，使用兩種防腐劑 Methylparaben (限量 0.4%以 acid 計)及 Propylparaben(限量 0.14%以 acid 計)之總量未超過化粧品防腐劑成分名稱及使用限制表之規定。
3. 根據本產品「清爽型防曬乳」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「清爽型防曬乳」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確認之。
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通過 ISO 11930:2019 Criteria A 之標準。

Table B.1 — Evaluation criteria

Log reduction values ($R_x = \lg N_0 - \lg N_x$) required[a]								
Micro organisms	**Bacteria**			***C. albicans***			***A. brasiliensis***	
Sampling time	T7	T14	T28	T7	T14	T28	T14	T28
Criteria A	≥ 3	≥ 3 and NI[b]	≥ 3 and NI	≥ 1	≥ 1 and NI	≥ 1 and NI	≥ 0[c]	≥ 1 and NI
Criteria B	Not performed	≥ 3	≥ 3 and NI	Not performed	≥ 1	≥ 1 and NI	≥ 0	≥ 0 and NI

a In this test, an acceptable range of deviation of 0,5 log is accepted (see 5.7).

b NI: no increase in the count from the previous contact time.

c $R_x = 0$ when $\lg N_0 - \lg N_x$ (no increase from the initial count).

5. 本產品使用之包裝材質為 LDPE，根據過去類似配方及此包材之使用經驗，評估此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 11 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 用於防曬產品之標準暴露值以計算安全邊際值(MoS)。此產品雖為駐留型產品，但部分成分之物理化學特性為不易皮膚吸收者，因此將皮膚吸收率納入考量估算因皮膚吸收而引起全身毒性之暴露劑量低；此外，氫氧化鈉雖然具有強腐蝕性及刺激性，但氫氧化鈉溶液係作為 pH 調節劑且最終成品 pH 為中性，故未進行該成分之安全邊際值(MoS)計算。
7. 此清爽型防曬乳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。
8. 目前此產品尚未出現不良影響和嚴重的不良影響，如有不良影響和嚴重不良影響的相關資訊會立即更新，並及時提供給安全資料簽署人員，以重新評估此產品之安全性。

（請簽名並加上日期）

安全資料簽署人員簽名及日期

附錄 1：產品及各成分之物理化學特性相關資料

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：Ethylhexyl Methoxycinnamate

		Page: 1
SAFETY DATA SHEET		Revision Date: 08/04/2020
		Print Date: 11/24/2020
		SDS Number:
		Version 1.4

29 CFR 1910.1200 (OSHA HazCom 2012)

SECTION 1. PRODUCT AND COMPANY IDENTIFICATION

Product identifier

Trade name : UV filters
™ Trademark, Ashland or its subsidiaries, registered in various countries

Substance name : 2-Ethylhexyl 4-methoxycinnamate

Substance No.
EC-No. : 226-775-7

CAS-No. : 5466-77-3

Relevant identified uses of the substance or mixture and uses advised against

Recommended use : Cosmetic additive

Details of the supplier of the safety data sheet	**Emergency telephone number** **Regulatory information** **Product Information**

SECTION 2. HAZARDS IDENTIFICATION

GHS Classification
Not a hazardous substance or mixture.

GHS label elements
Not a hazardous substance or mixture.

Other hazards
None known.

SECTION 3. COMPOSITION/INFORMATION ON INGREDIENTS

Substance / Mixture	:	Substance

Hazardous components
No hazardous ingredients

SECTION 4. FIRST AID MEASURES

General advice	:	No hazards which require special first aid measures.
If inhaled	:	If breathed in, move person into fresh air. If unconscious, place in recovery position and seek medical advice. If symptoms persist, call a physician.
In case of skin contact	:	First aid is not normally required. However, it is recommended that exposed areas be cleaned by washing with soap and water.
In case of eye contact	:	Remove contact lenses. Protect unharmed eye.
If swallowed	:	Do not give milk or alcoholic beverages. Never give anything by mouth to an unconscious person. If symptoms persist, call a physician.
Most important symptoms and effects, both acute and delayed	:	The most important known symptoms and effects are described in the labelling (see Section 2.2) and/or Section 11.
Notes to physician	:	No hazards which require special first aid measures.

SECTION 5. FIREFIGHTING MEASURES

Suitable extinguishing media	:	Use extinguishing measures that are appropriate to local circumstances and the surrounding environment. Water spray Foam Carbon dioxide (CO2) Dry chemical
Hazardous combustion products	:	Carbon dioxide (CO2) Carbon monoxide

		Hydrocarbons
Specific extinguishing methods	:	
		Product is compatible with standard fire-fighting agents.
Further information	:	Standard procedure for chemical fires.
Special protective equipment for firefighters	:	In the event of fire, wear self-contained breathing apparatus.

SECTION 6. ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures	:	Persons not wearing protective equipment should be excluded from area of spill until clean-up has been completed.
Environmental precautions	:	Prevent further leakage or spillage if safe to do so.
Methods and materials for containment and cleaning up	:	Soak up with inert absorbent material (e.g. sand, silica gel, acid binder, universal binder, sawdust). Keep in suitable, closed containers for disposal.
Other information	:	Comply with all applicable federal, state, and local regulations.

SECTION 7. HANDLING AND STORAGE

Advice on protection against fire and explosion		Normal measures for preventive fire protection.
Advice on safe handling		Smoking, eating and drinking should be prohibited in the application area. For personal protection see section 8.
Materials to avoid		No materials to be especially mentioned.
Further information on storage stability	:	No decomposition if stored and applied as directed.

SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Components with workplace control parameters
Contains no substances with occupational exposure limit values.

Engineering measures : General room ventilation should be adequate for normal conditions of use. However, if unusual operating conditions exist, provide sufficient mechanical (general and/or local exhaust) ventilation to maintain exposure below exposure guidelines (if applicable) or below levels that cause known, suspected or apparent adverse effects.

Personal protective equipment

Respiratory protection : In the case of vapour formation use a respirator with an approved filter within the capabilities of the respirator/filter combination.
Where concentrations are above recommended limits or are unknown, or a cartridge type respirator is not adequate, wear a positive-pressure supplied-air respirator.

Hand protection
Material : butyl-rubber
Break through time : 480 min
Glove thickness : > 0.5 mm

Remarks : The exact break through time can be obtained from the protective glove producer and this has to be observed. Gloves should be discarded and replaced if there is any indication of degradation or chemical breakthrough.

Eye protection : Not required under normal conditions of use. Wear splash-proof safety goggles if material could be misted or splashed into eyes.

Skin and body protection : Wear as appropriate:
Safety shoes
Wear resistant gloves (consult your safety equipment supplier).

Hygiene measures : General industrial hygiene practice.

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance : liquid

Physical state	:	liquid
Colour	:	light yellow
Odour	:	mild
Odour Threshold	:	No data available
pH	:	No data available
Melting point/freezing point	:	-13 °F / -25 °C
Boiling point/boiling range	:	387.9 - 392 °F / 197.7 - 200 °C (4 hPa)
Flash point	:	192.7 °C
Evaporation rate	:	not determined
Upper explosion limit	:	Upper explosion limit not determined
Lower explosion limit	:	Lower explosion limit not determined
Vapour pressure	:	not determined
Relative vapour density		not determined
Relative density	:	No data available
Density	:	1.005 - 1.013 g/cm3 (20 °C)
Solubility(ies)		
Water solubility	:	insoluble
Solubility in other solvents	:	No data available
Partition coefficient: n-octanol/water	:	not determined
Thermal decomposition	:	No data available
Viscosity		
Viscosity, dynamic	:	not determined
Viscosity, kinematic	:	not determined

Oxidizing properties : Not applicable

SECTION 10. STABILITY AND REACTIVITY

Reactivity : No decomposition if stored and applied as directed.

Chemical stability : Stable under recommended storage conditions.

Possibility of hazardous reactions : Product will not undergo hazardous polymerization.

Incompatible materials : strong bases
Strong oxidizing agents

Hazardous decomposition products : Carbon monoxide
Carbon dioxide (CO_2)

SECTION 11. TOXICOLOGICAL INFORMATION

Information on likely routes of exposure : Inhalation
Skin contact
Eye Contact
Ingestion

Acute toxicity
Not classified based on available information.
Skin corrosion/irritation
Not classified based on available information.
Serious eye damage/eye irritation
Not classified based on available information.
Product:
Remarks: Unlikely to cause eye irritation or injury.

Respiratory or skin sensitisation
Skin sensitisation: Not classified based on available information.
Respiratory sensitisation: Not classified based on available information.
Germ cell mutagenicity
Not classified based on available information.
Carcinogenicity
Not classified based on available information.
Reproductive toxicity
Not classified based on available information.

STOT - single exposure
Not classified based on available information.
STOT - repeated exposure
Not classified based on available information.
Aspiration toxicity
Not classified based on available information.
Product:
No aspiration toxicity classification

Further information
Product:
Remarks: No data available

Carcinogenicity:

IARC	No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.
OSHA	No component of this product present at levels greater than or equal to 0.1% is on OSHA's list of regulated carcinogens.
NTP	No component of this product present at levels greater than or equal to 0.1% is identified as a known or anticipated carcinogen by NTP.

SECTION 12. ECOLOGICAL INFORMATION

Ecotoxicity
Product:
Ecotoxicology Assessment

Short-term (acute) aquatic hazard	: Not classified based on available information.
Long-term (chronic) aquatic hazard	: Not classified based on available information.

Persistence and degradability
Product:

Biodegradability	: Result: Readily biodegradable. Biodegradation: 78 % Exposure time: 28 d Method: OECD Test Guideline 301F

No data available

Bioaccumulative potential
No data available
Mobility in soil
No data available
Other adverse effects
No data available
Product:
Additional ecological information : No data available

SECTION 13. DISPOSAL CONSIDERATIONS

Disposal methods

General advice : Dispose of in accordance with all applicable local, state and federal regulations.

Contaminated packaging : Empty remaining contents.

SECTION 14. TRANSPORT INFORMATION

International transport regulations

REGULATION

ID NUMBER	PROPER SHIPPING NAME	*HAZARD CLASS	SUBSIDIARY HAZARDS	PACKING GROUP	MARINE POLLUTANT / LTD. QTY.

U.S. DOT - ROAD

Not dangerous goods

CFR_RAIL_C

Not dangerous goods

U.S. DOT - INLAND WATERWAYS

Not dangerous goods

TDG_ROAD_C

Not dangerous goods

TDG_RAIL_C

Not dangerous goods

TDG_INWT_C

Not dangerous goods

INTERNATIONAL MARITIME DANGEROUS GOODS

Not dangerous goods

INTERNATIONAL AIR TRANSPORT ASSOCIATION - CARGO

Not dangerous goods

INTERNATIONAL AIR TRANSPORT ASSOCIATION - PASSENGER

Not dangerous goods

MX_DG

Not dangerous goods

***ORM = ORM-D, CBL = COMBUSTIBLE LIQUID**

Marine pollutant		no

Dangerous goods descriptions (if indicated above) may not reflect quantity, end-use or region-specific exceptions that can be applied. Consult shipping documents for descriptions that are specific to the shipment.

SECTION 15. REGULATORY INFORMATION

TSCA list
No substances are subject to TSCA 12(b) export notification requirements.

EPCRA - Emergency Planning and Community Right-to-Know Act

CERCLA Reportable Quantity
This material does not contain any components with a CERCLA RQ.

SARA 304 Extremely Hazardous Substances Reportable Quantity

This material does not contain any components with a section 304 EHS RQ.

SARA 311/312 Hazards : No SARA Hazards

SARA 302 : This material does not contain any components with a section 302 EHS TPQ.

SARA 313 This material does not contain any chemical components with known CAS numbers that exceed the threshold (De Minimis) reporting levels established by SARA Title III, Section 313.

US State Regulations

Pennsylvania Right To Know

2-Ethylhexyl 4-methoxycinnamate	5466-77-3

New Jersey Right To Know

2-Ethylhexyl 4-methoxycinnamate	5466-77-3

California Prop. 65

This product does not contain any chemicals known to State of California to cause cancer, birth defects, or any other reproductive harm.

The components of this product are reported in the following inventories:

DSL : All components of this product are on the Canadian DSL

AICS : On the inventory, or in compliance with the inventory

ENCS : On the inventory, or in compliance with the inventory

KECI : On the inventory, or in compliance with the inventory

PICCS : On the inventory, or in compliance with the inventory

IECSC : On the inventory, or in compliance with the inventory

TCSI : On the inventory, or in compliance with the inventory

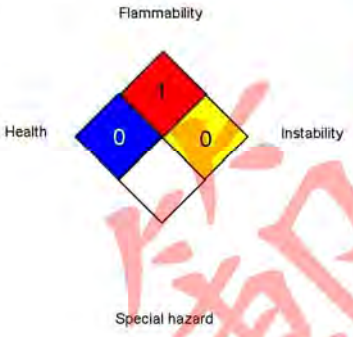
TSCA : On or in compliance with the active portion of the TSCA inventory

Inventories
AICS (Australia), DSL (Canada), IECSC (China), REACH (European Union), ENCS (Japan), ISHL (Japan), KECI (Korea), NZIoC (New Zealand), PICCS (Philippines), TCSI (Taiwan), TSCA (USA) - On or in compliance with the active portion of the TSCA inventory

SECTION 16. OTHER INFORMATION

Further information

NFPA 704:



HMIS® IV:

HMIS® ratings are based on a 0-4 rating scale, with 0 representing minimal hazards or risks, and 4 representing significant hazards or risks. The "*" represents a chronic hazard, while the "/" represents the absence of a chronic hazard.

Full text of H-Statements

Full text of other abbreviations

AICS - Australian Inventory of Chemical Substances; ASTM - American Society for the Testing of Materials; bw - Body weight; CERCLA - Comprehensive Environmental Response, Compensation, and Liability Act; CMR - Carcinogen, Mutagen or Reproductive Toxicant; DIN - Standard of the German Institute for Standardisation; DOT - Department of Transportation; DSL - Domestic Substances List (Canada); ECx - Concentration associated with x% response; EHS - Extremely Hazardous Substance; ELx - Loading rate associated with x% response; EmS - Emergency Schedule; ENCS - Existing and New Chemical Substances (Japan); ErCx - Concentration associated with x% growth rate response; ERG - Emergency Response Guide;

Sources of key data used to compile the Safety Data Sheet :

Revision Date : 08/04/2020

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：Ethylhexyl Methoxycinnamate

1. European Commission, Reports of the Scientific Committee on Cosmetology (Ninth Series): 2-Ethylhexyl-4-methoxycinnamate (5466-77-3), 1999.

S 28: *2-ETHYLHEXYL-4-METHOXYCINNAMATE*

1. General

1.1 Primary name

2-ethylhexyl-4-methoxycinnamate

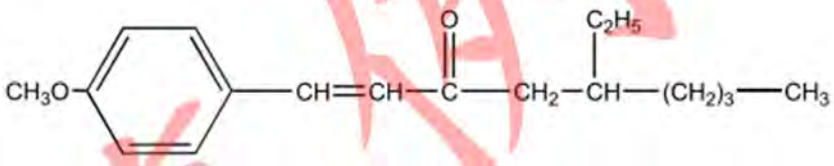
1.2 Chemical names

2-ethylhexyl-4-methoxycinnamate

1.3 Trade names and abbreviations

Parsol MCX

1.5 Structural formula



1.6 Empirical formula

Emp. formula: $C_{18}H_{26}O_3$
Mol weight: 290

1.8 Physical properties

Appearance: Colourless pale yellow slightly oily liquid.

1.9 Solubility

Miscible with alcohols, propylene glycol, etc.
Immiscible with water.

2. Function and uses

Use level up to 10 %.

TOXICOLOGICAL CHARACTERISATION

3. Toxicity

3.1 Acute oral toxicity

Oral LD_{50}: Mouse, greater than 8 g/kg b.w. Rat, greater than 20 ml/kg b.w.

3.4 Repeated dose oral toxicity

Rat. Three week oral study. Groups of 5 male and 5 female animals were given 0, 0.3, 0.9 and 2.7 mg/kg b.w./day by gavage for 3 weeks. All animals of the top dose groups exhibited loss of body weight and a reduced relative and absolute weight of the thymus. Male rats showed a decrease in absolute weight of the left kidney and female rats showed a decrease in the absolute weight of the heart. At the two lower doses, the only significant alteration observed was an increased absolute weight of the pituitary gland in male rats receiving the lowest dose. As the number of animals was small, the investigators considered this not to be biologically significant. The NOAEL was put at 0.9 ml/kg b.w./day.

3.7 Subchronic oral toxicity

Rat. Thirteen week oral study. Four groups of 12 male and 12 female SPF rats received the compound in the diet at levels of 0, 200, 450 and 1000 mg/kg b.w./day. During the experiment the usual clinical observations were carried out, as well as extensive haematological and biochemical studies. Full gross necropsy was carried out on all survivors. Histological investigations were carried out in half the animals of the control and top dose groups. The organs studied included the heart, lungs, liver, stomach, kidneys, spleen, thyroid and retina. In the remaining animals histological examination of the liver only was carried out. Six control animals and 6 top dose animals were allowed to recover over 5 weeks, and then examined.

The results of the experiment showed no dose related mortality. The kidney weights of top dose animals were increased, but were normal in the recovery animals; the increase was attributed to a physiological response to an increased excretion load. There was a diminution of glycogen in the liver, and a slight increase in iron in the Kupfer cells in the high dose animals. Two of these also showed minimal centrilobular necrosis of the liver with some infiltration; similar less marked findings were made in 2 of the control animals as well. These findings were attributed to infection. High dose females had increased GLDH which reversed during the recovery period. The NOAEL was put at 450 mg/kg b.w./day.

3.8 Subchronic dermal toxicity

Rat. Thirteen week dermal study. Four groups of 10 male and 10 female SD rats were treated by an application of various concentrations of a.i. in light mineral oil. The doses were 0, 55.5, 277 and 555 mg/kg b.w./day applied to shaved skin 5 days a week for 13 weeks. (The top dose is believed to be about 135 times the amount which would be used daily by the average consumer). Various laboratory and clinical tests were carried out during the experiment.

All animals survived. All animals showed a slight scaliness at the site of application, which was attributed to the vehicle. Body weight gain was greatest at the low dose. Haematological investigations showed no significant change. SAP was elevated in high dose animals, but not significantly. The relative liver weight in high dose animals was elevated, but appeared normal on microscopical examination. The authors put the NOAEL at 555 mg/kg b.w./day, but in view of the liver findings this may be 227 mg/kg b.w./day.

6. Teratogenicity

Rabbit. Groups of 20 female animals were mated and given a.i. in doses of 0, 80, 200 and 500 mg/kg b.w./day by gavage during the period of organogenesis. Except for a slight reduction of maternal and foetal weight in the top dose animals, no abnormality was found.

Rat. Following a pilot study, groups of 36 rats were mated and treated with 0, 250, 500 and 1000 mg/kg b.w./day of a.i. (probably by gavage) during days 6-14 of pregnancy. Owing to an error, the preparation of the control foetuses led to their destruction, so this part of the test was repeated under identical conditions. Subgroups of each dose group were allowed to litter normally and rear the offspring. The percentage of resorptions in the high dose group was elevated by comparison with the other groups. The investigator records, however, that this relatively high rate is the usual one with this strain of rat in this laboratory, and he attributes the difference to an unusually low level of resorption in the other groups. No other abnormality was found.

7. Toxicokinetics (incl. Percutaneous Absorption)

Tests for percutaneous absorption.

(a) *In vitro* tests. Rat. Naked rat skin. This was studied in a chamber experiment. Most of the material was found in the stripped skin; there was less in the stratum corneum, and least in the chamber. The approximate amounts found in the chamber were: after 6 hrs, 1.13 %; after 16 hrs, 11.4 %; and at 24 hrs 17,9 %. The figures for the horny layer and the strippings combined were, respectively, 31.4 %, 44.4 % and 45.7 % (percentages of applied doses). Solutions of 3 % and 20 % of a.i. gave similar results. In another set of experiments, various amounts of "Parsol 1789" (4-tert-butyl-4'-methoxydibenzoylmethane) were added to the a.i. in the formulation. There seemed to be no effect on the absorption of the a.i.

Pig. A similar experiment using mini-pig skin was carried out in which "Parsol 1789" was used as well as the a.i. Using 3 sorts of formulation, about 3 % of a.i. was found in the chamber in 6 hrs. Using the concentrations proposed for a particular commercial use (i.e., 7.5 % of "Parsol 1789" and 2 % of a.i.) about 2.2 % was found in the chamber. It is calculated by the authors that the total absorption for a 75 kg consumer would be about 70 mg, or 0.9 mg/kg b.w. (Note however that the maximum proposed use level of a.i. is 10 %).

Man. A test on human abdominal skin in a chamber was carried out. With 7.5 % a.i., about 0.03 % is found in the camber in 2 hours, 0.26 % in 6 hours, and 2.0 % in 18 hours. Various combinations of a.i. and "Parsol 1789" were investigated.

(b) *In vivo* tests. Man. Eight healthy volunteers had small amounts of radioactive a.i. applied to the interscapular region. One group of 4 had the material applied under a watch glass; the other 4 had it applied on gauze, whith occlusion in one case. Tests for absorption of a.i. were negative except for about 0.2 % in urine. The concentrations used were not stated.

In a preliminary experiment, a capsule containing 100 mg of a.i. was taken orally. As a lipophilic substance, the a.i. is very likely to be metabolised; it is known in any case to be hydrolysed by plasma esterases, although slowly. The cumulative excretion of 4methoxycinnamate in the urine over 24 hours was studied by GC/MS of the methyl ester

derivative. (This method would also detect 4-hydroxycinnamic acid). Over 24 hours, 13.2 % of the amount ingested was recovered, equivalent to 21.5 % of the amount that would be expected if the a.i. were completely absorbed. In the main part of the experiment, an o/w cream containing 10 % a.i. was used. Applications of 2 grams of this material (= 200 mg a.i.) were made to the interscapular area of each of 5 male subjects, aged 29 to 46. The area of skin covered was 25x30 cm. After application, the area was covered with 3 layers of gauze, left in place for 12 hours. Blood was taken at times 0, 0.5, 1, 2, 3, 5, 7, and 24 hours. Urine was collected at 0, 1, 2, 3, 4, 5, 6, 7, 12, 24, 48, 72 and 96 hours.

The control plasma samples showed a level equivalent to about 10 ng/ml before any application had been made. There was no evidence of any rise in plasma levels during the experiment. The urine showed a "physiological" level of 100 to 300 ng/ml. No significant increase in this amount was found in any sample. The authors conclude that very little, if any, of the compound was absorbed under the conditions of the experiment.

8. Mutagenicity

Salmonella mutagenesis assays were performed on the usual strains. There was a positive result with TA 1538 without metabolic activation. This was thought to have been a batch effect. From another laboratory, a very weak positive was found with TA 1538 without activation, at 10 µl/plate; it was not found in 2 replicates, nor in a second Ames test. A test for mutagenesis and crossing over in *S. cerevisiae* was negative. A test using Chinese hamster V 79 cells showed a very slight increase in mutant colonies with dose. A test in human lymphocytes *in vitro* was negative.

A test for cell transformation in Balb/c 3T3 cells was negative. A test for unscheduled DNA synthesis was negative.

Tests in *Drosophila:* There was an increase in the frequency of sex-linked recessive lethals. There was no evidence of mutagenicity in feeding tests (adults and larvae). Somatic mutation and combination tests using wing structure were negative. Mouse. Micronucleus test. No effect was found up to 5000 mg.

Test for photomutagenic activity. These were carried out in cells of *S. cerevisiae*, which had previously been shown not to be affected by a.i. *(supra)*. Doses of a.i., dissolved in DMSO, ranged from 0.06 to 625 µg/ml, and radiation up to 500000 J m^{-2} UVA and up to 12000 UVB (50 and 1.2 J cm^{-2}). Chlorpromazine was used as the positive control. Suitable negative controls were also employed. The experiment appears to have been well carried out. The results show that UVA and (more markedly) UVB are mutagenic; and that the a.i. protects against this effect in a dose dependent manner.

10. Special investigations

Test for capacity to produce phototoxicity. Man. In 10 subjects, patches were applied for 24 hours and the areas then exposed to a suberythematous dose of UV irradiation. There was no evidence of phototoxicity.

Test for capacity to produce photosensitization. Tests which "showed that the product did not provoke photosensitization." No details supplied.

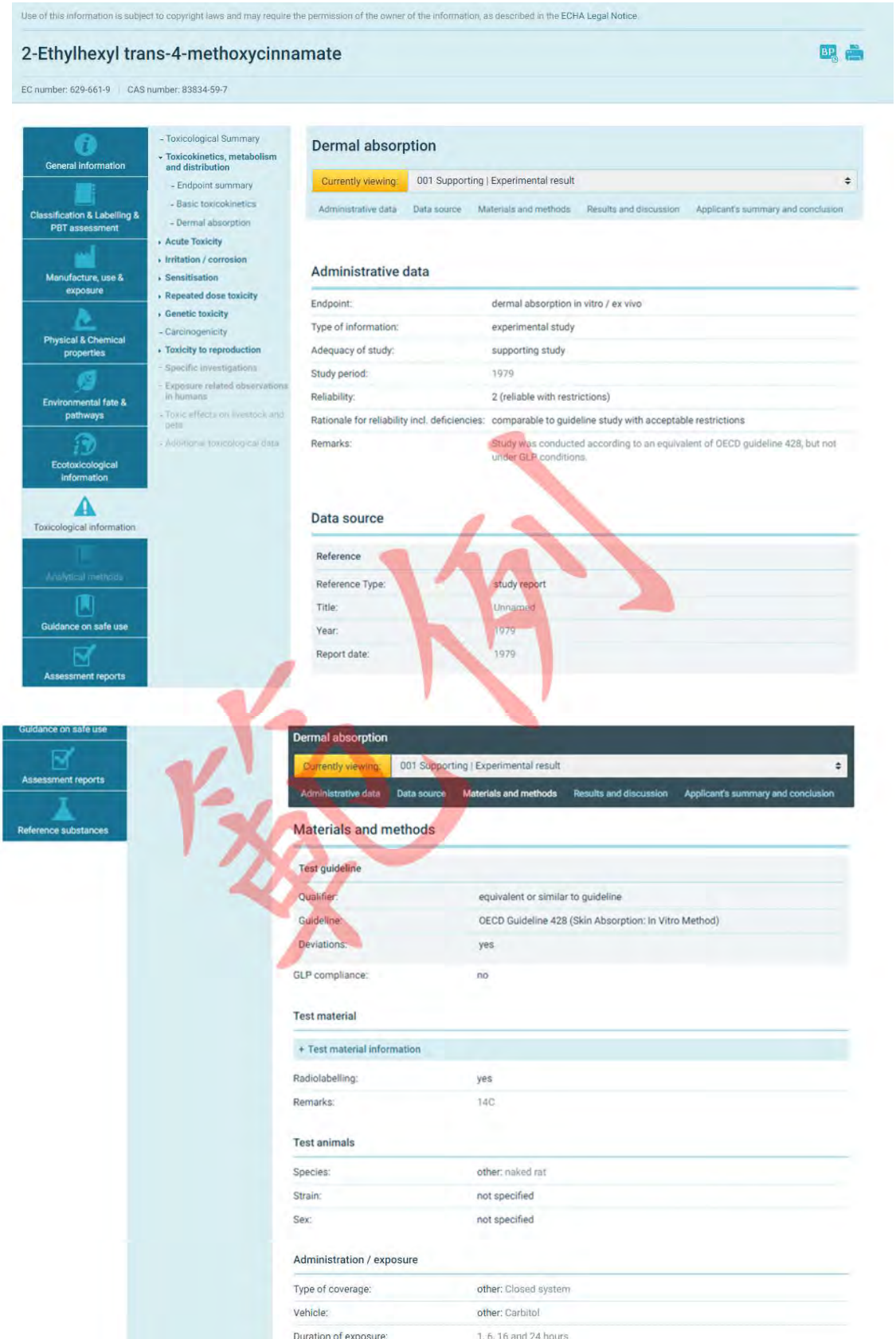
Test for inhibition of UV-induced tumors. Hairless mouse. The animals were exposed to repeated doses of UV simulating the solar energy spectrum. After a rest period, 3 applications a week were made to an area of skin of 12-o-tetradecanoyl phorbol-13-acetate (at first at 10 g/ml, but later at 2 g/ml, as the higher concentration was found to be irritant). Suitable controls were used. The test group was completely protected by 50 % a.i., and 7.5 % gave an effect equivalent to reducing the insolation four-fold. It had been suggested that the a.i. could itself have been a promoter, but there was no evidence of this.

11. Conclusions

The compound appears to have low acute and subchronic toxicity, orally and dermally; it does not irritate the mucous membranes in conventional animal tests. The data presented suggest that the compound is not an irritant or sensitizer in animals and man; however, tests for sensitization were carried out at levels below the proposed maximum use level. Clinical investigation shows that this compound is very rarely responsible for allergic contact dermatitis in man. There is no carcinogenicity study, but an extensive range of mutagenicity studies were nearly all negative. A test for photomutagenicity was negative, although the dose of UVB used was rather low. Animal studies for teratogenic activity were negative. Percutaneous absorption in man appears to be very low.

Classification: A

2.ECHA 網站: https://echa.europa.eu/registration-dossier/-/registered-dossier/15876/7/2/3 .



Dermal absorption

Currently viewing: 001 Supporting | Experimental result

Administrative data | Data source | Materials and methods | **Results and discussion** | Applicant's summary and conclusion

Remarks on result:	other: 16 hrs
Remarks:	Based on amount of test material in stripped skin and chamber liquid

Any other information on results incl. tables

Percentage of substance absorbed after 24 hrs:

1 % in carbitol: 44.3 %

3 % in carbitol: 35.6 %

10 % in carbitol: 22.7 %

About 70 - 90 % of the applied dose of Ethylhexyl Methoxycinnamate was found on the skin surface during the first 6 hours after application

The amount recovered from the stratum corneum was low and reached its maximum 24 hours after application. The steady state was attained within 6 hours.

The portion of Ethylhexyl Methoxycinnamate found in the stripped skin increased to its maximum within 16 hours. Lower levels of the test material were found 24 hours after application.

A significant part of the applied dose was found in the chamber liquid (7 - 17 %) after longer times of exposure.

Applicant's summary and conclusion

Conclusions:	In an in vitro system using naked rat skin, the skin penetration potential and resorption capacity of Ethylhexyl Methoxycinnamate were significant after longer times of exposure, based on the high amount of Ethylhexyl Methoxycinnamate found in the stripped skin, the low levels in the stratum corneum and the amount of activity recovered from the chamber liquid.
Executive summary:	Skin penetrating potential of Ethylhexyl Methoxycinnamate in naked rat skin was determined in a study using an in vitro system. The study was performed according to an equivalent of OECD guideline 428. Three concentrations of Ethylhexyl Methoxycinnamate in carbitol (1, 3 and 10 %) were applied and skin absorption rates were determined by the activity of the 14C-labelled test article. It was found that the higher amount of Ethylhexyl Methoxycinnamate is absorbed into the upper layer of the skin (stripped skin). The low levels in the stratum corneum and the amount of activity recovered from the chamber liquid indicate significant penetration and resorption capacities of Ethylhexyl Methoxycinnamate through the intact skin of the naked rat after longer times of exposure.

3. UV-Filters in Sun Protection Products, Opinion of the Federal Institute for Risk Assessment, 6th August, 2003.

Federal Institute for Risk Assessment (BfR)

UV-Filters in Sun Protection Products

Opinion of the Federal Institute for Risk Assessment, 6th August 2003

Background

The Federal States Baden-Württemberg and Bayern have reported several problems related to UV filters in sun protection products. Questions have been raised in particular concerning

1. combined effects of UV filters and a summation limit value for UV filters,
2. a limitation for the sun protection factor,
3. the photostability of UV filters and
4. the oral toxicity of UV filters in lipsticks and lip care products.

UV filters and their combinations have frequently been a subject matter of deliberations within the Committee for Cosmetic Products (Cosmetics Committee) at the Federal Institute for Risk Assessment (BfR). The questions and proposals of the Federal States were discussed at the 64th meeting of the Cosmetics Committee.

Result

1. BfR recommends using combinations of UV filters and ingredients in the formulations of cosmetic products in a manner that enables to keep the amount of individual filters and also the sum of the filters used for the protection aimed as low as possible. The permitted maximum concentrations for the individual UV filters must not be exceeded. Furthermore, UV filters added should contribute considerably to the sun protection factor of the finished product. The health safety and the skin tolerance of the finished products must be guaranteed. At present there are no hints with respect to a concrete risk for cumulative toxic effects or increased skin penetration in products with a UV filter combination.

2. BfR further recommends a limitation for the sun protection factor, SPF, in sun protection products for healthy skin. Along the lines of precautionary consumer protection BfR is of the opinion that even a lower maximum SPF than the maximum SPF of 50+ discussed in the Cosmetics Committee could be favourable. In Australia and in the USA protection factors are restricted to 30+. A restriction to a SPF of 30+ would also be beneficial with respect to the difficulties in reproducibility of high SPFs and the correspondingly long exposure time for volunteers when determining high SPFs. The declared SPF should also be achieved under application conditions.

   Products with high UVB protection should also provide high UVA protection. In order to determine UVA protection, a uniform international harmonised method should be elaborated for the wavelength range of 320 to 400 nm. The declaration of UVA protection should be comprehensible for the consumer. A declaration as a percentage of the filtered UVA rays, for example, could help to avoid confusion with the SPF, which is a time-based protection factor. Until the establishment of an internationally accepted determination method, the declaration of UVA protection should include a reference to the determination method.

3. Since the combination of various UV filters and the formulation play a decisive role for photostability, BfR generally recommends testing the stability of the UV filters in finished products under conditions which are as close as possible to application ones. This is within the responsibility of manufacturers.

4. According to current knowledge it can be assumed that the use of decorative lipsticks and lip care sticks with UV protection only leads to a minor increase in systemic exposure of consumers to UV filters. The margin of safety (MOS) for all evaluated UV filters is at least 100 in sun protection products. In the case of additional exposure to UV filters in lipsticks and lip care sticks, the MOS according to current knowledge, falls only below 100 in the case of one filter (4-methyl benzylidene camphor).

   The margin of safety is based on the assumption of daily, lifelong exposure. For sun protection products application throughout the year must be assumed. It is not currently felt that there is a risk to the consumer through additional exposure to UV filters in lipsticks and lip care sticks. For reasons of precautionary consumer protection, however, 4-methyl benzylidene camphor should not be used in lipsticks, lip care sticks or skin care products.

Further recommendations

Sun protection products do not offer complete protection against UV rays. Their use should not lead to extended exposure to the sun nor replace sun protection through clothes. This applies in particular to children. Infants and babies should not be exposed to direct sunlight at all.

Explanation

UVB rays (wavelengths of approx. 290 to 320 nm) encourage the formation of melanin in the melanocytes of the deepest epidermal layers and therefore also the darkening of the skin through delayed pigmentation. UVB is largely involved in the development of inflammatory reactions (sunburn). Even low doses of UVB rays lead to an immunosuppressant effect. UVA rays (wavelengths of approx. 320 to 400 nm) penetrate the horny layer and reach the epidermis and dermis. They have a comparatively low effect on the triggering of sunburn but may trigger pathological light reactions. UVA rays mainly lead to an immediate pigmentation by means of reversible oxidation of melanin precursors.

The light-related ageing of the skin and the formation of tumours can be attributed both to UVB and UVA rays. The rate of UV-ray-related tumours decreases with increasing wavelength up to 350 nm. There are, however, indications that rays in the range of 380 nm may also induce a higher rate of tumours (Rünger 1999).

Because of an expanding exposure of the majority of the population to the sun, UV protection takes on an increasingly important role. UV filters are, therefore, not only used in sun protection products but to an increasing degree in hair and facial care products and in decorative cosmetics.

UV filters in cosmetics require marketing authorisation. Their use is regulated in accordance with Directive 76/768/EEC (Cosmetics Directive) and in the German Cosmetics Regulation (KVO). Permitted UV filters are listed in Annex VII of the Cosmetics Directive and in Annex 7 of the KVO. The maximum concentrations and application restraints are also listed there. Moreover, manufacturers must guarantee the health safety of their products.

UV protection can be afforded by both organic and physical filters (titanium dioxide, zinc oxide). At present, 25 organic sun protection filters are listed (KVO, Annex 7, or Cosmetics Directive, Annex VII). The use of coated microfine titanium dioxide and coated, microfine zinc oxide as UV filters is admissible in accordance with § 3b KVO up to 31 December 2003.

Furthermore, titanium dioxide is also authorised pursuant to the Cosmetics Directive in relative maximum amounts up to 25 %.

1. Combined effects of UV filters and sum limitation value for UV light filter agents

Organic UV filters absorb light quants in a specific wavelength range and convert energy into infrared rays; physical filters (titanium dioxide and zinc oxide) scatter, reflect and absorb UV rays. In order to offer protection over the entire spectrum of relevant wavelengths of 290 to 400 nm, several UV filters with different absorption maxima must be combined. By choosing a suitable combination of organic and physical filters, the content of organic filters can be reduced whilst offering the same UV protection. This is desirable since in particular photounstable organic UV filters, depending on their concentration in the finished product, can trigger phototoxic and photoallergenic reactions.

The combination of UV filters can, moreover, influence photostability. The organic UVB filters octocrylene and methylbenzylidene camphor are known to stabilise the photounstable organic UVA filter butyl methoxydibenzoylmethane. Furthermore, a possible recrystallisation of dissolved UV filters can largely be prevented by a suitable combination with liquid filters.

The galenic auxiliary substances used in the formulation also play a major role in sun protection products. They should guarantee the stability of the UV filters and may, under certain circumstances, also influence their penetration to deeper skin layers. For UV protection it is, however, necessary for the filter substances to remain and act in the horny layer. The efficiency of a sun protection product does not, therefore, depend solely on the filters used but to a large degree on the composition of the overall formulation.

Fears have repeatedly been voiced that the combination of organic UV filters could lead to interactions in the formulations and to an addition or potentiation of toxic effects. However, the BfR has received no information or data, supporting this hypothesis. The authorised filters have mostly been assessed by the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) and must have a margin of safety (MOS) of at least 100 between the exposure in man achieved under application conditions and a dose which does not lead to any adverse effects in animal experiments (SCCNFP/0321/00/Final: *Notes of guidance for testing cosmetic ingredients for their safety evaluation*). The assessment of UV filters also takes into account the special situation of children. Compared with adults, children have a three-fold higher ratio of body surface to body weight. This problem has been extensively discussed by SCCNFP. SCCNFP came to the conclusion that a MOS of more than 100 is sufficient to guarantee the safety of children when exposed to UV filters (SCCNFP/0557/02/Final: *Position Statement on the Calculation of the Margin of Safety of ingredients incorporated in cosmetics which may be applied to the skin of children*).

From data provided by the surveying authorities, BfR knows that sun protection products with combinations of between two and six UV filters are on sale on the market. The sum of the UV filters may amount to 10 to 20 mass percent. Sun protection products for children may also contain several organic filters. Adverse reactions caused by products with UV filter combinations have not been reported to BfR up to now. The BfR Cosmetics Committee has discussed the combination of UV filters in sun protection products on several occasions. The experts do not currently see a concrete risk based on the cumulative toxic effects or a higher skin penetration in conjunction with UV filter combinations.

Recommendation

BfR recommends that UV filters and ingredients should be combined in the formulations in such a way that the number of filters as well as the relative amount of filters used for the

protection claimed is kept as low as possible. The permitted maximum concentrations for the individual UV filters must not be exceeded. Furthermore, the added UV filters should contribute to the sun protection factor of the finished product. The health safety and skin tolerance of the finished products must be guaranteed.

2. Limitation of the sun protection factor and UVA protection

The declaration of the sun protection factor serves as an indicator for the consumer related to the efficiency of the individual product to protect against sunburn. The SPF stated on the products describes UVB protection and indicates the time period were a stay in the sun should not lead to skin reddening when using the corresponding product (sunburn or erythema protection factor or erythema threshold value). With the principle of the SPF the individual skin type of the consumer is taken into account.

A limitation of the sun protection factor was deemed necessary by the experts of the Cosmetics Committee since use of sun protection products with a high SPF may encourage consumers to an extended stay in the sun. A limitation to a maximum SPF of 50+ with a minimum SPF of 60 was discussed by the Committee. An SPF of 60 implies arithmetically that individuals with sensitive skin (skin types I to II) could spend up to 10 hours in the sun without becoming sunburnt, individuals with insensitive skin (skin types III to IV) up to 30 hours. However when calculating the time periods protection is claimed for the following factors additionally have to be considered:

1. Even protection products with a high SPF do not completely filter UVB rays (sun protection products with an SPF of 20 approximately filter 95 %, products with an SPF of 50 approximately 98 % of the UVB rays).

2. The SPF is determined under standardised conditions in the laboratory by applying 2 mg of the product per cm^2 skin (Colipa Sun Protection Factor Test Method. Brussels; The European Cosmetic, Toiletry and Perfumery Association-COLIPA, 1994). If a smaller amount of the product is applied under application conditions, the declared SPF will not be achieved. Also the sun protection product may become rubbed off by clothing or towels with the consecution of a reduced protection.

3. Since the biological endpoint for the determination of the SPF is the UV erythema, the SPF is no indicator for a protection against UV-caused skin aging, tumour development or immunosuppression. High protection factors in the UVB range may give a false feeling of safety, as skin reddening as an alarm signal is delayed. Consumers therefore may become encouraged to a prolonged stay in the sun. In the consequence the exposure to UVA is increased, if the product does not offer UVA protection.

The determination methods for the SPF have widely been harmonised world-wide since 1999 and SPF declarations on products therefore are mainly comparable. At present, there is no harmonised method for the determination of UVA protection. The Australian Standard (AS/NSZ 2604, 1997) is the only standardised method so far and frequently used all over the world. Here the transmission spectrum of the product is determined at wavelengths of 320 to 360 nm. In order to comply with the standard, more than 90 % of the rays must be filtered. Further specification on UVA protection are derived from tanning determination *in vivo*, e.g. applying the Immediate Pigment Darkening Method (IPD) or the Persistent Pigment Darkening Method (PPD, the industrial standard in Japan since 1996). For these purposes test persons were exposed to rays with specific UVA doses and skin tanning is determined after several minutes (IPD) or several hours (PPD), respectively. Depending on the method used the numerical value given for the same protection may vary considerably. A comparison of UVA protection by different products is possible only to a limited degree.

Declarations, which also include UVB protection are the critical wavelength (at which 90 % of the area under the absorption curve is reached in the range of 290 to 400 nm) and the ratio of UVA to UVB protection.

For an additional qualitative description of sun protection products, the burden quotient was introduced. It is an index for the galenic quality of the product and describes the ratio of the overall amount of UV filters and the sun protection factor. However, it can only serve as additional information and not replace the declaration of efficiency on sun protection products.

Recommendation

BfR recommends a limitation for the SPF in sun protection products for healthy skin. Along the lines of precautionary consumer protection BfR is of the opinion that even a lower maximum SPF than the maximum SPF of 50+ discussed in the Cosmetics Committee could be favourable. In Australia and in the USA protection factors are restricted to 30 +[1]. A restriction to an SPF of 30+ would also be beneficial with respect to the difficulties in reproducibility of high SPFs and the correspondingly long exposure time for volunteers when determining high SPFs. The declared SPF should also be achieved under application conditions.

Products with high UVB protection should also provide high UVA protection. In order to determine UVA protection, an international harmonised method should be elaborated for the wavelength range of 320 to 400 nm. The declaration of UVA protection should be comprehensible for the consumer. A declaration as a percentage of the filtered UVA rays, for example, could help to avoid confusion with the SPF, which is a time-based protection factor. Until the establishment of an internationally accepted determination method, the declaration of UVA protection should include a reference to the determination method.

3. Photostability of UV filters

High sun protection factors imply long-lasting protection. However, this is only guaranteed when the UV filters remain stable over the protection period claimed or if their metabolites have a comparable protective effect. Various studies confirm differing photostability of permitted UV filters (e.g. Herzog and Sommer, 2000, Schwack and Rudolph, 1996, Johncoock, 1999). In order to standardise photostability tests for UV filters, corresponding methods for UVA and UVB filters were published by the umbrella association of the European cosmetics industry *Comité de Liaison des Associations Européennes de l'Industrie de la Parfumerie, des Produits Cosmétiques et de Toilette* (COLIPA), (Gonzenbach et al 1996). According to this method dissolved filters are applied under defined conditions to a glass surface, dried and exposed to UV rays. Subsequently the recovery of the amount of UV filter applied is analytically determined and absorption is measured and compared to a non-irradiated sample.

Recommendation

Since the combination of various UV filters and the formulation play a decisive role for photostability, BfR generally recommends testing the stability of the UV filters in finished products under conditions which are as close as possible to application ones. An appropriate method is currently being developed by COLIPA.

4. Oral toxicity of UV filters in lipsticks and lip care products

[1] In the USA sun protection products are considered to be over-the-counter drugs whose efficiency and safety must be proven. Products may be declared with a higher SPF than 30+ if the effect was previously proven.

Lips react more sensitively to UV rays than the rest of the facial skin. Therefore UV filters are increasingly being added to decorative lipsticks and lip care sticks. Even if no clinical studies are available to confirm the prevention of pre-cancerosis on the lip through UV filters in lip care products, it can be assumed that the sun protection for the skin also protects the lips. In this context various filter combinations are possible and the protective properties of the individual products differ. It is assumed that the relative amount of UV filters in these products is 10 % on average. From surveillance, however, also higher amounts of UV filters in lipsticks and lip care products were reported (in individual cases up to 27 %).

Exposure and Assessment

Usually the amount of lip care products applied is 10 mg per application according to estimates of SCCNFP (SCCNFP/0321/00/Final: *Notes of guidance for testing cosmetic ingredients for their safety evaluation*). For products with a high pigment content as much as 15 mg per application may be applied. In the case of daily four-fold application up to 60 mg of the products were applied to the lips. For lip care products 100 % systemic intake through swallowing is assumed. Under these preconditions for lip care products with a high pigment content and a relative amount of UV filters of 10 % a daily intake of 0.1 mg UV filter per kg body weight for adults (60 kg body weight) and 0.6 mg UV filter per kg body weight for children (10 kg body weight) can be expected.

It is difficult to estimate the systemic intake of UV filters via the skin from skin care and sun protection products. The intake depends on e.g.

- the frequency of application of products containing UV filters,
- the amount used,
- the relative amount of the filter(s),
- the filter combination and the galenics of the formulation as well as
- the ability of the UV filters to penetrate the skin.

The daily amount of skin care products applied (leave-on products: facial cream, body lotion, deodorant and hair products) amounts to 13.5 g according to estimates of SCCNFP (SCCNFP/0321/00 final: *Notes of guidance for testing cosmetic ingredients for their safety evaluation*). Skin care products may contain UV-absorbing agents both for product protection as well as for skin protection. Therefore consumers may additionally be exposed to UV filters through the daily use of these products.

The highest exposure to UV filters is certainly linked to the application of sun protection products. However, BfR has no data about the amounts of sun protection products used. It is generally assumed that 0.5 to 1.5 mg sun protection agent is used per application per cm^2 skin. Taking into account the skin penetration rates obtained in experiments and the filter-specific maximum concentration in conjunction with single application to the entire body surface (18,000 cm^2, application 1 mg/cm^2), systemic exposure was estimated for the individual filters by the Scientific Committee on Cosmetology (SCC) or by SCCNFP in conjunction with marketing authorisation (cf. selection in Table 1).

The estimated exposure to UV filters from decorative lipsticks and lip care sticks is estimated to be 0.1 mg per kg body weight for adults. Table 1 lists the estimated exposure from sun protection products for a selection of UV filters, which are also frequently used in lipsticks and lip care sticks and for which opinions are available from SCC and/or SCCNFP. For these UV filters the MOS was calculated in conjunction with parallel application of sun protection products and lip care products containing UV filters based on the assumption that the same filter is used in both products.

UV filter	amount in product [%]	dermal absorption [%]	filter $_S$ [mg/kg KG/d]	filter $_L$ [mg/kg KG/d]	NOAEL [mg/kg KG/d]	MOS $_S$	MOS $_{SL}$
S27	10	4,4	1,32	0,1	200	152	141
S28	10	2	0,6	0,1	450	750	643
S32	10	0,08	0,021	0,1	175	8333	1446
S60	4	1,9	0,228	0,1	25	110	**76**
S66	5	0,56	0,084	0,1	200	2381	1087
S69	5	1,5	0,23	0,1	1150	5000	3485

Table 1: Additional exposure of adults to UV filters in lipsticks and lip care sticks and changes in the margin of safety

S27: Isoamyl p-methoxycinnamate; S28:Octyl methoxycinnamate; S32:Octocrylene; S60: 4-Methyl benzylidene camphor; S66: Butyl methoxydibenzoyl methane; S69:Octyltriazone

Filter $_S$: estimated amount of UV filters taken up from sun products per kg body weight and day;

Filter $_L$: estimated amount of UV filters taken up from lipsticks and lip care sticks per kg body weight and day;

MOS_S: Margin of Safety for UV filters in sun protection products;

MOS_{SL}: Margin of Safety for UV filters, when used in parallel in sun protection products and lipsticks or lip care sticks

The margin of safety for all authorised UV filters is at least 100 when used in sun protection products. In the case of additional exposure of adults to the corresponding UV filters in lipsticks and lip care sticks, the MOS falls below 100 only in the case of one filter (4-methyl benzylidene camphor[2]). For children who have a three-fold higher ratio of body surface to body weight than adults, the MOS could be even lower under unfavourable conditions. Further exposure is possible from body care products, which may also contain UV filters.

The margin of safety for UV filters is based on the assumption of daily, life-long exposure. This should not, in principle, apply to sun care products although a year-round use must be assumed, as sun protection products may be used not only in summer but probably also during holidays and when using solariums.

Recommendation

It is not felt that there is a fundamental risk to the consumer through additional exposure to UV filters in lipsticks and lip care sticks. However, for reasons of precautionary consumer protection 4-methyl benzylidene camphor should not be used in lipsticks, lip care sticks or skin care products.

5. Further recommendations of BfR

Sun protection products do not offer complete protection against UV rays. Their use should therefore not lead to extended exposure to the sun nor replace sun protection through clothes.This applies in particular to children since data of the American Academy of Dermatology confirm that 80 % of sun damage takes place before the age of 18. Infants and babies up to the age of 2 should not be exposed, if at all possible, to direct sunlight.

[2] Consultations at SCCNFP are currently underway about UV filters with regard to possible bioaccumulation and the interpretation of thyroid effects in animal experiments.

References

Gonzenbach H, Berset G, Deflandre A, Mascotto RE, Jolley JDR, Lowell W, Pelzer R, Stiehm T, 1996 Proposed protocol for determination of photostability. Part I: Cosmetic UV-Filters. International Journal of Cosmetic Science 18, 167-177

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Johncook W, 1999 Sunscreen Interactions in Formulations. Allured's Cosmetics and Toiletries Magazine 114, 9, 75-82

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Rünger TM, 1999 Role of UVA in the pathogenesis of melanoma and non-melanoma skin cancer. Photodermatol. Photoimmunol. Photomed. 15, 212-216

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化粧品產品資訊檔案(範例)

<玩色染髮-瞬時棕>

＜PIF **無特定之格式**，本範例**僅提供參考用**＞

中華民國 111 年 7 月

目　錄

頁 次

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)	玩色染髮-瞬時棕 (第一劑、第二劑) Hair dye Brown (First dose、Second dose)
產品類別	頭髮用化粧品類
產品劑型	第一劑-乳劑、第二劑-液劑
用途	染髮
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：oo 市 oo 路 oo 段 XX 號 公司負責人：李○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：0123XXXXTEST1000000000

選擇組合式產品：染髮劑第一劑
產品類型：單一產品
產品型號：瞬時棕
染髮劑第一劑-成分資訊 * -單位：%(W/W)

序號	* 成分名稱	* 含量	限量成分用途 *公告限量成分才需填寫	提醒事項
1	P-Phenylenediamine 查詢	標誌量 2.0000000000000	染髮劑(使用於氧化性染髮劑)	用途：染髮劑(使用於氧化性染髮劑),限
2	Resorcinol 查詢	標誌量 1.0000000000000	染髮劑(使用於氧化性染髮劑)	用途：染髮劑(使用於氧化性染髮劑),限
3	M-Aminophenol 查詢	標誌量 0.3000000000000	染髮劑(使用於氧化性染髮劑)	用途：染髮劑(使用於氧化性染髮劑),限
4	Sodium Bisulfite 查詢	標誌量 0.5000000000000	其他 填寫內容，確保屬實，	用途：防腐劑,限量 0.0000%~0.2000%
5	Ammonium Laureth Sulfate 查詢	適量		
6	Polysorbate 80 查詢	適量		
7	DIMETHICONE 查詢	適量		
8	Alcohol 查詢	適量		
9	Ammonia 查詢	標誌量 2.0000000000000	染髮劑	用途：染髮劑,限量 0.0000%~6.0000%
10	Disodium EDTA 查詢	適量		
11	Fragrance 查詢	適量		
12	Water 查詢	適量		

選擇組合式產品：染髮雙氧水第二劑
產品類型：單一產品
產品型號：瞬時棕
染髮雙氧水第二劑-成分資訊 * -單位：%(W/W)

序號	* 成分名稱	* 含量	限量成分用途 *公告限量成分才需填寫	提醒事項
1	Hydrogen Peroxide 查詢	標誌量 10.000000000000	染髮劑	用途：染髮劑,限量 0.0000%~12.0000%
2	GLYCERIN 查詢	適量		
3	UREA 查詢	標誌量 1.0000000000000	其他(使用於染髮產品)	用途：其他(使用於其他產品),限量
4	Fragrance 查詢	適量		
5	WATER 查詢	適量		

(3) 全成分名稱及其各別含量

第一劑

	INCI Name	Cas No.	w/w%	功能
1	Aqua	7732-18-5	55.0	溶劑
2	Alcohol	64-17-5	30.0	溶劑
3	Polysorbate 80	9005-65-6	5.0	界面活性劑-乳化
4	Dimethicone	63148-62-9 / 9006-65-9 / 9016-00-6	3.0	皮膚調理-潤膚
5	Ammonia (28% Solution)	7664-41-7	2.0	鹼劑
6	p-Phenylenediamine	106-50-3	2.0	染髮劑
7	Resorcinol	108-46-3	1.0	染髮劑
8	Ammonium Laureth Sulfate	32612-48-9 / 67762-19-0	1.0	界面活性劑
9	Sodium Bisulfite	7631-90-5	0.5	抗氧化劑
10	m-Aminophenol	591-27-5	0.3	染髮劑
11	Disodium EDTA	6381-92-6	0.1	螯合劑
12	Fragrance*		0.1	香精
Total			100.0	

第二劑

	INCI Name	Cas No.	w/w%	功能
1	Aqua	7732-18-5	84.5	溶劑
2	Hydrogen Peroxide (28% Solution)	7722-84-1	10.0	氧化劑
3	Glycerin	56-81-5	4.0	保濕劑
4	Urea	57-13-6	1.0	保濕劑
5	Fragrance*		0.5	香精
Total			100.0	

*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 第一劑(正反面)	 
內包裝/容器 第二劑 (正反面)	 

外盒	
標籤/仿單	內容物：玩色染髮-瞬時棕染髮劑(第一劑、第二劑)、拋棄式手套、梳子。 品名：玩色染髮-瞬時棕(第一劑、第二劑) 用途：染髮 用法： (1)染髮前：請先將頭髮洗淨擦拭，濕度呈半乾燥狀態。 (2)戴上拋棄式手套，將第一劑及第二劑等比例混合攪拌均勻。 (3)使用梳子沾取混合後玩色染髮-瞬時棕染髮劑均勻塗抹於髮絲上，直到玩色染髮-瞬時棕染髮劑覆蓋所有頭髮。 (4)等待 30~40 分鐘，建議不超過 60 分鐘。(靜置時間越久可能導致髮色呈深黑色)將剩餘玩色染髮-瞬時棕染髮劑建議丟棄，混合後染髮劑放置過久會失去染髮作用。 (5)靜置時間完成後，請徹底將頭髮上玩色染髮-瞬時棕染髮劑沖洗乾淨，並將髮絲吹整至乾燥。 (6)染髮後髮色會因為個人髮色與髮質有所不同。 保存方法：避免高溫及日光直射，置於孩童伸手不及之場所。 使用注意事項：染髮劑使用前、染髮操作、避免使用染髮劑對象、儲放注意事項請詳見外盒標示，並依據使用方法正確使用。 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 製造日期及保存期限： 製造日期：2021.07.05、保存期限：2024.07.04。 批號：P018AUG 容量： 第一劑 40 mL / 第二劑 40 mL 全成分-第一劑： 特定用途成分：

	Ammonia(28% Solution)...2.0%、p-Phenylenediamine...2.0%、Resorcinol...1.0%、m-Aminophenol...0.3% 其他成分：Aqua、Alcohol、Polysorbate 80、Dimethicone、Ammonium Laureth Sulfate、Sodium Bisulfite、Disodium EDTA、Fragrance 全成分-第二劑： 特定用途成分：Hydrogen Peroxide (28% Solution)...10.0%、Urea...1.0% 其他成分：Aqua、Glycerin、Fragrance 染髮安全事項: 一、使用染髮劑前應注意下列事項： (一) 使用前請詳閱說明書，並依據使用方法正確使用。 (二) 染髮劑可能引起過敏反應。 (三) 不得使用於眉毛、睫毛等頭髮以外之部位。 (四) 剛修臉或剃臉後，應避免使用染髮劑。 (五) 同時混合使用不同廠牌之染髮劑，可能易造成傷害。 (六) 染髮一星期前後不建議進行燙髮。 二、染髮操作之注意事項： (一) 染髮操作時應戴手套。 (二) 建議使用前諮詢皮膚科醫師或進行皮膚過敏試驗。 (三) 應避免染髮劑接觸臉部或頸部。若不慎接觸臉部或頸部，應立即沖洗。 (四) 應避免染髮劑於操作及沖洗時接觸眼睛。若不慎接觸眼睛，應立即以大量清水沖洗，並迅速就醫。 (五) 染髮後若皮膚有任何異常現象，應迅速就醫。 三、下列情況者應避免使用： (一) 因使用染髮劑(不限本產品)，曾引發過敏反應或身體不適等症狀者。 (二) 經皮膚過敏試驗後，呈異常者。 (三) 頭、頸、臉部有腫脹、受傷或皮膚疾病者。 (四) 頭皮或皮膚呈現過敏、發炎狀態或其他身體狀況(患病、病後恢復、生理期及懷孕期間等)。 (五) 腎臟疾患或血液疾病之患者。 四、儲放注意事項： (一) 本產品應放置於孩童伸手不及之場所儲存。 (二) 儲放場所應避免高溫及日光直射。

(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：

製造廠（場所）地址：

核定劑型及作業項目：

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)

符合化粧品優良製造準則聲明書(範例)

符合化粧品優良製造準則聲明書

Declaration of Conformity

本業者／本人(製造或輸入)之化粧品符合中華民國之化粧品優良製造準則，產品資料如下：

I hereby declare that the products described below manufactured in conformity with Cosmetic Good Manufacturing Practice

一、製造廠名稱：

Manufacturer's Name

二、製造廠地址：

Manufacturer's Address

三、產品劑型：

Product forms

四、作業項目：

The process of operations

以上聲明書所保證之內容，如有造假不實或違背相關法規等情事，本業者／本人願自行負擔法律上一切責任。

Where violations of this declaration occur, I agree to take the legal responsibilities.

立聲明書人：　　(Signature)

Applicant

負責人/代表人：　　(Signature)

Person in charge

統一編號或身分證字號：

Company Tax ID No. / ID Number

地址：

Address:

申請廠商蓋公司章

負責人或代表人章

中 華 民 國　　年　　月　　日

Date　　year　　month　　day

(6) 製造方法、流程

第一劑

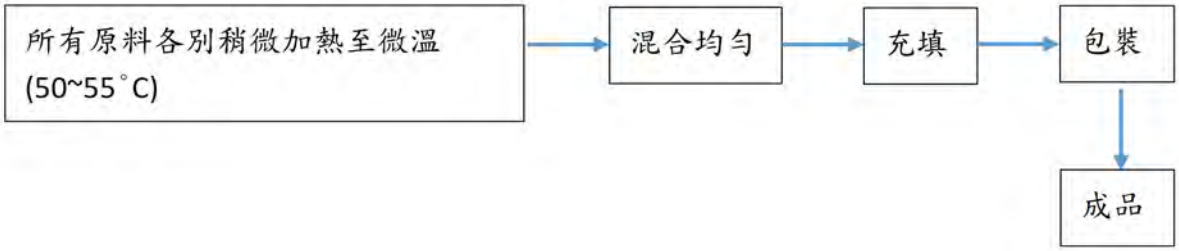
INCI Name	w/w%
Aqua	55.0
Alcohol	30.0
Polysorbate 80	5.0
Dimethicone	3.0
Ammonia (28% Solution)	2.0
p-Phenylenediamine	2.0
Resorcinol	1.0
Ammonium Laureth Sulfate	1.0
Sodium Bisulfite	0.5
m-Aminophenol	0.3
Disodium EDTA	0.1
Fragrance	0.1

製程簡述：

1. 將所有原料各別稍微加熱至微溫(50~55°C)。
2. 確認混合均勻即可。

注意事項：染料中間體的添加溫度一般控制在 50~55°C，以防發生自動氧化，且配製時應盡量避免與空氣接觸。

製程流程圖：



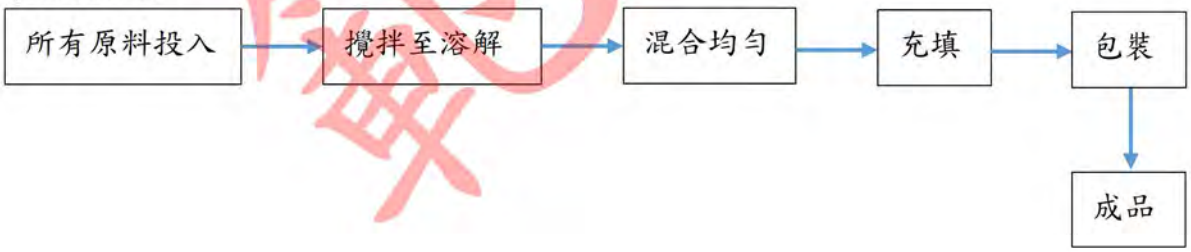
第二劑

INCI Name	w/w%
Aqua	84.5
Hydrogen Peroxide (28% Solution)	10.0
Glycerin	4.0
Urea	1.0
Fragrance	0.5

製程簡述：

1. 將所有原料投入料桶，攪拌至完全溶解。
2. 確認混合均勻即可。

製程流程圖：



(7) 使用方法、部位、用量、頻率及族群

使用方法：

(1)染髮前：請先將頭髮洗淨擦拭，濕度呈半乾燥狀態。

(2)戴上拋棄式手套，將第一劑及第二劑等比例混合攪拌均勻。

(3)使用梳子沾取混合後染髮劑均勻塗抹於髮絲上，直到染髮劑覆蓋所有頭髮。

(4)等待 30~40 分鐘，建議不超過 60 分鐘。(靜置時間越久可能導致髮色呈深黑色)將剩餘染髮劑建議丟棄，混合後染髮劑放置過久會失去染髮作用。

(5)靜置時間完成後，請徹底將頭髮上染髮劑沖洗乾淨，並將髮絲吹整至乾燥。

(6)染髮後髮色會因為個人髮色與髮質有所不同。

使用部位：頭髮。

用量：每次染髮使用第一劑 40 mL、使用第二劑 40 mL。

使用族群：適用於頭髮及頭皮無受損之成年人。

使用頻率：每 3 個月 1 次 (每次染髮至少間隔 3 個月) 。

(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立即更新於本產品資訊檔案，並及時提供給安全資料簽署人員。

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

第一劑

第一劑 成品 CoA			
檢測項目	規格	實際檢驗結果	檢驗方法
外觀	乳霜狀	乳霜狀	目視
顏色	淡黃色~黃色	淡黃色~黃色	目視
氣味	添加香精	具香氣	嗅覺
pH	9.5 ± 0.5	10.00	使用已校正之 pH meter 依 pH meter 檢測方法測定
黏度	7000 ~9000 mPas	8100 mPas	使用已校正之黏度計依黏度計檢測方法測定
密度	1.15 ± 0.05 g/cm^3	1.1 g/cm^3	定量杯
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)	

第二劑

第二劑 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	白色不透明	白色不透明	目視
氣味	添加香精	具香氣	嗅覺
pH	4.0 ± 0.5	3.85	使用已校正之 pH meter 依 pH meter 檢測方法測定
密度	1.05 ± 0.05 g/cm^3	1.02 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； 綠膿桿菌 陰性； 金黃色葡萄球菌 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 公布建議檢驗方法-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	6.0~8.5	7.15	使用已校正之線上(on line) pH meter 測定
導電度	<20 µS/cm	16.9 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：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：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：Dimethicone

Certificate of Analysis

(Representative Sample Certificate)

Product Name: Cyclo-Dimethicone
INCI Name: Cyclomethicone, Dimethicone
CAS Number: 9006-65-9, 541-02-6 & 69430-24-6

Expiration Date: 24 months from production date

Property	Specification	Analysis
Appearance	Clear, Viscous Liquid	PASS
Viscosity cps @22°C X9590	5000-10000 CPS	9600 CPS
Specific Gravity @ 22°C	0.95-0.97	0.956
Refractive Index @ 22°C	1.350-1.450	1.399
% Non-Volatiles	13.0-18.0%	16.5%

INCI name：Ammonia (28% Solution)

Product Name: **AMMONIA 28% Solution AR**

Alternate Name(s) Ammonium hydroxide; aqua ammonia; ammonium hydrate.

Description

Solution in water of flammable, toxic gas with a pungent odour. Suffocating smell. Extremely dangerous to the eyes.

Properties

Chemical Formula:

Molecular Weight: 35.05

General Information:

Corrosive to Cu, Ni, Zn & Sn and their alloys such as brass.

Product Code: AA005

CAS No.: 1336-21-6

Hazard and Safety Data

UN Group:	III
Class:	8
UN Number:	2672
Hazchem code:	2R
CS MSDS Code:	1CH0U
Poison schedule:	S6
Emergency Procedure Guide No.:	37

Quality Specification

Typical Assay: 28.0 - 30.0 % w/w

Specific Properties and Impurities [Typical levels]:

Appearance	Passes test
Residue after ignition	≤ 0.002%
Carbon dioxide (CO2)	≤ 0.002%
Chloride (Cl)	≤ 0.00005%
Nitrate (NO3)	≤ 0.0002%
Phosphate (PO4)	≤ 0.0002%
Sulfate (SO4)	≤ 0.0002%
Heavy metals (as Pb)	≤ 0.00005%
Substances reducing permanganate	Passes test
Aluminium (Al)	≤ 0.0001%
Barium (Ba)	≤ 0.00001%
Boron (B)	≤ 0.00002%
Cadmium (Cd)	≤ 0.000005%
Calcium (Ca)	≤ 0.0001%
Chromium (Cr)	≤ 0.000002%
Cobalt (Co)	≤ 0.000002%
Copper (Cu)	≤ 0.000002%
Iron (Fe)	≤ 0.00005%
Lead (Pb)	≤ 0.000005%
Lithium (Li)	≤ 0.000002%
Magnesium (Mg)	≤ 0.0001%
Manganese (Mn)	≤ 0.000002%
Molybdenum (Mo)	≤ 0.000002%

INCI name：p-Phenylenediamine

Chemical Name	p-Phenylenediamine
CAS No.	106-50-3
Molecular Formula:	C6H8N2
Molecular Weight:	108.14
EINECS:	203-404-7

Boiling point	267 °C(lit.)
Storage temp.	2-8°C
Density	1.135 g/cm3 (20°C)

p-Phenylenediamine 為強皮膚致敏劑，純度相關 COA

10.5 Impurities

ORTHO-PHENYLENEDIAMINE (1,2-DIAMINOBENZENE) CONTENT, 0.1% MAXIMUM; AND IRON CONTENT, 50 MG/KG MAXIMUM.

IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). Available at: https://monographs.iarc.fr/ENG/Classification/index.php, p. V16 126 (1978)

▸ Hazardous Substances Data Bank (HSDB)

10.6 Formulations/Preparations

ONE TECHNICAL GRADE OF PARA-PHENYLENEDIAMINE AVAILABLE IN THE USA HAS THE FOLLOWING SPECIFICATIONS: PURITY, 99.2% MINIMUM; MOISTURE CONTENT, 0.1% MAXIMUM; ORTHO-PHENYLENEDIAMINE (1,2-DIAMINOBENZENE) CONTENT, 0.1% MAXIMUM; AND IRON CONTENT, 50 MG/KG MAXIMUM.

IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). Available at: https://monographs.iarc.fr/ENG/Classification/index.php, p. V16 126 (1978)

▸ Hazardous Substances Data Bank (HSDB)

INCI name：Resorcinol

Product Name:	Resorcinol
Catalog Number:	BCN5881
Batch Number:	KLKH12b01

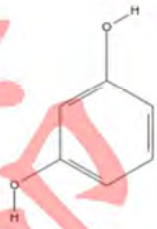
1. PHYSICAL AND CHEMICAL PROPERTIES

Molecular Formula:	C6H6O2
Molecular Weight:	110.1
Purity:	>98%
Cas Number:	108-46-3
Physical Description:	White powder

2. ANALYTICAL DATA

HPLC:	Shows >98% purity
NMR:	Consistent with structure

3. CHEMICAL STRUCTURE

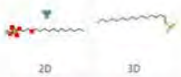


4. USAGE GUIDE

Storage:	Store the product in sealed, cool and dry condition.
General tips:	For obtaining a higher solubility, please warm the tube at 37 degrees Celsius (98.6 degrees Fahrenheit) and shake it in the ultrasonic bath for a while.

INCI name：Ammonium Laureth Sulfate

Ammonium lauryl ether sulfate

PubChem CID	61913
Structure	 2D 3D Find Similar Structures
Chemical Safety	 Corrosive Irritant Laboratory Chemical Safety Summary (LCSS) Datasheet
Molecular Formula	$C_{14}H_{33}NO_5S$
Synonyms	Ammonium lauryl ether sulfate Ammonium laureth sulfate 32612-48-9 azane;2-dodecoxyethyl hydrogen sulfate Ammonium laureth-5 sulfate More...
Molecular Weight	327.48
Parent Compound	CID 24761 (2-Dodecoxyethyl hydrogen sulfate)
Component Compounds	CID 222 (Ammonia) CID 24761 (2-Dodecoxyethyl hydrogen sulfate)
Dates	Modify 2021-10-30 Create 2005-08-08

3.1 Computed Properties

Property Name	Property Value	Reference
Molecular Weight	327.48	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Hydrogen Bond Donor Count	2	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Hydrogen Bond Acceptor Count	6	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Rotatable Bond Count	15	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Exact Mass	327.20794433	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Monoisotopic Mass	327.20794433	Computed by PubChem 2.1 (PubChem release 2021.05.07)
Topological Polar Surface Area	82.2 $Å^2$	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Heavy Atom Count	21	Computed by PubChem
Formal Charge	0	Computed by PubChem
Complexity	284	Computed by Cactvs 3.4.8.18 (PubChem release 2021.05.07)
Isotope Atom Count	0	Computed by PubChem
Defined Atom Stereocenter Count	0	Computed by PubChem
Undefined Atom Stereocenter Count	0	Computed by PubChem
Defined Bond Stereocenter Count	0	Computed by PubChem
Undefined Bond Stereocenter Count	0	Computed by PubChem
Covalently-Bonded Unit Count	2	Computed by PubChem
Compound Is Canonicalized	Yes	Computed by PubChem (release 2021.05.07)

INCI name：Sodium Bisulfite

Product Specification

Product Name:
Sodium bisulfite - ACS reagent

$NaHSO_3$

Formula:	NaHSO3
Formula Weight:	104.06 g/mol

TEST	Specification
Appearance (Color)	White
Appearance (Form)	Powder or Crystals
Infrared spectrum	Conforms to Structure
Titration by Na2S2O3	≥ 58.5 %
% SO2	
Insoluble matter	≤ 0.005 %
Chloride Content	≤ 0.02 %
Heavy Metal	≤ 0.001 %
As Lead	
Iron (Fe)	≤ 0.002 %
Meets ACS Requirements	Current ACS Specification

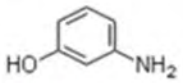
INCI name：m-Aminophenol

TECHNICAL DATA SHEET

Product: ***m-Aminophenol***

CAS No.: 591-27-5

Molecular structure:



Molecular formula: C6H7NO

Molecular weight: 109.13

Specifications:

Purity	*99% Min.*
Moisture	*0.5% Max.*
Ash	*0.1% Max.*
Melting Point	*119℃-123℃*

Application:

Intermediate of dye and pharmaceutical, used to produce antitubercular drug, p-amino salicylic acid, stabilizer, developer, etc.

Storage:

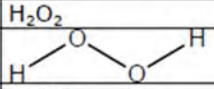
Keep container tightly closed in a dry, cool and well-ventilated place.

INCI name：Disodium EDTA

Product name: **Disodium edetate**

Tests	Requirement	Result	Unit	Standard remark
Appearance	White or almost white, crystalline powder	Conform		
Identification A	Conform	Conform		IR-spectrum
Identification B	No precipitate	Conform		
Identification D	Conform	Conform		Sodium
Appearance of solution	Clear and colourless	Conform		5%m/V H2O
pH	4,0 - 5,5	5,0		5%m/V H2O
Impurity A	<= 0,1	Conform	%	HPLC
Iron	<= 80	Conform	ppm	
Heavy metals	<= 20	Conform	ppm	
Assay Disodium edetate dihydrate	98,5 - 101,0	99,7	%m/m	
Microbial contamination	Conform	Conform		
Total Aerobic Microbial Count (TAMC)	<= 10	< 1	CFU/g	
Total Yeasts and Moulds Count (TYMC)	<= 1	< 1	CFU/g	
Residual solvents	CPMP/ICH/283/95	Conform		DP
TSE/BSE-statement	No contamination with TSE/BSE-risk materials	Conform		DP

INCI name：Hydrogen Peroxide (28% Solution)

CAS-No.	7722-84-1
EINECS-No.	231-765-0
Other No. (CIPAC, ELINCS)	None
IUPAC Name	Hydrogen peroxide
Common name, synonyma	Dihydrogen dioxide, hydrogen dioxide, hydrogen peroxide
Molecular formula	H_2O_2
Structural formula	
Molecular weight (g/mol)	34.01

Subsection	Method	Purity[a])	Results
Melting point	Thermal analysis (freezing temperature)	100%	-0.40 – -0.43°C
Boiling point	Extrapolation of H_2O_2/H_2O vapour pressure composition curves	100%	150.2°C at 101.3 kPa
Bulk density/ relative density	Measurements	100%	1.44 g/cm^3 liquid at 25°C 1.71 g/cm^3 solid at –20°C

Vapour pressure	Extrapolation from the measured H_2O_2/H_2O vapour pressure curve	100%	214 Pa, at 20°C (293 K) : 299 Pa, at 25°C (298 K) :
Solubility in water		100%	miscible in water in all proportions
Henry´s Law Constant H	Measurement; equilibrium gas-phase	100%	$7.5*10^{-4}$ Pa*m^3/mol at 20°C
Dissociation constant	Measurement	100%	K_a= 2.4 * 10^{-12} at 25°C pKa: 11.62
Surface tension	Capillary rise method	100%	result: 83.3 mN/m at 0°C result: 80.4 mN/m at 20°C
Partition coefficient n-octanol/water	Calculation	100%	log Kow = -1.57
Viscosity	Measured	100%	1.249 mPa*s at 20°C

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：Urea

CERTIFICATE OF ANALYSIS

Name of Product : Urea AR

CAS No. : 57-13-6

TESTS	RESULTS	PRESCRIBED
DESCRIPTION	Complies	White crystals or crystalline powder.
CLARITY	Complies	Solution of 5 g in 50 ml of water is clear and colourless.
GUARANTEE ANALYSIS		
ASSAY	99.48%	NLT 99.5 %
MELTING RANGE	132.0 - 133.0°C	132.0 - 133.0°C
MAXIMUM LIMITS OF IMPURITIES		
BIURET	< 0.05%	0.05%
SULPHATE(SO_4)	< 0.001%	0.001%
ACIDITY	0.00064%	0.002%
ALKALINITY	Not detected	0.002%
WATER INSOLUBLE MATTER	0.001%	0.003%
SULPHATED ASH	0.00084%	0.005%
IRON(Fe)	< 0.0001%	0.0001%
HEAVY METALS (as Pb)	< 0.0002%	0.0002%
CHLORIDE(Cl)	< 0.0005%	0.0005%

(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之各個成分毒理資料，另存放於玩色染髮-瞬時棕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：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 1000 cm^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 等人(2001)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/生化變化較小。雌性大鼠的生化變化較小，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.

2. 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 中的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]

- 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 進行的亞慢性研究(NTP, 1992a)顯示，NOAEL 相當於 4500mg/kg bw/day。在大鼠膳食亞慢性研究(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畸形的差異。[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]
- 細胞/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，對照均達到預期的結果。[1]
- 皮膚刺激性：在人體刺激性研究中，乙氧基化的聚山梨酯 60 (100%)，Polysorbate 80 (100%)和脫水山梨糖醇單硬脂酸酯(25%)對皮膚無刺激性。[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

3. INCI name：Dimethicone

◆ 經皮吸收：在一項皮膚滲透研究中，試圖確定二甲基矽油(Dimethicone)是否與角質層脂質微結構相互作用。從一名健康的 50 歲女性的大腿內側和一名健康的 26 歲男性腹部獲得切除的人角質層組織樣本。含有角質層脂肪酸的體外模型脂質系統也用於模擬皮膚屏障。這些組織樣品用 0.001% m/m 胰蛋白酶抑制劑沖洗，並在室溫、76%濕度下儲存 48 小時，以達到大約 20%的水合水平。然後將水合樣品在不同粘度的過量聚二甲基矽氧烷(332.5、475、950 或 19000 kg/m·s)中在 37 °C 下處理 20 分鐘，取出纖維素組織，並使用熱剖面、x-射線衍射、偏光顯微鏡和透射電子顯微鏡分析變化。所

有結果顯示二甲基矽油不會干擾或與表皮上層結構相互作用，因此不太可能穿透皮膚屏障。[1]

- 毒理動力學：在狗、大鼠和猴子中進行的幾項急性毒理動力學研究報告指出，Dimethicone 的胃腸道吸收極少，通過排泄可恢復高達99.99%的給藥劑量。在重複劑量研究中，比格犬以 300 mg/kg bw/day 的劑量餵食 91% Dimethicone，持續 120 天。雖然一隻雌性出現脾臟萎縮，另一隻雌性在胃附近有輕微發紅的皺襞和腸道黏液，但在任何器官中均未檢測到 Dimethicone。在人體研究中，在攝入含有低分子量聚合物的 Dimethicone 樣品後，在人體中觀察到吸收現象。男性背部皮膚暴露於 Dimethicone 10 天，不會增加血液或尿液中的矽酮濃度。[1]
- 急性毒性：5 隻雄性和 5 隻雌性 Sprague-Dawley 大鼠透過管飼法在玉米油中以 2000 mg/kg bw 的單劑量二甲基矽油(57000 kg/m·s)給藥。在給藥後 14 天的觀察期內沒有觀察到明顯的全身毒性跡象，所有大鼠體重均增加，研究期間無動物死亡，且未觀察到大體屍檢病變。雄性和雌性大鼠中 Dimethicone 的急性口服 LD_{50} 為> 2000 mg/kg bw。在大鼠和兔子中，二甲聚矽氧烷的皮膚 LD_{50}>2000 mg/kg。[1]
- 皮膚刺激性：大多數使用兔子進行的皮膚刺激性研究都將 Dimethicone 列為最低刺激性。根據 Draize 量表對反應進行評分的研究報告的主要刺激指數(Primary Irritation Index, PII)為≤2.8（測試樣品中含有 5%至 100%的 Dimethicone）。[1]
- 眼睛刺激性：大多數使用兔子的眼睛刺激研究將 Dimethicone 分類為輕度至中度刺激性，濃度範圍為 10%至 35%。最常見的發現是結膜刺激反應。[1]
- 皮膚致敏性：在使用小鼠和豚鼠的四種測定中，Dimethicone（未經稀釋測試，濃度為 79%）非屬致敏成分。在使用 83 位病患臨床 5.0% Dimethicone 人體反覆刺激斑貼試驗 (Human Repeat Insult Patch Test, HRIPT)中，結果同樣顯示它不易造成致敏。[1]
- 重複劑量毒性：三組 10 隻紐西蘭兔子（每種性別的數量未指定）透過封閉貼劑經皮給藥 4 週(28 天)，劑量為 0、100、300 或 1000 mg/kg bw /day。每天在施用前檢查兔子的皮膚刺激，並在去除貼劑前暴露於測試材料 6 小時。每週測量兩次體重，並在雄性第 29 天和雌性第 30 天採集血液樣本進行血液學和血液化學評估。沒有發

生與試驗相關的死亡或不良事件，體重、血液學、血液化學以及選定器官的大體和微觀評估顯示沒有被認為具有毒理學意義的變化。因此，本研究中家兔皮膚施用 Dimethicone 的 NOAEL 被認為是 1000 mg/kg bw/day。四組 30 隻雄性 Fischer 344 大鼠和四組 30 隻雌性 Fischer 344 大鼠在飲食中以 0(對照)、100、300 或 1000 mg/kg bw /day 的劑量施用 Dimethicone (10 cm^2/sec)，分別為 12 個月。在給予 Dimethicone 12 個月後，將來自每個試驗組的四組 10 隻雄性和四組 10 隻雌性犧牲進行解剖檢查。在 12 個月的試驗期後，觀察每個試驗組的四組 20 隻雄性大鼠和四組 20 隻雌性大鼠的慢性恢復，持續 12 個月。在大鼠解剖檢查中，與試驗品相關的毒理學作用僅限於雌性 300 mg/kg bw/day 組和雄性及雌性 1000 mg/kg bw/day 組眼部混濁的發生率增加。同樣，在慢性康復組中，所有接受試驗的雄性組的眼部混濁程度均增加，且無劑量相關性。角膜炎和角膜營養不良的顯微鏡檢查結果進一步支持了該結果。Dimethicone 的全身毒性的 NOAEL 為等於最高測試劑量 1000 mg/kg bw/day。[1]

- 致癌性：在使用小鼠進行的口服(測試濃度為 91%)和皮膚(測試濃度未知)劑量致癌性試驗中均為陰性。[1]
- 生殖毒性：在許多口服劑量(使用大鼠)和皮膚劑量(使用大鼠、兔子、猴子)的生殖和發育毒性研究中測試了 Dimethicone，及在一些研究中，接受治療的雄性體重顯著降低和/或睾丸、精囊重量降低。[1]
- 致突變性：在所有誘變分析中，Dimethicone 均為陰性。[1]
- 其他安全資料：2003 年， CIR 專家小組審查了 Dimethicone 以及主要用作皮膚和頭髮調理劑的相關矽聚合物的現有文獻和安全數據，並得出結論目前使用的 Dimethicone 是安全的。FDA 審查了 Dimethicone 的安全性，並批准其在非處方藥之藥物產品中用作皮膚保護劑，濃度為 1~30%。CIR 專家小組審查了一組矽聚合物結構、組成和用途相似的衍生物，包括 Dimethicone。專家小組認為，由於這些聚合物的分子量較大，任何有機矽聚合物都不太可能被皮膚大量吸收。特定於 Dimethicone 的人體臨床和實驗室吸收研究報告顯示，它在皮膚接觸後不會被吸收。實驗室研究支持單次或多次口服、皮膚或吸入暴露於 Dimethicone 的安全性。實驗室和人體臨床研究顯示 Dimethicone 不會刺激皮膚，也不會引起皮膚過敏反應(即非皮膚致敏物)。據報導，它對眼睛的刺激性也很小。在多項實驗室生殖和發育毒性研究中也顯示 Dimethicone 不會引起基因突變

（即無基因毒性）。在對小鼠進行的幾項歷史實驗室研究中，終生口服或在皮膚上施用 Dimethicone，沒有證據顯示腫瘤發生率增加（即不致癌）。評估所有可用的科學數據，CIR 得出結論，Dimethicone（和其他相關的矽聚合物）目前用於化粧品和個人護理產品中是安全的。[2]

- 參考資料：

1. Amended Safety Assessment of Dimethicone, Methicone, and Substituted-Methicone Polymers as Used in Cosmetics. CIR, 2021.
2. Cosmetics Info 網站：
   https://cosmeticsinfo.org/ingredient/dimethicone

4. INCI name：Ammonia

- 不純物：根據美國藥典的規定，強氨溶液的限制包括，重金屬限度為 0.0013%、不揮發殘留物不超過 5 mg (0.05%)和易氧化的物質在 10 分鐘內不能沒有完全消失。[1]
- 毒理動力學：氨(Ammonia)是氨基酸代謝的主要副產物，肝臟是代謝 Ammonia 的主要器官。它是由腸道中的含氮物質分解以及在小腸中使用谷氨酰胺作為新陳代謝的燃料而產生的，並被肝臟吸收，在肝臟中通過轉化為尿素和較小程度的谷氨酰胺而被解毒。大量代謝產生的 Ammonia 被吸收到腸道中及血液，並通過門靜脈被肝臟排毒。由於氨具有劇毒，因此會在許多組織中轉化為谷氨酰胺和丙氨酸，以運輸到肝臟。然後，Ammonia 通過肝臟中的尿素循環轉化為尿素，尿素從尿中排出。有證據顯示氨可以穿過血腦屏障 (Blood-Brain Barrier, BBB)，主要是通過離子轉運蛋白，而不是經由氣態氨的被動擴散。[1]
- 急性毒性：已發表的文獻中未發現 Ammonia 的急性經皮毒性研究，也未有相關數據。在單次口服動物實驗中，對氨氣沒有影響或沒有嚴重影響。但是，當透過管飼法(33.3 mg/kg）向大鼠施用 0.3%的氨水時，在 5 分鐘內觀察到胃粘膜損傷。據研究顯示，大鼠對氫氧化銨的急性口服 LD_{50} 為 350 mg/kg，透過管飼法向大鼠口服 1%或 3%氫氧化銨（w/w）會產生嚴重的出血性病變。
- 重複劑量毒性：在接受飲用水中添加 0.01% Ammonia 大鼠試驗 8 週中，觀察到胃竇的粘膜萎縮以及胃竇和身體的粘膜增生區擴大，

磷酸二銨的一般毒性的 NOAEL 為 250 mg/kg bw/day。在大鼠口服 5 週試驗中一般毒性的 LOAEL 為 750 mg/kg bw/day。[1]

- 皮膚致敏性：在公開的文獻中未找到關於 Ammonia 的皮膚致敏性數據。[1]
- 眼睛刺激性：據研究顯示氨可以迅速滲透到眼睛中，並且在低至 20 ppm 的濃度下會引起眼睛刺激或損害。[1]
- 致突變性/遺傳毒性：在沒有代謝激活的體外測定中，Ammonia 對大腸桿菌 Sd-4-73 株無遺傳毒性。[1]
- 致癌性：當 10 隻小鼠反覆吸入接觸 12% Ammonia 蒸氣 8 週時，2 隻小鼠觀察到鼻粘膜癌。小鼠口服氨(溶解於水；42 mg/kg bw/day) 4 週後，沒有致癌性的證據。小鼠(Swiss 和 C3H)以氨 193 mg/kg bw/day 的劑量口服服藥 2 年後，沒有致癌性的證據，也沒有對乳腺腺癌(與 C3H 小鼠品係有關)的自然發展產生影響。[1]
- 生殖毒性：在一項生殖毒性研究中，從懷孕第 1 天到哺乳第 21 天，妊娠大鼠中飲食中暴露於 293 mg/kg bw/dayAmmonia，後代的雄性體重降低 25%和雌性體重降低 16%。在繁殖前 6 週到妊娠第 30 天，母豬吸入暴露於～7 ppm 或～35 ppm 的 Ammonia 中，此研究沒有發現生殖或發育毒性。在涉及大鼠的磷酸二銨的生殖和發育毒性研究中，據研究結果顯示 NOAEL 為 1500 mg/kg bw/day，LOAEL 為 >1500 mg/kg bw/day。[1]
- 人體數據：對於 Ammonia 來說"急性"吸入(14 天或更短)吸入的最低風險水平(Minimum Risk Level, MRL)為 1.7 ppm。該研究涉及 16 位暴露於氨氣(50 ppm、80 ppm、110 ppm 或 140 ppm)的受試者。MRL 基於 50 ppm LOAEL，暴露於氨氣中 2 小時的受試者中有 6 名受試者眼睛產生輕微刺激，有 20 名受試者鼻子產生輕微刺激和有 9 名受試者喉嚨產生輕微刺激。一名工作了 18 年的 68 歲男性患者，在工作中經常暴露於縮微膠卷相機的無水氨洩漏，他因吸入氨觀察到整個肺部明顯的瀰漫性間質纖維化，被診斷為間質性肺病和嚴重的限制性肺病。[1]
- 其他安全資料：Ammonia 是一種氣體，當溶解在水中時，氨形成氫氧化銨(H_5NO)。氨和氫氧化銨用於多種產品，包括染髮劑、頭髮脫色產品、剃鬚膏和美髮產品。Ammonia 被列入歐盟化粧品指令，允許以最高濃度 6% Ammonia 使用限量，且如果添加濃度高於 2%，則必須標明含有 Ammonia。[2]

◆ 參考資料：

1. Safety Assessment of Ammonia and Ammonium Hydroxide as Used in Cosmetics. CIR, 2017.
2. Cosmetics Info 網站：
https://cosmeticsinfo.org/ingredient/ammonia

5. INCI name：p-Phenylenediamine

◆ 急性毒性：在口服、皮下、腹膜內和局部使用，對多種物種進行了急性毒性研究後，得到試驗結果：大鼠口服後的 LD_{50} 為 80~100 mg/kg bw，小鼠 290 mg/kg bw，兔子 250 mg/kg bw 和貓 100 mg/kg bw。皮下施用後，大鼠、兔子和狗的 LD_{50} 值分別為 170、200 和 100 mg/kg bw，物種之間存在一些差異。有幾篇關於人為故意或意外的對苯二胺(p-Phenylenediamine, PPD)中毒的報導，但尚無攝入量的詳細資訊，報告的症狀包括聲門水腫和急性腎功能衰竭。[1]

◆ 皮膚刺激性/眼睛刺激性：將含有 0.05%亞硫酸鈉(Sodium Sulfite)的 2.5% PPD 水溶液施用於被紗布覆蓋的磨損或完整的兔子皮膚時，具有中度刺激性。在 Draize 兔子眼睛刺激性測試中，主要刺激指數估計為 0.3。當在 2.5%的水溶液中使用時，PPD 對皮膚和眼睛沒有刺激性或腐蝕性。[1]

◆ 皮膚致敏性：高濃度 PPD 濃度使用於預測性致敏性測試，實驗動物豚鼠和小鼠 100%致敏。通過計算引起刺激指數 3 (EC3 值)所需的化學物質濃度，可以在小鼠局部淋巴結試驗(Local Lymph Node Assay, LLNA)中估計相對的皮膚致敏能力。在兩個實驗室進行了多次測試，以評估實驗室內和實驗室間的差異，PPD 的 EC3 值在 0.06%和 0.20%之間。局部淋巴結試驗(LLNA)結論是，受試物質 PPD 在小鼠中是一種極強的皮膚致敏劑。[1]

◆ 經皮吸收：皮膚滲透在施用劑量的 0.1%至 0.2%之間。對於整個染料配方，這相當於吸收的累積值約為 1.9~2.4 μg/cm²。對於所有製劑，PPD 的最大累積吸收發生在施用後 4 小時，之後由於 30 分鐘的水沖洗除去 PPD 而使滲透減慢。體外研究中的累積吸收值約 1.9~2.4 μg /cm² 和體內研究中的累積吸收值約 4.5 μg /cm²。[1]

◆ 重複劑量毒性：對來自 Crl：CD (SD) BR 品系(VAF plus)的 5 組 20 隻大鼠（10 隻雄性和 10 隻雌性）進行了為期 14 天的研究。動物每天接受以 5、10、20 和 40 mg/kg bw/day(游離鹼)的劑量溶解在去離

子水測試物。對照組動物僅施予安慰劑。所有劑量均以相同體積 10 ml/kg bw 給予。給予 40 mg/kg bw/day 的雄性平均肝臟和相對體重增加，給予 10 mg/kg bw/day 或更高的雌性平均甲狀腺相對重量增加。在所採用的實驗條件下，NOAEL <5 mg/kg bw/day。根據 OECD 408（1981 年），對 150 隻 Crl：CD (SD) BR 大鼠（5 組，每隻雌性 15 隻動物）進行了為期 13 週的研究。PPD 透過飼餵食法以 2、4、8 和 16 mg/kg bw/day 的相應劑量水平給藥，而對照組僅接受去離子水。所有劑量均以相同的 10 mL/kg bw 體積施用。根據這些結果，將 PPD 的 NOAEL 設定為 4 mg/kg bw/day。歐盟消費者安全科學委員會(Scientific Committee on Consumer Safety, SCCS)對觀察到的腎臟和肝臟作用的判斷，並且在 90 天的毒性研究中，對於這些作用，可以將 4 mg/kg bw/day 視為 NOEL 而不是 NOAEL。因此，SCCS 將 PPD 亞慢性毒性的 NOAEL 視為 8 mg/kg bw/day，對於皮膚表面積為 580 cm^2 作為安全邊際值(Margin of Safety, MoS)計算。[1,3]

- 致突變性/遺傳毒性：在實驗條件下，細菌的基因突變試驗中，使用的 PPD 不具遺傳毒性/致突變性。[1]
- 致癌性：非致癌性。[1]
- 生殖毒性：將含有 3% PPD 和等量過氧化氫溶液混合的染髮劑配方每週兩次，在交配前 4 週以及整個交配和妊娠過程中局部施用於雌性大鼠，研究結果沒有觀察到母體毒性或致畸胎作用的證據。[1]
- 毒理代謝動力學：對大鼠局部給藥後人體皮膚和血漿分析的代謝研究結果顯示，局部施用的 PPD 在人和動物皮膚中轉化為 N-單-或 N, N'-二乙酰化代謝物(分別為 MAPPD 和 DAPPD)。[1]
- 人體數據：在東非和印度偶然有意外攝入染髮劑的情況。主要成分是 PPD，已知會引起血管神經性水腫、橫紋肌溶解和腎衰竭，也有致命的心肌炎病例報告。PPD 是一種已知的極端皮膚致敏劑，除在德國以外，對歐洲濕疹患者診斷皮膚 Patch test)的基線系列已將其包括在內，在德國，使用常規診斷 Patch test 進行主動致敏試驗，PPD 被認為是不可接受的高致敏風險。對染髮劑中 PPD 的立即致敏反應的頻率未知，但是與所使用含有 PPD 的染髮劑相比，劇烈的反應似乎很少見。[1]
- 其他安全資料：CIR 專家小組評估了科學數據並得出結論，PPD、對苯二胺鹽酸鹽和對苯二胺硫酸鹽作為染髮劑成分是安全的。PPD、對苯二胺鹽酸鹽、對苯二胺硫酸鹽和含有這些化合物的永久性染髮

劑的廣泛安全測試數據顯示，毒性程度隨濃度、測試系統和受試者而異，數據支持了這些化合物既不是發育毒物也不是致癌物的結論。流行病學數據不足以佐證染髮劑使用與癌症之間的因果關係。CIR 專家小組指出，PPD 及其鹽類是致敏劑，某些人在預期使用條件下可能會致敏。CIR 專家小組預計，遵循染髮劑產品的標籤說明將識別出有刺激和過敏反應的人，並讓他們避免大量接觸。對於對這種染髮劑成分不敏感的人，CIR 專家小組得出結論，PPD 及其鹽類可安全用於染髮產品。[4]

- 參考資料：

1. SCCS opinion on p-Phenylenediamine. COLIPA n°A7 SCCS/1443/11, 2012.
2. Provisional Peer-Reviewed Toxicity Values for p-Phenylenediamine. EPA, 2016.
3. Safety Assessment of p-Phenylenediamine, p-Phenylenediamine HC1, and p-Phenylenediamine Sulfate. CIR, 2007.
4. Cosmetics Info 網站：https://cosmeticsinfo.org/ingredient/p-phenylenediamine

6. INCI name：Resorcinol

- 毒理動力學：大鼠和兔子的毒理動力學研究顯示，口服間苯二酚(Resorcinol)主要以單葡萄醣醛酸結合物的形式迅速吸收、代謝和排泄到尿液中（2004a, EFSA 2010, Garton et al. 1949, Kim and Matthews 1987, Merker et al. 1982），次要代謝物包括單硫酸鹽結合物、混合硫酸鹽-葡萄醣醛酸結合物和二葡萄糖結合物。在大鼠 (Kim and Matthews 1987) 中，大部分口服 [^{14}C]- Resorcinol 在 24 小時內通過尿液排泄 (90.8~92.8%)，少量通過糞便排泄 (1.5 ~2.1%)。當[^{14}C]-Resorcinol 皮下或口服給藥於大鼠時，現有數據未顯示任何器官或組織中的蓄積，包括甲狀腺。[1]
- 皮膚吸收率：來自 8 名接受整形手術的女性捐贈者 4 個乳房和 4 個腹部人體皮膚樣本。在氧化條件下，Resorcinol 在與過氧化氫 (1:1, w/w)混合之前，將其以 2.50% (w/w)與 2.45% (w/w)的 PPD 結合到典型的染髮配方中，最終濃度為 1.25% (w/w)。在非氧化條件下，將其以 2.50% (w/w)加入不含初級中間體的相同配方中，然後與水(1:1, w/w)混合，最終濃度為 1.25% (w/w)。將 20 mg/cm^{2}的氧化性和非氧化性測試製劑施用於皮膚樣本表面 30 分鐘後，使用標準洗滌程序去除皮膚表面上的剩餘製劑。施用後 24 小時，Resorcinol 的

經皮吸收通過測量以下間隔的濃度來估計：可移動劑量、角質層(通過膠帶剝離)、皮膚(活表皮+真皮)和受體液。氧化條件下的皮膚遞送(活表皮、真皮和受體液中測得的量的總和)為 1.04±0.51 μg/cm²(範圍為 0.37~2.0 μg/cm²)；0.40±0.18 %(範圍 0.15~0.74%)。SCCS 認為由於在氧化條件下的實驗中可評估間隔太少，平均值+ 2 SD = 2.06 μg/cm² (1.04 + 2 x 0.51)將用於計算氧化條件下 Resorcinol 的 MoS。[1]

- 急性毒性： 5 隻雌性大鼠試驗中在單次口服管飼劑量為 500 mg/kg bw 後 1 隻死亡，另一隻在接受 2000 mg/kg bw 劑量後死亡。大鼠單次給藥後 Resorcinol 的最大非致死劑量為 200 mg/kg bw。[1]
- 皮膚刺激性：當將 2.5% Resorcinol 的水溶液塗在兔子皮膚上時，不會產生刺激性。[1]
- 眼睛刺激性：濃度為 2.5%的 Resorcinol 會引起兔眼睛輕度結膜刺激。Resorcinol 被分類為眼睛刺激 Category 2 (H319) 和皮膚刺激 Category 2。[1]
- 皮膚致敏性：Resorcinol 在小鼠局部淋巴結試驗(LLNA)中引起接觸致敏。根據 SCCS 使用的分級(SCCP/ 0919/05)，Resorcinol 應被視為強致敏劑。[1]
- 重複給藥毒性：在對 F344/N 大鼠和 B6C3F1 小鼠進行的為期 17 天口服毒性研究中，每週 5 天以 0、27.5、55、110、225 和 450 mg/kg bw/day 的劑量給予雄性和雌性大鼠（每種性別 5 隻動物/劑量），在雄性和雌性小鼠中按 0、37.5、75、150、300 和 600 mg/kg bw/day (每種性別 5 隻動物/劑量 SA) (2010 年)根據口服管飼後的短期急性效應得出以下 NOAEL：大鼠的 NOAEL 為 27.5 mg/kg bw/day，小鼠的 NOAEL 為 75 mg/kg bw/day。根據一項 CIT 研究中，四組 10 隻雄性和 10 隻雌性 Sprague-Dawley 大鼠每天透過管飼法以 0、40、80 或 250 mg/kg bw/day 接受測試項目至少 13 週，250 mg/kg bw/day 組的絕對和相對甲狀腺重量略有下降(分別為-19%和-13%)。 根據研究作者的說法，這些影響被認為沒有毒理學重要性(沒有劑量反應關係，也沒有相關的組織病理學異常)。然而，在 SCCS 看來，由於在生殖研究中也觀察到了對甲狀腺的一些影響，這些影響可能是相關的，SCCS 將 80 mg/kg bw/day 視為 NOAEL。[1]
- 致突變性：沒有致突變性。[1]
- 遺傳毒性：沒有遺傳毒性[1]
- 致癌性：非致癌物質。[1]

- 其他安全資料：2-甲基間苯二酚(2-methylresorcinol)和 Resorcinol 的安全性已經過化粧品成分審查(CIR)專家小組的評估。CIR 專家小組評估了科學數據並得出結論，2-methylresorcinol 和 Resorcinol 作為化粧品成分是安全的。2006 年，CIR 專家小組審議了有關 2-methylresorcinol 和 Resorcinol 的現有新數據，並重申了上述結論。CIR 專家小組根據審查數據表示，皮膚長期接觸 Resorcinol 和 2-methylresorcinol 後沒有影響。數據顯示，Resorcinol 和 2-甲基間苯二酚是溫和的皮膚刺激物和少有的致敏物。然而，在化粧品和個人護理產品中使用的濃度下，這些成分在對人類志願者進行測試時沒有發生刺激性、致敏性或光敏性。這些成分的致突變性和致癌性測試均為陰性。[2]
- 參考資料：

1. SCCS opinion on Resorcinol. SCCS/1619/20, 2021.
2. Cosmetics Info 網站：
   https://cosmeticsinfo.org/ingredient/resorcinol

7. INCI name：Ammonium Laureth Sulfate

- 急性毒性：據研究顯示在大鼠中口服 LD_{50} 範圍為 630 ~ > 2000 mg/kg bw (ChemID plus Advanced; CIR, 1983; Tusing, 1962; Walker AIT et al., 1967; HPV, 2006)。觀察到的亞致死效應包括腹瀉和抑制中樞神經系統。[2,3]
- 皮膚刺激性：在 CIR (1983)報告的研究中，該組中的大多數化學品在完整的兔子皮膚上進行了測試，濃度在 5~61%之間，不良反應從輕微到嚴重刺激不等，刺激的嚴重程度隨著濃度的增加而增加。在月桂醇聚醚硫酸銨的研究中，在 7.5~12%的濃度下觀察到輕度紅斑。在 12-61% 的濃度下觀察到中度至重度刺激且會在實驗動物中產生眼睛和/或皮膚刺激反應。[2,3]
- 眼睛刺激性：月桂醇聚醚硫酸銨在 7.5~20%的濃度下對眼睛有輕度刺激，在 25~60%的濃度下對眼睛有嚴重刺激反應。[2,3]
- 皮膚致敏性：非皮膚致敏物。[1]
- 重複給藥毒性：在一項為期 13 週的大鼠口服研究中，月桂醇聚醚硫酸鈉 NOAEL 為 1000 ppm。在 CIR(1983 年)研究報告中，大鼠(每組 12 隻雄性和 12 隻雌性)被餵食了 40、200、1000、5000 mg/kg

bw/day 的化學物質。屍檢時僅檢查了對照組和 5000 mg/kg bw/day。屍檢時沒有組織學或病理學變化的證據，雄性(腎臟)和雌性(心臟、肝臟和腎臟)的器官重量增加沒有統計學意義。在 CIR (1983) 的一項研究，一項為期 105 週的口服研究中，將月桂醇聚醚硫酸鈉以 0.1%和 0.5%的飲食濃度給予大鼠(每組 30 隻)。52 週後，處死每組 10 隻動物，105 週後處死剩餘的存活大鼠，與對照組相比，實驗動物的大體或微觀病理學沒有顯著差異。[2,3] 根據現有數據，認為 Ammonium lauryl sulfate 不會因反覆口服接觸而對健康造成嚴重損害。根據各種重複劑量毒性研究，可以確定 NOAEL 約為 100 mg/kg bw/day (OECD, 2007; NICNAS, 2007)。[3]

- 致突變性/遺傳毒性：體外致突變性試驗和體內染色體突變試驗皆為陰性。[1]
- 致癌性：非致癌性。[1]
- 生殖毒性：非生殖毒性物質。[1]
- 毒理代謝動力學：容易被人體和大鼠的胃腸道吸收，主要通過尿液排出體外。[1]
- 光毒性：無光毒性。[1]
- 人體數據：在 CIR (1983)報告的研究中，月桂醇聚醚硫酸鈉在 18%濃度的 24 小時封閉 Patch Test 中對受試者造成低水平刺激。在 CIR (2010)報導的一項研究中，月桂醇聚醚硫酸銨在 0.9~0.18%濃度下對 20 名受試者沒有刺激性。[1,2]
- 其他安全資料：月桂基硫酸鈉和月桂基硫酸銨的安全性已由化粧品成分審查(CIR)專家小組在兩個不同的時間進行評估(1983、2002)，得出結論顯示這些成分在用於短暫、不連續使用，從皮膚表面徹底沖洗乾淨的配方中是安全的。在長時間與皮膚接觸的產品中，濃度不應超過 1%。自 1998 年以來，網上流傳著月桂基硫酸鈉會致癌。這一指控是沒有根據的和虛假的，事實上，在 2002 年的安全審查中，CIR 專家小組評估了有關十二烷基硫酸鈉的所有數據並得出結論：月桂基硫酸鈉或月桂基硫酸銨這些成分的致癌性，可能只是謠言。[4]
- 參考資料：

1. Final Report of the Amended Safety Assessment of Sodium Laureth Sulfate and Related Salts of Sulfated Ethoxylated Alcohols. CIR, 2010.
2. Final Report on the Safety Assessment of Sodium Lauryl Sulfate

and Ammonium Lauryl Sulfate. CIR, 1983.
3. Sodium and ammonium laureth sulfate: Human health tier II assessment. IMAP Group Assessment Report, 2013.
4. Cosmetics Info 網站：https://cosmeticsinfo.org/ingredient/ammonium-lauryl-sulfate

8. INCI name：Sodium Bisulfite

- 毒理動力學：亞硫酸鹽也可以代謝為硫代硫酸鹽（亞硫酸鹽與二硫鍵的酵素反應）。在正常人或大鼠的尿液中檢測到濃度非常低的硫代硫酸鹽和 S-磺酸鹽，但被亞硫酸鹽氧化酶缺乏的人大量代謝。研究指出，與人類相比，大鼠的肝臟亞硫酸鹽氧化酶活性估計高 10 至 20 倍。[1]
- 急性毒性：經證明亞硫酸氫鈉(Sodium Bisulfite)的急性致死劑量 LD_{50} 雄性大鼠為 2.90 ml/kg bw，雌性為 3.85 ml/kg bw。[2]
- 皮膚腐蝕性和刺激性：將 Sodium Bisulfite(0.5 mL 的 38%溶液)施加在紗布墊下用橡膠布鬆散地包裹貼到 6 隻白化病兔子的後背上，總暴露時間為 4 小時，然後清洗部位，並在首次使用後 24 和 48 小時進行觀察，Sodium Bisulfite 沒有刺激性及腐蝕性。[1,2]
- 眼睛刺激性：將 Sodium Sulfite 和 Sodium Bisulfite 溶液(水溶液中 38%)滴入兔子的眼睛在任何時候都不會影響角膜和虹膜。滴注後直至 24 小時，在幾隻動物中僅觀察到表現為紅斑和浮腫的輕微結膜作用。[1,2]
- 皮膚致敏性：非皮膚致敏物。[2]
- 重複給藥毒性：在 1982 年二氧化硫(Sulphur Dioxide)、Sodium Sulfite、Sodium Bisulfite 和亞硫酸氫鉀(Potassium Bisulfite)以及焦亞硫酸鈉(Sodium Pyrosulfite)和焦亞硫酸鉀(Potassium Metabisulfite)被 FDA 分類為是安全的(Generally Recognized As Safe, GRAS)。這種結果得到了美國實驗生物學學會聯合會的評價的支持。在他們的評估中，他們使用動物研究來估計人類二氧化硫的 NOAEL 約 30~100 mg。1983 年，世界衛生組織食品添加劑聯合專家委員會(The Joint FAO/WHO Expert Committee on Food Additives, JECFA)建立了 0.7 mg/kg 體重的 Sulphur dioxide 每日攝取容許量(Accepatble Daily Intake, ADI)。在三代動物研究中，NOAEL 為 72 mg/kg bw/day (相對於二氧化硫)，約該 ADI 100 倍的安全係數。[2]
- 發育/生殖毒性：Sodium bisulfite 的劑量分別為 150、110、120 和

100 mg/kg，對小鼠、大鼠、倉鼠或兔子皆無致畸作用，非生殖毒性物質。[1]

- 致癌性：非致癌性。[1]
- 人體數據：先前被診斷患有重症肌無力的女性患者接受了高熱量的輸液，其中包含 0.04%的 Sodium Bisulfite。輸液開始三天後，患者大部分部位都出現了紅色的瘙癢性小丘疹。停止輸注後，全身 IV 型過敏反應逐漸消失。對 0.1%的亞硫酸氫鈉、1%的亞硫酸氫鈉（凡士林）、含 0.002%亞硫酸氫鈉的高熱量輸液，和含 0.04%亞硫酸氫鈉的高熱量輸液進行了 48 小時封閉型皮膚斑貼測試(Closed Patch Epicutaneous Test Under Occlusion)。根據國際接觸性皮膚炎研究小組(The International Contact Dermatitis Research Group, ICDRG)的建議，測試後的 48 小時和 72 小時確定反應。據研究顯示對 0.1%和 1%的亞硫酸氫鈉 Patch Test 呈陽性反應；在 0.04%的亞硫酸氫鈉輸液 Patch Test 部位觀察到搔癢；含有 0.002%亞硫酸氫鈉的輸液 Patch Test 反應陰性。亞硫酸鹽的攝入也可能引起 IV 型過敏反應，導致全身性 IV 型過敏反應。[2]
- 其他安全資料：Sodium Sulfite、亞硫酸鉀(Potassium Sulfite)、亞硫酸銨(Ammonium Sulfite)、亞硫酸氫鈉(Sodium Bisulfite)、亞硫酸氫銨(Ammonium Bisulfite)、焦亞硫酸鈉和焦亞硫酸鉀的安全性已由化粧品成分審查(CIR)專家小組評估並得出結論，所有七種成分在用於化粧品和個人護理產品時都是安全的，亞硫酸鈉、焦亞硫酸鈉和焦亞硫酸鉀在致突變性研究中均為陰性。在哺乳動物中，硫酸鹽氧化酶的存在會將所有亞硫酸鹽轉化為硫酸鹽。此外，這些成分的高電荷性質會導致相對較低的皮膚滲透。[3]
- 參考資料：

1. Safety Assessment of Sulfites as Used in Cosmetics. CIR, 2020.
2. SCCS opinion on Inorganic Sulfite and Bisulfite., COLIPA n° P51 SCCNFP/0648/03, final, 2003.
3. Cosmetics Info 網站：https://cosmeticsinfo.org/ingredient/sodium-bisulfite

9. INCI name：m-Aminophenol

- 毒理代謝動力學：具有高水溶性，預計很容易經由口服和吸入途徑吸收，並通過血液迅速分佈到全身。當以 63 mg/kg bw/day，單劑

量或十倍劑量經皮給藥於大鼠時，皮膚的可利用性低，不到 0.2%的塗抹總量會透過皮膚被吸收。60 ml 氧化型染髮劑配方樣品中該間-氨基苯酚(m-Aminophenol)的最高濃度估計為 1.2%。在此濃度下，與口服途徑相比，預估通過皮膚吸收較差。[2,3]

- 急性毒性：使用"固定劑量法"研究 m-Aminophenol 的急性口服毒性。四隻雌性透過口服強飼法用 500 mg/kg bw 體重的測試物質處理，2 週後檢查臨床體徵和死亡率，沒有死亡現象發生。在第 1 天，所有動物中都觀察到活動力減退或較鎮靜、脫毛和呼吸困難，但第 2 天完全恢復，體重增加和肉眼檢查未見異常情況，最大非致死劑量 >500 mg/kg bw。[1]據研究顯示，大鼠 LD_{50} 在 812~1000mg/kg bw 範圍內。[2]
- 皮膚吸收率：m-Aminophenol 與甲苯-2,5-二胺硫酸鹽結合到典型的染髮配方中與最終濃度 1.2%的過氧化氫混合後的皮膚吸收估計在使用條件下最多為 7.14 μg/cm²，SCCS 認為該值可用於計算 MoS。[1]
- 皮膚刺激性：2%的 m-Aminophenol 對兔子皮膚無刺激性。[1]
- 眼睛刺激性：2%的 m-Aminophenol 被認為對兔子眼睛無刺激性。[1]
- 皮膚致敏性：m-Aminophenol 在小鼠局部淋巴結試驗中誘導接觸致敏，並被認為具有很強的致敏潛力。[1]
- 重複給藥毒性：動物接受以 0、20、70、200 或 600 mg/kg bw/day 測試物質的劑量，在 0.5%甲基纖維素水溶液+ 1% d-異抗壞血酸的賦形劑中每日管飼，持續 13 週。每天檢查動物的臨床症狀和死亡率，每週記錄一次食物消耗和體重。對照組和高劑量組動物在試驗期前進行眼科檢查，對照組動物在第 13 週進行眼科檢查，200 和 600 mg/kg bw/day 組，在第 13 週所有動物進行血液學、生物化學和尿液分析，沒有觀察到與試驗相關的死亡，雖然在 20 mg/kg bw/day 組中沒有觀察到臨床症狀，但在 70 mg/kg bw/day 一些動物和在 200 和 600 mg/kg bw/day 時所有動物都觀察到有熱病情況。根據對甲狀腺活動和腎臟的影響，NOAEL 被認為是 20 mg/kg bw/day。[1]
- 致突變性：在實驗條件下，間氨基苯酚在細菌基因突變測試中具有微弱基因誘變毒性。[1]
- 遺傳毒性：在使用的實驗條件下，間氨基苯酚會導致染色體畸變增加，因此在體外人淋巴細胞中具有遺傳毒性。[1]
- 致癌性：口服或皮膚施用途徑均未發現致癌潛力，從研究中無法得

出有關致癌性的結論。[1]

- 生殖毒性：儘管並非所有研究都符合公認的方法，但可以說對胺基苯酚不太可能致畸胎。它僅在高劑量（500 mg/kg bw/day）下對實驗動物的生育力或妊娠、胚胎發育、泌乳或斷奶指數產生影響。在一項研究中觀察到致畸胎作用，但僅在母體毒性劑量下才觀察到。
- 人類數據：在人體反覆刺激斑貼試驗和診斷斑貼試驗期間，都觀察到暴露於該化學品的人體會致敏。在兩次半封閉性反覆刺激斑貼試驗中，6 週的時間內，將 0.1ml 劑量的化學物質（舒爾茨載體 II 中的 3% 溶液或類似溶液）施用於 98 和 99 名測試對象的背部。在 48~72 小時內連續施用 10 次誘導貼劑，然後 1 天不施用。在休息期後 48 小時在背部先前未暴露的皮膚上進行挑戰貼片施用。在這兩項研究中，在誘導期的幾個受試者中都觀察到刺激作用(紅斑)。在第一項研究(98 名受試者)中，沒有觀察到對挑戰貼片的反應。在第二項研究(99 名受試者)中，兩名受試者在使用挑戰貼片以及身體不同部位的額外再挑戰貼片後出現反應。在澳洲的一項案例研究中，對 164 名在皮膚科診所出現過敏性接觸性皮膚炎的美髮師和美髮學徒進行美髮沙龍中使用的 36 種化學品的 Patch Test，在工作場所接觸 3-氨基苯酚的 4 名受試者在用該化學品進行 Patch Test 時出現了陽性反應(Lyons et al., 2013)。[2]
- 其他安全資料：氨基酚染髮劑的安全性已經過 CIR 專家小組的評估。CIR 專家小組評估了科學數據並得出結論，p-、m-和 o-氨基酚(p-Aminophenol, m-Aminophenol, o-Aminophenol)可作為染髮劑。2005 年，CIR 專家小組審議，關於 p-Aminophenol, m-Aminophenol, o-Aminophenol 的現有新數據，並重申了上述結論。CIR 專家小組認為，p-Aminophenol, m-Aminophenol, o-Aminophenol 的代謝途徑與對乙酰氨基酚的代謝途徑相似。當體內穀胱甘肽(一種與其他化合物結合通常會導致毒性降低的化合物)劑量低時，對乙酰氨基酚和氨基酚可以代謝為基因毒性化合物。這些基因毒性化合物的形成可以在體外發生基因毒性試驗。CIR 專家小組認為用於篩選氨基酚的體外誘變試驗未能模擬體內情況，因此，他們認為體外試驗顯示的氨基酚的誘變潛力與使用在染髮產品中無關。這結論得到了含有 p-Aminophenol, m-Aminophenol, o-Aminophenol 的染髮產品在局部應用時不會誘發癌症的支持。[5]
- 參考資料：

1. SCCS opinion on m-Aminophenol., COLIPA N° A15. SCCP/0978/06, 2006.
2. Phenol, 3-amino-: Human health tier II assessment. IMAP Single Assessment Report, 21 April 2016.
3. Final Report on the Safety Assessment of p-Aminophenol, m-Aminophenol, and o-Aminophenol. CIR, 1988.
4. SCCS opinion on p-Aminophenol., COLIPA N° A16. SCCS/1409/11, 2011.
5. Cosmetics Info 網站：https://cosmeticsinfo.org/ingredient/m-aminophenol

10. INCI name：Disodium EDTA

- 不純物：預計無重大雜質，但應監測重金屬。CIR 指出，化粧品級乙二胺四乙基二鈉(Disodium EDTA)中的重金屬含量一般低於 10 ppm，甲醛含量低於 100 ppm。[2]
- 急性毒性：大鼠的 LD_{50} 2800 mg/kg bw，急性吸入毒 LOAEL 為 30 mg/m³ air。[2]
- 刺激性：對皮膚沒有刺激性，對眼睛沒有刺激性。[2]
- 皮膚致敏性：無數據。參考 Na_3EDTA 類似化合物不具致敏性。[2]
- 重複給藥毒性：在一項為期兩年的研究中，33 隻大鼠分 5 組給予 0、0.5、1 和 5% Disodium EDTA。5%實驗組比其他組的大鼠表現出腹瀉和食慾減少，沒有觀察到對體重增加的顯著影響，凝血時間、紅細胞計數或骨頭也沒有受到不利影響。動物的死亡率與 Disodium EDTA 量無關，死亡率最高的是對照組。各種器官的肉眼和顯微鏡檢查顯示兩組之間無顯著差異。在一項為期 13 週的重複給藥毒性研究中，餵食 Disodium EDTA（0%、1%、5%、10%）的大鼠在最高劑量下顯示出死亡率，此外，在 5%（約 4206 mg/kg bw/day）及以上的劑量下，食物消耗減少（消瘦 10%）和腹瀉。Disodium EDTA NOAEL 為 1%（約 692 mg/kg bw/day）。[3]
- 致突變性/遺傳毒性：高劑量的體外和體內研究具弱致突變性，可能是由於次要機制[1]，不致引起人類致突變性。[4]
- 致癌性：無數據。參考 Na3EDTA 類似化合物以 7500 ppm 劑量餵食大鼠及小鼠達 103 週，結果無致癌性。[1]
- 遺傳毒性：施用 Disodium EDTA 對 5178Y 小鼠淋巴瘤細胞進行小鼠

淋巴瘤測定，細胞用 250~ 2000 μg/mL 100%純度的 Disodium EDTA 處理，在有或沒有代謝活化之試驗物質是被認為不具誘變性的。[1]

- 毒理代謝動力學：不太可能通過皮膚吸收，但可以用作滲透促進劑。大鼠的口服吸收率<3%。[2]
- 光毒性：無數據。但 Disodium EDTA 不認為會吸收光。[2]
- 人體數據：四個正常血鈣患者在 4 小時內靜脈滴注 4 g Sodium EDTA 或 Calcium EDTA，分別導致更多的鈣排泄率分別為 75%~88%和 57%~70%。服用 Disodium EDTA 4 小時內，約有 60%~80%的過量鈣被排泄出來。當給三個人服用放射性劑量(未指定劑量)的 Calcium EDTA 時，24 小時之內就會排泄 100%的螯合物。口服的 Sodium EDTA 及 Calcium EDTA (6 g/day，共 6 天)在人體的胃腸道中吸收差。然而，在接受 Calcium EDTA 的受試者糞便中鈣的含量有增加情況。[2]
- 其他安全資料：CIR 專家小組評估了科學數據並得出結論，Sodium EDTA 和相關成分用於化粧品和個人護理產品是安全的。化粧品和個人護理產品中使用濃度下的 EDTA 和相關成分不是皮膚刺激物或致敏劑。研究顯示，這些成分不是致癌物質。由於這些成分結合正常細胞分裂所需的金屬，一些研究顯示這些化合物具有弱致突變性。另研究資料顯示，口服暴露於大劑量金屬螯合劑後會對生殖和發育產生影響，這可能是正常生殖和發育所需的金屬結合的影響。CIR 專家小組審查了 EDTA 和相關成分，發現其不易透過皮膚吸收。因此，通過使用含有這些成分的化粧品和個人護理產品，皮膚接觸 EDTA 或 HEDTA 會導致非常少的皮膚滲透和全身暴露量，遠低於口服研究中顯示的產生不良影響的劑量。[5]
- 參考資料：

1. Safety Assessment of EDTA & Salts as Used in Cosmetics. CIR, 2019.
2. Final Report on the safety assessment of EDTA, Calcium Disodium EDTA, Diammonium EDTA, Dipotassium EDTA, Disodium EDTA, TEA-EDTA, Tetrasodium EDTA, Tripotassium EDTA, Trisodium EDTA, HEDTA, and Trisodium HEDTA. Int J Toxicol 21 (Suppl. 2), 2002.
3. SIDS Initial Assessment Profile, COCAM 3, SIDS, 16-18 October 2012.
4. Disodium and Calcium Disodium Salts. http://www.inchem.org/documents/jecfa/jecmono/v05je25.htm

5. Cosmetics Info 網站：
https://cosmeticsinfo.org/ingredient/disodium-edta

11. INCI name：Hydrogen Peroxide

- 經皮吸收：在大鼠體內施用 5%至 30%的過氧化氫溶液的幾分鐘內，可以在切除的表皮中偵測到少量的過氧化氫。相較之下，對於體外人屍體皮膚，只有在施用高濃度過氧化氫數小時後，或在用羥胺（過氧化氫酶抑制劑）預處理後，才能在真皮中檢測到過氧化氫。根據組織化學分析，過氧化氫不在表皮中代謝，而是經表皮通過的，迴避了皮膚附屬物“預先形成的路徑”。由氧釋放引起的皮膚氣腫所在位置很大部分與組織內過氧化氫酶活性分佈有關。[1]
- 急性毒性：通常急性皮膚和口服毒性作用取決於濃度和劑量。小鼠的皮膚暴露過氧化氫 LD_{50}>8000 mg/kg；在這項研究中，28%過氧化氫和 10%過氧化氫水溶液相比時，更多的小鼠死亡。在一項研究中，經皮施用過氧化氫 6900 mg/kg 不會導致任何(n = 6)大鼠死亡，6 隻中有 2 隻在經皮施用過氧化氫 8280 mg/kg 下死亡。在另一項研究中，50%的大鼠（n 未定）在 4060 mg/kg 下死亡。兔子的皮膚 LD_{50} 在 35%過氧化氫水溶液中> 2000 mg/kg。分別使用 70%過氧化氫水溶液 9200 mg/kg 和 90%過氧化氫水溶液 690 mg/kg，在封閉情況下給藥 24 小時，臨床症狀包括流淚和流鼻涕。當過氧化氫以 4361 mg/kg 的 90%水溶液經皮給藥時，沒有貓死亡。當以 2760 mg/kg 的劑量經皮施用過氧化氫時，5 頭豬中有 2 頭死亡。[1]
- 皮膚刺激性/腐蝕性：在兔子施用 10%的過氧化氫溶液對皮膚有輕微刺激性，35%的過氧化氫溶液被證明具有中度刺激性，並導致延遲的表皮壞死和脫落，而>50%的過氧化氫溶液則具有嚴重刺激性和腐蝕性。[1]
- 眼睛刺激性：用過氧化氫施用於兔子眼睛，發現角膜損傷通常不僅取決於過氧化氫的濃度，還取決於角膜上皮的完整性。將 0.5%~5%過氧化氫水溶液滴入兔子眼睛中，導致角膜表面混濁和結膜反應，但這些影響在 24 小時內恢復。8%過氧化氫水溶液的對兔子眼睛有刺激性，滴注 10%~30%過氧化氫水溶液會導致角膜表面混濁，如果角膜上皮有缺陷，可能會導致角膜基質局部腫脹和混濁。小鼠眼睛暴露於過氧化氫蒸氣(90%水溶液)，顯示出眼睛混濁和微觀損傷。[1]
- 皮膚致敏性：過氧化氫引起皮膚過敏的可能性非常低。[1]

- 重複給藥毒性：在一項測試霧化過氧化氫對皮膚影響的研究中，將大鼠剃毛皮膚部位（未指定品系和數量）暴露於過氧化氫蒸氣(0.1~10.1 mg/m^3)中，每天 5 小時，每週 5 天，長達 4 個月。以 1 mg/m^3 給藥 2 個月後，對大鼠背部表皮的檢查顯示單胺氧化酶(Monoamine Oxidase, MAO)和菸鹼醯胺腺嘌呤二核苷酸(Nicotinamide Adenine Dinucleotide, NAD)-黃遞酶的活性增加，並且 4 個月後，MAO、NAD-心肌黃酶、琥珀酸脫氫酶活性(succinate dehydrogenase, SDH)和乳酸脫氫酶增加。4 個月時，大鼠皮膚角質層出現明顯功能障礙，評估皮膚中酶活性的 LOAEL 為 1.0 mg/m^3，NOAEL 為 0.1 mg/m^3。[1] 一項對缺乏過氧化氫酶的小鼠進行了為期 90 天的可靠、良好的研究，發現飲用水中劑量為 3000 ppm 時體重會下降(Freeman 1997)。一項 90 天小鼠飲水試驗結果顯示，飲用水中過氧化氫的 NOAEL 為 100 ppm，這意味著雄性的每日劑量為 26 mg/kg bw，雌性為 37 mg/kg bw。[1`2]LOAEL 為 300 ppm（雄性為 76 mg/kg/day，雌性為 103 mg/kg/day），基於劑量相關的食物和水消耗量減少以及觀察到一名雄性十二指腸粘膜增生。男性和女性在 1000 和 3000 ppm 的較高水平上皆發現增生（相對應的每日劑量為雄性 239 mg/kg、雌性 328 mg/kg 及每日劑量為雄性 547 mg/kg、雌性 785 mg/kg），在恢復期完全可逆，在最高劑量 3000 ppm 時，血漿總蛋白和球蛋白濃度降低。[2]
- 致突變性/遺傳毒性：多種體外測試系統中的發現過氧化氫是致突變誘變劑和遺傳毒性劑。但現有的體內條件研究下不認為過氧化氫具有顯著遺傳毒性/致突變性。[1]
- 致癌性：證據不足以得出有關致癌性的結論。[1]
- 生殖毒性：沒有適當的研究結果可用於全面評估過氧化氫生殖和發育毒性。[1]
- 人類數據：據報導在人類皮膚以 3%過氧化氫水溶液施用於皮膚會導致短暫的（開始暴露 1 分鐘後持續 10 到 15 分鐘）皮膚變白。對接受標準過敏原系列（包括 15 種美髮品）和補充“美髮系列”（18 種額外美髮品）的皮膚炎患者(n = 210)皮膚 Patch Test 結果進行了檢查，皮膚炎最常見的部位是頭皮、面部和手，患者的職業差異很大，最常見的職業是化粧師(10.5%)、家庭主婦(9.5%)和美容師(5.2%)。觀察到 1%的測試對象，對 3%過氧化氫水溶液有陽性過敏反應；1.4%的受試者對刺激呈陽性反應。曾擔任美髮師且疑似會對其職業

中使用的化學品過敏之受試者(n = 121)，根據歐洲化粧品和美髮系列標準，進行皮膚 Patch Test 或點刺激試驗，一名受試者(0.9%)對過氧化氫有陽性反應。在 1991 年至 1997 年期間，芬蘭職業健康研究所(Finnish Institute of Occupational Health)針對疑似患有職業性皮膚病的美髮師(n = 130)進行 Patch Test，包括過氧化氫（濃度未指定），沒人對過氧化氫的過敏反應呈陽性；但一名則有刺激性皮膚反應。1995 年至 1996 年，圖爾庫大學皮膚科對 59 名疑似因美髮化合物引起濕疹的患者進行了 Patch Test，結果顯示沒有患者對過氧化氫有過敏或刺激性反應，又依據芬蘭職業病登記處的數據顯示，1975 年至 1997 年期間職業性過敏性皮膚病總數為 10,806 例，經 Patch Test 結果，這些都不是由過氧化氫引起的。同期，共有 29,803 例職業性皮膚病提交給芬蘭職業病登記處，四個被證明是由過氧化氫引起的。1974-1993 年在芬蘭美髮師接觸性皮膚炎回顧性研究，所有患者(n = 355)均未檢測出過氧化氫致敏陽性反應。6%過氧化氫牙齒美白貼片的使用安全性在單一地點進行，由 4 年期間積累的臨床試驗數據庫進行檢查的。每個上頜骨貼片攜帶大約 12 mg 總過氧化氫。受試者（總共 n = 148）在 2 週的時間內每天使用貼片兩次，每次 30 分鐘，在所有研究中通過檢查和訪談方法評估安全性，對彙整的科學數據進行了分析。總體而言，平均 22%（臨床試驗範圍 4%~31%）的受試者發生口腔刺激，平均 20%（臨床試驗範圍 10% ~ 28%）的受試者發生牙齒敏感，其他副作用並不顯著，只有 1 名受試者(0.7%)由於不良事件而提前停止治療，在這種情況下，中度軟組織疼痛在停止研究後 1 天完全消失。在幾乎所有情況下，不良事件的持續時間都是短暫的。發病通常較早並在治療期間解決，不會影響貼片的使用，臨床檢查無明顯異常，其他副作用較少。[1]

- 其他安全資料：美國食品藥物管理局將過氧化氫列入一般公認安全(Generally Recognized As Safe, GRAS)用於食品的物質清單。過氧化氫在牛奶和奶酪製品、酒、醋、澱粉和速溶茶等食品中作為抗菌劑、氧化劑和還原劑和漂白劑。FDA 還允許在非處方(Over-the-Counter, OTC)急救消毒劑中使用過氧化氫。國際癌症研究機構(International Agency for Research on Cancer, IARC)得出結論，過氧化氫不能歸類為對人類致癌性。歐盟委員會消費品科學委員會(European Commission's Scientific Committee on Consumer Products, SCCP)評估過氧化氫在牙齒美白產品中的安全性，SCCP 的結論是，使用含有

高達 1%過氧化氫的產品是安全的。SCCP 還得出結論，在諮詢並獲得牙醫批准後，可以使用含有高達 6%過氧化氫的產品。在歐盟過氧化氫可用於護髮、護膚、指甲硬化和口腔衛生產品，最大濃度分別為 12%、4%、2% 和 0.1%。含有過氧化氫的護髮、護膚和指甲硬化產品必須標明：“含有過氧化氫。避免接觸眼睛。如果產品接觸到它們，請立即沖洗。”含有過氧化氫的美髮產品必須建議在使用產品時戴上手套。[4] SCCNFP 建議牙齒美白產品中的過氧化氫含量限制在 6%（添加或釋放），每天限制為 50 mg 過氧化氫。含有超過 0.1%過氧化氫（或過氧化氫釋放物質的等效物）的牙齒美白產品應僅在牙醫的監督下使用。不建議在牙齒修復之前或之後立即使用牙齒美白產品。如牙齒已發生組織損傷或同時有抽菸和/或飲酒等條件可能會加劇過氧化氫的毒性作用。[1]

- 參考資料：

1. CIR Safety Assessment of Hydrogen Peroxide as Used in Cosmetics., 2018.
2. EPA Provisional Peer Reviewed Toxicity Values for p-Aminophenol., 2005
3. EU risk assessment for hydrogen peroxide. European Commission, 2003.
4. Cosmetics Info 網站：https://cosmeticsinfo.org/ingredient/hydrogen-peroxide-0

12. 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，針對人類甘油的口服 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。[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，當她避免使用含甘油的化粧品時，她的濕疹得到了緩解。[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實驗中是安全的（即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

13. INCI name：Urea

- 不純物：尿素中 CH_4N_2O 的含量不低於 99.0%且不超過 100.5%。[1]
- 急性毒性：口服途徑說明了尿素的急性毒性，反芻動物特別是牛和綿羊以外的哺乳動物，其毒性低，其中反芻動物的微生物具有脲酶活性，並能將尿素代謝為氨。在小鼠和大鼠中，尿素即使通過皮下和靜脈內途徑也具有低毒性。在使用雌性大鼠或小鼠進行的急性口服研究中，未觀察到尿素的毒性高達 2000 mg/kg。口服劑量達 4 g/kg 尿素的雄性豬 5 天未觀察到毒性跡象。口服 5 至 30 g/L 尿素 4 至 10 天的狗有中毒跡象，包括虛弱、厭食、嘔吐、腹瀉和體溫下降，因而導致昏迷。[1]
- 經皮吸收：尿素在正常和磨損的人類皮膚上的吸收分別為 9.5%± 2.3%和 67.9%± 5.6%。[1]
- 重複給藥毒性：在餵飼 4500、9000 或 45000 ppm（小鼠高達約 6750 mg/kg bw/day 和大鼠約 2250 mg/kg bw/day）的小鼠和大鼠中進行的慢性毒性和致癌性篩選研究，在各個器官中未發現任何有關的毒性綜合症，在任何劑量濃度下，無論動物性別或物種屍體解剖檢驗時都沒有發現體重減輕。因此小鼠的 NOAEL 約為 6750 mg/kg bw/day，大鼠的 NOAEL 約為 2250 mg/kg bw/day。使用尿素軟膏分別以 10%、20%和 40%的濃度，將軟膏塗在背部皮膚的 20 cm^2 區域上，進行了 4 週和 25 週的大鼠皮膚重複劑量毒性研究，未發現相關的持續毒性作用。但因未有尿素的使用量之數據，因此無法確定經皮途徑的 NOAEL 值，但可得到的結論是尿素經皮膚途徑的重複

劑量毒性較低。[2]

- 致突變性/遺傳毒性：在幾種細菌和哺乳動物試驗中，尿素沒有遺傳毒性。[1]
- 致癌性：餵飼 Fisher 344 大鼠或 C57B1/6 小鼠含高達 4.5%尿素，結果顯示尿素沒有致癌性。[1]
- 生殖毒性/發育毒性：：CIR 專家小組確定尿素可安全用於化粧品和個人護理產品。急性和慢性毒性研究顯示，即使在高暴露情況下，也幾乎沒有不良反應的證據。皮膚刺激不顯著，生殖和發育毒性研究未引起相關毒性反應，致癌性研究呈陰性。CIR 專家小組認為尿素不具有基因毒性，除非濃度非常高。CIR 專家小組注意到尿素可以增加其他成分的經皮吸收，在進行產品安全評估時應考慮到這一點。[4]
- 參考資料：

1. Final Report of the Safety Assessment of Urea, International Journal of Toxicology, 24(Suppl. 3):1–56, CIR, 2005.
2. Urea-Registration Dossier- ECHA https://echa.europa.eu/registration-dossier/-/registered-dossier/16152/7/6/1
3. SIDS Urea CAS N°: 57-13-6, 2002.
4. Cosmetics Info 網站： https://cosmeticsinfo.org/ingredient/urea-0

(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、密度項目進行 6 個月產品加速安定性試驗，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	玩色染髮-瞬時棕染髮劑第一劑			
包裝材質	鋁管			
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	乳霜狀	乳霜狀	乳霜狀	乳霜狀
顏色	淡黃色~黃色	淡黃色~黃色	淡黃色~黃色	淡黃色~黃色
氣味	具香氣	具香氣	具香氣	具香氣
pH	9.72	9.41	9.63	9.30
黏度	8100 mPas	8250 mPas	8078 mPas	8630 mPas
密度	1.1 3g/cm^3	1.1 8g/cm^3	1.13 g/cm^3	1.17 g/cm^3
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)

產品名稱	玩色染髮-瞬時棕染髮劑第二劑			
包裝材質	HDPE			
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	白色不透明	白色不透明	白色不透明	白色不透明
氣味	具香氣	具香氣	具香氣	具香氣
pH	3.85	3.72	4.17	3.94
密度	1.02 g/cm^3	1.05 g/cm^3	1.07 g/cm^3	1.04 g/cm^3
微生物檢測結果	未檢出	未檢出	未檢出	未檢出
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

玩色染髮-瞬時棕染髮劑第一劑含氨0.56%，且含酒精濃度約30%，符合ISO 29621: 2017微生物低風險性含氨≥0.5%及含酒精濃度>20%之條件，判斷屬於低微生物風險產品，此類產品無須進行防腐效能試驗及微生物檢測，在此不須提供微生物檢測報告。玩色染髮-瞬時棕染髮劑第二劑雖然含有H_2O_2，但因含量未達3%以上，非屬低微生物風險產品，此類產品仍須進行防腐效能試驗及微生物檢測。

產品名稱	玩色染髮-瞬時棕染髮劑-第二劑		
產品批號	P018AUG		
產品製造日期	110.07.05		
包裝材質	HDPE	試驗日期	110.07.08
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 公布建議檢驗方法-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

玩色染髮-瞬時棕染髮劑第一劑含氨0.56%，且含酒精濃度約30%，符合ISO 29621: 2017微生物低風險性含氨≥0.5%及含酒精濃度>20%之條件，判斷屬於低微生物風險產品，此類產品無須進行防腐效能試驗及微生物檢測，在此不須提供防腐效能試驗報告。玩色染髮-瞬時棕染髮劑第二劑雖然含有H_2O_2，但因含量未達3%以上，非屬低微生物風險產品，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)	玩色染髮-瞬時棕染髮劑第二劑				
測試日期(Date Tested): 110/06/01~110/06/30					
試驗參考方法(Method Code): ISO 11930:2019					
測試菌種 (Organism)					
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	9.8×10^5	8.2×10^5	9.4×10^5	8.6×10^4	7.7×10^4
第 7 天	<10	<10	<10	$1.4X10^2$	$3.3X10^2$
第 14 天	<10	<10	<10	<10	<10
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

染髮劑相關功能性測定，如染髮色度測試驗等。

(15) 與產品接觸之包裝材質資料

包裝材料	材質
玩色染髮-瞬時棕染髮劑 第一劑-瓶身	鋁
玩色染髮-瞬時棕染髮劑 第一劑-瓶蓋	HDPE
玩色染髮-瞬時棕髮劑 第二劑-瓶身	HDPE
玩色染髮-瞬時棕髮劑 第二劑-瓶蓋	HDPE

III. 安全評估資料

(16) 產品安全資料

玩色染髮-瞬時棕染髮劑每日皮膚暴露量計算

參考 2021 年 3 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 11 版(SCCS/1628/21)，並依用途、部位、頻率進行皮膚暴露量計算，及說明染髮劑不是每天使用，因此，不應將全年的每日劑量平均化。但是，安全邊際值(Margin of Safety, MoS)是通過將每日使用的劑量反應點(Point of Departure, PoD)除以每日使用的全身暴露量(Systematic Exposure Dose, SED)來計算的，以較保守嚴謹之評估方法。SCCS 根據成分（即前體和成色劑）而不是反應後產物的毒理學評估來進行氧化染髮劑的安全性評估。

基本數據	
平均體重	60 kg
接觸部位	頭皮
接觸種類	產品
每日使用頻率	1/month=1/30
駐留因子	0.01
染髮劑使用表面積(cm^2) SSA	580

*參考 SCCS 2021 年 3 月發布化粧品成分測試及其安全性評估指引第 11 版：氧化性染髮劑，通常在 30~45 分鐘內使用 20 mg/cm^2（取決於預期用途）。

$SED = (DAa \times 10^{-3} \times SSA \times f)/bw$

DAa ($\mu g/cm^2$)：在使用中模擬條件下的分析得出的皮膚吸收量（單位面積上的皮膚吸收量）

SSA (cm^2)：預計使用化粧品產品的皮膚表面積

f (day^{-1})：產品的使用頻率

bw (kg bw)：人體體重（默認值：60 公斤）

玩色染髮-瞬時棕染髮劑各個成分 MoS 值計算

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

SED= Eproduct (每日皮膚暴露量)×C/100(配方百分比)×DAp/100(皮膚吸收率)

MoS= PODsys/SED

SED (mg /kg bw/day)為全身暴露劑量；Eproduct (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；PODsys 一般常用 NOAEL 估算。或者是 BMDL、LOAEL 。

p-Phenylenediamine、Resorcinol 及 m-Aminophenol 採用文獻之皮膚吸收量。SCCS 化粧品成分測試及其安全性評估指引第 11 版 (SCCS/1628/21) 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 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:

第一劑

INCI name	配方百分比 C(%)	皮膚吸收率 DAa (%)	NOAEL (mg /kg bw/day)	SED (mg /kg bw/day)	MoS
Aqua	55.0	-	-	-	>100
Alcohol	30.0	60	1200	0.0193	62176
Polysorbate 80	5.0	10	730	0.0032	228125
Dimethicone	3.0	6	311.1	0.0019	1637367
Ammonia (28% Solution)	2.0	2.97	77.8	0.0010	77800
p-Phenylenediamine	2.0	4.47	8	0.0014	5714
Resorcinol	1.0	2.06	2.6	0.0007	3714
Ammonium Laureth Sulfate	1.0	2	50	0.0006	83333
Sodium Bisulfite	0.5	1	36	0.0003	120000
m-Aminophenol	0.3	7.14	10	0.0023	4347
Disodium EDTA	0.1	0.2	346	0.0001	3460000
Fragrance	0.1	-	-	-	>100

第二劑

INCI name	配方百分比 C(%)	皮膚吸收率 DAa (%)	NOAEL	SED	MoS
Aqua	84.5	-	-	-	>100
Hydrogen Peroxide (28% Solution)	10.0	5.6	13	0.0018	7222
Glycerin	4.0	8	611.1	0.0026	235038
Urea	1.0	2	1125	0.0006	1875000
Fragrance	0.5	-	-	-	>100

INCI name	NOAEL 校正說明
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。
Polysorbate 80	大鼠膳食亞慢性研究(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。
Dimethicone	通過封閉貼劑經皮給藥4週(28天)，家兔皮膚施用二甲基矽油的NOAEL被認為是1000 mg/kg bw/day，考慮試驗天數之不確定因子，將1000*28/90 =311.1 mg/kg bw/day。
Ammonia (28% Solution)	參照在飲用水中添加0.01%氨水大鼠試驗8週中，磷酸二銨NOAEL為250 mg/kg bw/day，考慮口服生物可用率50%及試驗天數之不確定因子，將250*50%*56/90=77.8 mg/kg bw/day。
p-Phenylenediamine	參照SCCS將PPD亞慢性毒性的NOAEL視為8 mg/kg bw/day作為MoS計算，故未以不確定因子進行校正。
Resorcinol	為期17天口服毒性研究中，大鼠的NOAEL為27.5 mg/kg bw/day，考慮口服生物可用率50%及試驗天數之不確定因子，將27.5*50%*17/90=2.6 mg/kg bw/day。
Ammonium Laureth Sulfate	105週大鼠口服毒性得知NOAEL約為100 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，將100*50% =50 mg/kg bw/day。
Sodium Bisulfite	參照世界衛生組織食品添加劑聯合專家委員會在三代動物研究中，NOAEL為72 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，將72*50% =36 mg/kg bw/day。
m-Aminophenol	管飼13週動物試驗得知NOAEL 20 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，20*50% =10mg/kg bw/day。
Disodium EDTA	為期13週餵食大暑試驗中得知NOAEL為692 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，692*50% =346 mg/kg bw/day。

Hydrogen Peroxide (28% Solution)	一項90天小鼠飲水試驗結果顯示，飲用水中過氧化氫的NOAEL為26 mg/kg bw，考慮口服生物可用率50%等不確定因子，將26*50% =13 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。
Urea	大鼠口服試驗的NOAEL約為2250 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2250*50% =1125mg/kg bw/day。。

玩色染髮-瞬時棕染髮劑安全評估結論

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據以結論，推定玩色染髮-瞬時棕染髮劑在預期正常合理使用條件下，本產品為可安全使用之產品，不致對人體健康造成傷害。

標籤警語和使用說明

玩色染髮-瞬時棕染髮劑產品的包裝材料/標籤上已刊載使用說明，且使用注意事項已依「染髮劑之標籤、仿單或包裝應標示事項」規定刊載。

由於產品標籤和產品描述足以定義產品作為染髮劑的用途，產品中之每種成分沒有使用到其毒理學和/或物理性質或因在成品中的濃度比例需要額外標示之警語及注意事項，但因為成分中含有高致敏性物質，如：p-Phenylenediamine、Resorcinol、m-Aminophenol，故建議可加註注意事項如下：

*在每次染髮前 48 小時進行皮膚過敏測試(過敏測試)。在塗抹測試染劑後約 30 分鐘和 48 小時後，分 2 次對測試部位進行觀察。此時，塗抹部位出現皮疹、發紅、發癢、水泡、刺激等皮膚異常時，不要用手搓，請立即沖洗掉，不得使用染髮劑。中途，即使未滿 48 小時，感覺到同樣的皮膚異常時，請立即停止測試，立即將測試染劑沖洗掉，不得使用染髮劑。

*一旦皮膚測試的結果出現異常，請前往醫院皮膚科進行診治。

另建議可於包裝外盒上使用注意事項加註「建議每 3 個月使用 1 次 (每次染髮至少間隔 3 個月)」提醒消費者。

安全評估理由

玩色染髮-瞬時棕染髮劑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. 根據本產品「玩色染髮-瞬時棕染髮劑」之化粧品的物理/化學特性、安定性試驗報告、第二劑微生物檢測報告及防腐效能試驗評估，結果由數據顯示產品符合規格特性，證實了「玩色染髮-瞬時棕染髮劑」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確認之。
3. 玩色染髮-瞬時棕染髮劑第一劑經評估屬於低微生物風險產品，故無需進行防腐效能試驗及微生物檢測。第二劑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通過 ISO 11930:2019 Criteria A 之標準。

Table B.1 — Evaluation criteria

Log reduction values ($R_x = \lg N_0 - \lg N_x$) required[a]								
Micro organisms	Bacteria			*C. albicans*			*A. brasiliensis*	
Sampling time	T7	T14	T28	T7	T14	T28	T14	T28
Criteria A	≥ 3	≥ 3 and NI[b]	≥ 3 and NI	≥ 1	≥ 1 and NI	≥ 1 and NI	≥ 0[c]	≥ 1 and NI
Criteria B	Not performed	≥ 3	≥ 3 and NI	Not performed	≥ 1	≥ 1 and NI	≥ 0	≥ 0 and NI

a In this test, an acceptable range of deviation of 0,5 log is accepted (see 5.7).

b NI: no increase in the count from the previous contact time.

c $R_x = 0$ when $\lg N_0 = \lg N_x$ (no increase from the initial count).

4. 與本產品接觸之包材 HDPE (high-density polyethylene，高密度聚乙烯)，硬度大，且可耐各種腐蝕性液體的侵蝕，耐熱度約 90-110℃，因此常被用於製造塑膠袋、軟片盒、廚具、電池外殼、紙容器表面的 PE 淋膜、及食用油容器等。HDPE 一般無毒性，即使在極高濃度下，也僅對動物產生可逆性的肝臟傷害(如肝脂肪增加)；另外 PE 不會增加罹癌的機會，因此在使用上具有相當的安全性。
5. 根據“SCCS 化粧品成分測試及其安全性評估指引第 11 版”計算化粧品中產品和每種成分的暴露程度。對於暴露計算，以正常合理的可預見方式使用染髮劑，每月使用 1 次計算，雖然此產品使用說明頻率建議為 3 個月使用 1 次，計算安全邊際值仍以 SCCS 建議每月使用 1 次較保守的條件下進行估算。針對此款染髮劑中包含的每種原料成份，計算各別之安全邊際值(MoS)皆高於 100，成品中的所有原材料和成分被評估為在產品中作為化粧品成分使用是安全的，這支持此產品的安全性。
6. 目前此產品在市面上尚未出現不良影響和嚴重的不良影響，如有不良影響和嚴重不良影響的相關資訊會立即更新，並及時提供給安全資料簽署人員，以重新評估此產品之安全性。

(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(亦須包含 Fragrance 內含成分)之品質規格或各成分之檢驗報告(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：Ammonia

SAFETY DATA SHEET

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name : Ammonia solution 28-30% for analysis EMSURE® ACS,Reag. Ph Eur

1.2 Other means of identification

No data available

1.3 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Reagent for analysis, Chemical production

1.4 Details of the supplier of the safety data sheet

1.5 Emergency telephone

SECTION 2: Hazards identification

2.1 GHS Classification

Skin corrosion/irritation (Category 1), H314
Serious eye damage/eye irritation (Category 1), H318
Specific target organ toxicity - single exposure (Category 3), Respiratory system, H335
Short-term (acute) aquatic hazard (Category 1), H400

Long-term (chronic) aquatic hazard (Category 2), H411

For the full text of the H-Statements mentioned in this Section, see Section 16.

2.2 GHS Label elements, including precautionary statements

Pictogram

Signal word: Danger

Hazard statement(s)

H314	Causes severe skin burns and eye damage.
H335	May cause respiratory irritation.
H400	Very toxic to aquatic life.
H411	Toxic to aquatic life with long lasting effects.

Precautionary statement(s)

Prevention

P261	Avoid breathing dust/ fume/ gas/ mist/ vapors/ spray.
P264	Wash skin thoroughly after handling.
P271	Use only outdoors or in a well-ventilated area.
P273	Avoid release to the environment.
P280	Wear protective gloves/ protective clothing/ eye protection/ face protection.

Response

P301 + P330 + P331	IF SWALLOWED: Rinse mouth. Do NOT induce vomiting.
P303 + P361 + P353	IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water/ shower.
P304 + P340 + P310	IF INHALED: Remove person to fresh air and keep comfortable for breathing. Immediately call a POISON CENTER/ doctor.
P305 + P351 + P338 + P310	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/ doctor.
P363	Wash contaminated clothing before reuse.
P391	Collect spillage.

Storage

P403 + P233	Store in a well-ventilated place. Keep container tightly closed.
P405	Store locked up.

Disposal

P501	Dispose of contents/ container to an approved waste disposal plant.

2.3 Other hazards - none

SECTION 3: Composition/information on ingredients

Substance / Mixture : Mixture

3.2 Mixtures

Hazardous ingredients

Component		Classification	Concentration
ammonia solution			
CAS-No. EC-No.	1336-21-6 215-647-6	1B; 1; STOT SE 3; Aquatic Acute 1; Aquatic	>= 25 - < 30 %

Index-No.	007-001-01-2	Chronic 2; H314, H318, H335, H400, H411 Concentration limits: >= 5 %: STOT SE 3, H335; M-Factor - Aquatic Acute: 10	

For the full text of the H-Statements mentioned in this Section, see Section 16.

SECTION 4: First aid measures

4.1 Description of first-aid measures

General advice
First aiders need to protect themselves.

If inhaled
After inhalation: fresh air. Call in physician.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower. Call a physician immediately.

In case of eye contact
After eye contact: rinse out with plenty of water. Immediately call in ophthalmologist. Remove contact lenses.

If swallowed
After swallowing: make victim drink water (two glasses at most), avoid vomiting (risk of perforation). Call a physician immediately. Do not attempt to neutralise.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Use extinguishing measures that are appropriate to local circumstances and the surrounding environment.

Unsuitable extinguishing media
For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture
Nitrogen oxides (NOx)
Not combustible.
Ammonia solution itself is not flammable, but can form an ignitable ammonia/air-mixture by outgassing.
Ambient fire may liberate hazardous vapours.
Fire may cause evolution of:
nitrogen oxides

5.3 Advice for firefighters
Stay in danger area only with self-contained breathing apparatus. Prevent skin contact by keeping a safe distance or by wearing suitable protective clothing.

5.4 Further information
Cool closed containers exposed to fire with water spray. Suppress (knock down) gases/vapors/mists with a water spray jet. Prevent fire extinguishing water from contaminating surface water or the ground water system.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures
Advice for non-emergency personnel: Do not breathe vapors, aerosols. Avoid substance contact. Ensure adequate ventilation. Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions
Do not empty into drains.

6.3 Methods and materials for containment and cleaning up
Cover drains. Collect, bind, and pump off spills.Observe possible material restrictions (see sections 7 and 10).Take up with liquid-absorbent and neutralising material (e.g. Chemizorb® OH^-, Merck Art. No. 101596). Dispose of properly. Clean up affected area.

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling

Advice on safe handling
Observe label precautions.

Hygiene measures
Immediately change contaminated clothing. Apply preventive skin protection. Wash hands and face after working with substance.
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
No metal or light-weight-metal containers.
Tightly closed.

Recommended storage temperature see product label.

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

Appropriate engineering controls
Immediately change contaminated clothing. Apply preventive skin protection. Wash hands and face after working with substance.

Personal protective equipment

Eye/face protection
Tightly fitting safety goggles

Skin protection
This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Full contact
Material: butyl-rubber
Minimum layer thickness: 0.7 mm
Break through time: 480 min
Material tested:Butoject® (KCL 898)

This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0.40 mm
Break through time: 240 min
Material tested:Camatril® (KCL 730 / Aldrich Z677442, Size M)

Body Protection
protective clothing

Respiratory protection
required when vapours/aerosols are generated.

Control of environmental exposure
Do not empty into drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: liquid Color: colorless
b)	Odor	stinging, ammoniacal
c)	Odor Threshold	0.03 - 0.05 ppm - Ammonia
d)	pH	> 12 at 20 °C strongly alkaline

e)	Melting point/freezing point	Melting point: ca.-72 °C
f)	Initial boiling point and boiling range	ca.32 °C
g)	Flash point	Not applicable
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	No data available
j)	Upper/lower flammability or explosive limits	Upper explosion limit: 33.6 %(V) Lower explosion limit: 15.4 %(V)
k)	Vapor pressure	635 hPa at 20 °C
l)	Vapor density	No data available
m)	Relative density	No data available
n)	Water solubility	at 20 °C soluble
o)	Partition coefficient: n-octanol/water	log Pow: -1.38 - (anhydrous substance), Bioaccumulation is not expected.
p)	Autoignition temperature	No data available
q)	Decomposition temperature	No data available
r)	Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: No data available
s)	Explosive properties	No data available
t)	Oxidizing properties	No data available

9.2 Other safety information

Minimum ignition energy	380 - 680 mJ

SECTION 10: Stability and reactivity

10.1 Reactivity

No data available

10.2 Chemical stability

Ammonia solution itself is not flammable, but can form an ignitable ammonia/air-mixture by outgassing.

10.3 Possibility of hazardous reactions

A risk of explosion and/or of toxic gas formation exists with the following substances:
Oxidizing agents
Mercury
Oxygen
silver compounds
nitrogen trichloride
hydrogen peroxide
silver
antimony hydride

Halogens
Acids
Calcium
Chlorine
Chlorites
auric salts
perchlorates
sodium hypochlorite
mercury compounds
halogen oxides
Heavy metals
Heavy metal salts
Acid chlorides
Acid anhydrides
Risk of ignition or formation of inflammable gases or vapours with:
Boranes
Boron
Oxides of phosphorus
Nitric acid
silicon compounds
chromium(VI) oxide
chromyl chloride
Exothermic reaction with:
Acetaldehyde
Acrolein
Barium
boron compounds
Bromine
halogen-halogen compounds
hydrogen bromide
silane
Hydrogen chloride gas
halogen compounds
dimethylsulfate
nitrogen oxides
Fluorine
Hydrogen fluoride
chlorates
carbon dioxide
Ethylene oxide
polymerisable

10.4 Conditions to avoid
Heating.

10.5 Incompatible materials
Aluminum, Lead, Nickel, silver, Zinc, Copper, metal alloys, various metals

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Mixture

Acute toxicity
Oral: No data available
Symptoms: mucosal irritations, Cough, Shortness of breath, bronchitis, Possible damages:, damage of respiratory tract
Dermal: No data available

Skin corrosion/irritation
Skin - Rabbit
Result: Severe irritations
Remarks: (29% solution)
(RTECS)
Dermatitis Necrosis

Serious eye damage/eye irritation
Eyes - Rabbit
Result: Severe irritations
Remarks: (29% solution)
(RTECS)
Mixture causes serious eye damage. Risk of blindness!

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
No data available

Carcinogenicity
No data available

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
Mixture may cause respiratory irritation. - Respiratory system

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information

Cough
Shortness of breath
bronchitis
gastric pain
Bloody vomiting
Nausea
collapse
shock
Unconsciousness

Other dangerous properties can not be excluded.
Handle in accordance with good industrial hygiene and safety practice.

Components

ammonia solution

Acute toxicity
Oral: No data available
Inhalation: Material is extremely destructive to the tissue of the mucous membranes and upper respiratory tract.
Dermal: No data available

Skin corrosion/irritation
Causes skin burns.

Serious eye damage/eye irritation
Causes serious eye damage.

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
No data available

Carcinogenicity
No data available

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
May cause respiratory irritation.

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

SECTION 12: Ecological information

12.1 Toxicity

Mixture
No data available

12.2 Persistence and degradability
Biodegradability Remarks: No data available

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
PBT/vPvB assessment not available as chemical safety assessment not required/not conducted

12.6 Other adverse effects
Biological effects:
Harmful effect due to pH shift.
Forms toxic and corrosive mixtures with water even if diluted.

Discharge into the environment must be avoided.
No data available

Components

ammonia solution

Toxicity to fish	flow-through test LC50 - Pimephales promelas (fathead minnow) - 0.068 mg/l - 96 h Remarks: (in analogy to similar products) (ECHA) The value is given in analogy to the following substances: ammonium sulphate
Toxicity to daphnia and other aquatic invertebrates	static test LC50 - Daphnia magna (Water flea) - 101 mg/l - 48 h Remarks: (ECHA) anhydrous

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product

Waste material must be disposed of in accordance with the national and local regulations. Leave chemicals in original containers. No mixing with other waste. Handle uncleaned containers like the product itself. See www.retrologistik.com for processes regarding the return of chemicals and containers, or contact us there if you have further questions. The chemical must be disposed or recycled in accordance with Waste Disposal Act. See www.epa.gov.tw for the information of chemical waste disposal companies and their contacts.

SECTION 14: Transport information

14.1 UN number

ADR/RID: 2672 IMDG: 2672 IATA-DGR: 2672

14.2 UN proper shipping name

ADR/RID: AMMONIA SOLUTION
IMDG: AMMONIA SOLUTION
IATA-DGR: Ammonia solution

14.3 Transport hazard class(es)

ADR/RID: 8 IMDG: 8 IATA-DGR: 8

14.4 Packaging group

ADR/RID: III IMDG: III IATA-DGR: III

14.5 Environmental hazards

ADR/RID: yes IMDG Marine pollutant: yes IATA-DGR: no

14.6 Special precautions for user

None

14.7 Incompatible materials

Aluminum, Lead, Nickel, silver, Zinc, Copper, metal alloys, various metals

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture

No data available

SECTION 16: Other information

Training advice Provide adequate information, instruction and training for operators.

Full text of H-Statements referred to under sections 2 and 3.

H314	Causes severe skin burns and eye damage.
H318	Causes serious eye damage.
H335	May cause respiratory irritation.
H400	Very toxic to aquatic life.
H411	Toxic to aquatic life with long lasting effects.

The branding on the header and/or footer of this document may temporarily not visually match the product purchased as we transition our branding. However, all of the information in the document regarding the product remains unchanged and matches the product ordered. For further information please contact mlsbranding@sial.com.

Literature references	About detail information, please refer to each section The information contained herein is based on the present state of our knowledge. It characterises the product with regard to the appropriate safety precautions. It does not represent a guarantee of any properties of the product.		
Organization that prepared the SDS	Name:Merck KGaA LS-QH		
	Address/Telephone number:64271 Darmstadt Germany/+49 6151 72-0		
Date that the SDS was prepared	01.07.2021	Print Date	26. 10. 2021

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：Ammonia

1. Safety Assessment of Ammonia and Ammonium Hydroxide as Used in Cosmetics. CIR, 2017.

Safety Assessment of
Ammonia and Ammonium Hydroxide as Used in Cosmetics

Status: Scientific Literature Review for Public Comment
Release Date: July 7, 2017
Panel Date: September 11-12, 2017

All interested persons are provided 60 days from the above date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Interim Director, Dr. Bart Heldreth.

The 2017 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Interim Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, and Ivan Boyer, Ph.D., Toxicologist.

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INTRODUCTION

The safety of Ammonia and Ammonium Hydroxide in cosmetics is reviewed in this Cosmetic Ingredient Review (CIR) safety assessment. According to the *International Cosmetic Ingredient Dictionary and Handbook*, both ingredients are reported to function as pH adjusters in cosmetic products.[1] Additionally, Ammonia is reported to function as an external analgesic and fragrance ingredient and Ammonium Hydroxide is reported to function as adenaturant in cosmetic products. Functioning as an external analgesic is not a cosmetic use and, therefore, the Panel will not evaluate safety in relation to that use in cosmetics. Additionally, the function of fragrance may be excluded from the purview of the Panel, and is not assessed herein.

An Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile for Ammonia was published in 2004, and many of the toxicity studies summarized in this document are also included in this CIR safety assessment.[2] Pertinent information (e.g., number of animals tested and study details) that is missing from some of the study summaries in this safety assessment is being sought.

More recently, an Environmental Protection Agency (EPA) toxicological review that covers gaseous Ammonia (NH_3) and Ammonia dissolved in water (Ammonium Hydroxide, NH_4OH) was published in 2016.[3] It should be noted that portions of the EPA review are adapted from the toxicological profile for Ammonia that was developed by the ATSDR, and that this CIR safety assessment also includes toxicity data on Ammonia/Ammonium Hydroxide that have become available since the ATSDR and EPA documents were published.

In addition to the safety test data on Ammonia and Ammonium Hydroxide that are included in this safety assessment, the following data on surrogate chemicals are also included: data on ammonium ion (reproductive and developmental toxicity, genotoxicity, and carcinogenicity data) that are included in the ATSDR toxicological profile for Ammonia; diammonium phosphate (repeated dose (short-term) oral toxicity and reproductive and developmental toxicity data); ammonium chloride (genotoxicity data [micronucleus test]); ammonium sulfate (oral carcinogenicity and chronic oral toxicity data); and diammonium phosphate (reproductive toxicity data). The European Chemicals Agency (ECHA) registration dossier on Ammonia is the source of the safety test data on diammonium phosphate, ammonium chloride, ammonium sulfate, and ammonium sulfate.[4] The CIR Expert Panel will determine whether or not these data on surrogate chemicals are useful in evaluating the safety of Ammonia and Ammonium Hydroxide in cosmetic products.

Furthermore, in addition to the ASTDR and EPA reports on Ammonia, an expert assessment, prepared by a 14-member task group, of the effects on human health and the environment posed by Ammonia is available.[5] This assessment was published under the joint sponsorship of the United Nations Environment Program, the International Labor Organization, and the World Health Organization.

CHEMISTRY

Definition and General Characterization

Ammonia, ammonia gas, anhydrous ammonia, and liquid ammonia are terms that are often used interchangeably to refer to the ingredient, Ammonia, in either its liquid or gaseous state.[6] Ammonia dissolved in water is referred to as aqueous ammonia, ammonia solution, and the ingredient name, Ammonium Hydroxide. In an aqueous formulation, these two ingredients will each comprise at least some of the other.

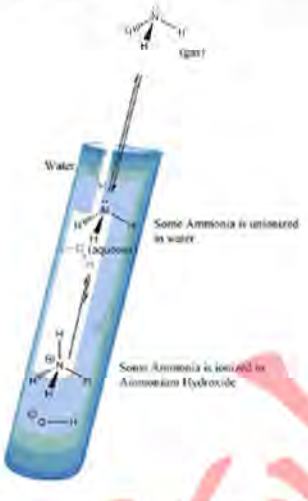


Figure 1. The aqueous relationship of Ammonia and Ammonium Hydroxide

Most inorganic hydroxides are alkaline salts formed by treating oxides with water, or via decomposing salts by adding other soluble hydroxides to a solution thereof. However, some Ammonium Hydroxide is formed simply by the hydrolysis of Ammonia. Regardless of whether the ingredient is named Ammonia or Ammonium Hydroxide, if the formulation or test article is aqueous, both are present due to an equilibrium. At or near neutral pH, more than 99% is in the form of dissolved (i.e. molecular) Ammonia, and less than 1% is Ammonium Hydroxide. In more alkaline (i.e. higher pH) solutions, the Ammonium Hydroxide concentration can be significantly higher though (e.g., at pH 9.25 the ratio of Ammonia to Ammonium Hydroxide is about 1:1; pK_b ~4.8 at room temperature). Accordingly, the ratio of dissolved molecular Ammonia versus the ions of Ammonium Hydroxide is dependent, *inter alia*, on the pH of the formulation. Saturation in water, at room temperature and atmospheric pressure, is approximately 34%.[7]

Application of ammonia gas (i.e., anhydrous ammonia) to cosmetics, without addition to water seems unlikely, unless some other reaction product is desired. Since the functions of external analgesic and fragrance may be excluded from the purview of the CIR Expert Panel, the only function of Ammonia under review herein is pH adjuster. The term "pH" refers to a ratio of hydroxide and hydronium ions in water. Accordingly, any ingredient that functions as a pH adjuster must do so in an aqueous formation. *Ipso facto*, this assessment addresses only the safety of the ingredient, Ammonia, as used in aqueous formulations. And, Ammonium Hydroxide does not exist outside of an aqueous solution. Therefore, whether Ammonia or Ammonium Hydroxide is on the cosmetic ingredient label, the chemical moieties contained therein are the same.

The definitions, structures, and functions in cosmetics of these ingredients are presented in Table 1.

Chemical and Physical Properties

Ammonia is a small nitrogenous compound with a molecular weight of 17, that is a gas at standard temperature and pressure.[8] It is a weak base that exists in equilibrium with the Ammonium Hydroxide as shown in Figure 1. Ammonium Hydroxide is a salt, formed by hydrolysis of Ammonia,that essentially does not exist outside of aqueous solution.

Chemical and physical properties of Ammonia and Ammonium Hydroxide are presented in Table 2.[2,9,10]

Method of Manufacture

Ammonia can be formed from water gas and producer gas via the Haber-Bosch process.[7]

Ammonium Hydroxide can be produced by passing Ammonia gas into water.[11]

Composition

According to the *Food Chemicals Codex*, Ammonium Hydroxide contains not less than 27% and not more than 30% by weight NH_3.[12] The monograph on strong Ammonia solution in the *United States Pharmacopoeia* states that this is a solution of NH_3, containing not less than 27% and not more that 31 % (w/w) NH_3.[13]

Impurities

According to the *Food Chemicals Codex*, the acceptance criteria for Ammonium Hydroxide include: lead (not more than 0.5 mg/kg), nonvolatile residue (not more than 0.02%), and readily oxidizable substances (pink color does not completely disappear within 10 minutes).[12] Similarly, according to the *United States Pharmacopoeia*, the limitations on strong Ammonia solution include: heavy metals (0.0013% limit), nonvolatile residue (not more than 5 mg of residue remains [0.05%]), and readily oxidizable substances (pink color does not completely disappear within 10 minutes).[13]

USE

Cosmetic

The safety of Ammonia and Ammonium Hydroxide is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database.[14] Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.[15]

According to 2017 VCRP data, Ammonia is being used in 599 cosmetic products (mostly rinse-off products) and Ammonium Hydroxide is being used in 1354 cosmetic products (mostly rinse-off products) (Table 3).[14] The results of a concentration of use survey provided by the Council in 2017 indicate that the highest maximum cosmetic use concentration of Ammonia is 4.6 % (in rinse-off products [hair dyes and colors]) and that the highest maximum cosmetic use concentration of Ammonium Hydroxide is 12.5% (in rinse-off products [hair dyes and colors]) (Table 3).[15] Regarding use concentrations in leave-on products, the highest maximum cosmetic use concentrations are 0.73% (Ammonia - in tonics, dressings, and other hair grooming aids) and 1.5% (Ammonium Hydroxide - in face and neck products [not spray]).

Cosmetic products containing Ammonia or Ammonium Hydroxide may be applied to the skin and hair or, incidentally, may come in contact with the eyes (at maximum use concentrations up to 0.58% [Ammonium Hydroxide] in eye area) and mucous membranes (Ammonium Hydroxide, in bath soaps and detergents). Products containing Ammonia or Ammonium Hydroxide may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Ammonia is on the European Union's list of substances that cosmetics must not contain, except when subject to the following restriction: maximum concentration in ready for use preparation (6% [as NH_3]).[16] Furthermore, the following phrase appears in the "wording of conditions of use and warnings" category: Above 2%: contains Ammonia. Ammonium Hydroxide does not appear on the European Union's list of substances that cosmetics must not contain.

Noncosmetic

Ammonia is a common industrial, and naturally formed, chemical with diverse uses, such as fertilizer and as a refrigerant.[17] It is also used in production of dyes, plastics, synthetic fibers, pesticides, and the purification of water, explosives, refrigerants, and pharmaceuticals.[6]

Ammonium Hydroxide is affirmed as generally recognized as safe (GRAS) as a direct human food ingredient.[11] This designation also means that Ammonium Hydroxide meets the specifications of the *Food Chemicals Codex* (see Impurities section).[12] Anhydrous Ammonia is used or intended for use as a source of nonprotein nitrogen in cattle feed.[18]

In Australia, Ammonia and Ammonium Hydroxide are listed in the *Poisons Standard*, the standard for the uniform scheduling of medicines and poisons (SUSMP) in schedules 5 and 6.[19] Under schedule 5, Ammonia and Ammonium Hydroxide are permitted in preparations containing $\leq$ 5% Ammonia, with the following exceptions: in preparations for human internal therapeutic use; in preparations for inhalation when absorbed in an inert solid material; or in preparations containing $\leq$ 0.5% free Ammonia. Schedule 5 chemicals are defined as substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label; schedule 5 chemicals are labeled with "Caution".

Ammonia, as an intravenously-injected prescription drug, is included on the list of FDA-approved drug products.[20] Ammonia solution has been classified as an over-the-counter (OTC) drug active ingredient as a skin protectant and external analgesic, and the same is true for Ammonium Hydroxide as a skin protectant. However, FDA has determined that there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses.[21]

TOXICOKINETIC STUDIES

Because of the equilibrium nature of these two ingredients, the studies that follow will simply recite "Ammonia" for most cases, regardless of whether Ammonia or Ammonium Hydroxide was reported.

Absorption, Distribution, Metabolism, and Excretion

Ammonia is the principle byproduct of amino acid metabolism, and the liver is the central organ of Ammonia metabolism.[8] It is generated from the breakdown of nitrogenous substances in the gut and from the use of glutamine as a metabolic fuel in the small intestine, and is taken up by the liver where it is detoxified by conversion to urea and, to a lesser extent, glutamine.[22,23] The main source of Ammonia generation occurs in the intestines, from lysis of blood-borne urea and also from protein digestion/deamination by urease-positive bacteria and microbial deaminase.[24,25] A large amount of metabolically-generated Ammonia is absorbed into the blood and, via the portal vein, is detoxified by the liver.[24,26,27] The normal concentration of Ammonia in the portal blood varies from 300 to 600 µM, but in the blood leaving the liver, the concentration is reduced to 20–60 µM. This indicates that the liver occupies a central position in the regulation of Ammonia levels in the organism.[28,29]

The substrates from which Ammonia may be formed in the gut comprise derivatives of ingested nitrogenous material, epithelial and bacterial debris, and compounds secreted from the circulation to the mucosal cells and lumen (e.g., certain peptides, amino acids, and smaller diffusible substances such as urea).[30] Both the gut and kidneys generate substantial amounts of Ammonia from the deamidation of glutamine.[8] The glutamine-glutamate cycle in the body works in conjunction with the glucose alanine cycle to shuttle Ammonia from peripheral to visceral organs.

Ammonia in aqueous solution (e.g., in the blood) is present as NH_3 and NH_4OH (Ammonia and Ammonium Hydroxide, respectively), with the ratio NH_3/NH_4OH depending on the pH, as defined by the Henderson-Hasselbach equation. However, contrary to expectations of simple solution phase kinetics, under physiological conditions with a blood pH of 7.4, more than 98% is in the form of NH_4OH.[24,31] Renal regulation of acid-base balance involves the formation and excretion of NH_3 to buffer hydrogen ions that are excreted in the urine. Approximately two-thirds of urinary NH_4OH is derived from the amide nitrogen of glutamine, a reaction that is catalyzed by the glutaminase enzyme in renal tubular cells.[8]

The urea cycle, a cycle of biochemical reactions that produces urea from Ammonia, is the major pathway for Ammonia detoxification in terrestrial mammals.[32] In the liver, the urea cycle is essential to the conversion of excess nitrogen from Ammonia and aspartate into urea.[33] When the supply of Ammonia in mammals exceeds the capacity for its detoxification, the excretion of orotic acid in the urine increases.[32] Orotic acid (from the urea cycle) is an intermediate product in the biosynthesis of pyrimidines.

Animal

Inhalation

Brain glutamine levels have been shown to increase in rats that inhaled 25 or 300 ppm Ammonia vapor for 6 hours/day for 5 days, which is likely a result of Ammonia metabolism by the astrocytic glutamate-glutamine cycle.[34,35]

Continuous exposure of rats for 24 h to concentrations up to 32 ppm Ammonia resulted in significant increase in blood Ammonia levels.[36] Exposures to 310 - 1157 ppm led to significantly increased blood concentrations of Ammonia within 8 h of exposure initiation, but blood Ammonia returned to pre-exposure values within 12 hours of continuous exposure and did not change over the remainder of the 24-hour exposure period.

Parenteral

Following the administration of [^{13}N]Ammonia to rats [via either the carotid artery or cerebrospinal fluid], most metabolized label was in glutamine (amide) and little was in glutamate (plus aspartate).[37]

Human

Oral

The first step in the degradation of most amino acids is the removal of an α-amino residue, and an amino residue is transferred to α-ketoglutaric acid to produce glutamate.[38] Glutamate dehydrogenase converts glutamate to α- ketoglutarate and Ammonia. Since Ammonia is highly toxic, it is converted to glutamine and alanine in a number of tissues for transportation to the liver. Ammonia is then converted to urea via the urea cycle in the liver, and urea is excreted in the urine.

TOXICOLOGICAL STUDIES

Because of the equilibrium nature of these two ingredients, the studies that follow will simply recite "Ammonia" for most cases, regardless of whether Ammonia or Ammonium Hydroxide was reported.

Acute Toxicity Studies

Acute toxicity studies (animal studies) are summarized in Table 4 (oral studies) and in Table 5 (inhalation studies). Human inhalation studies relating to Ammonia (ranging from 5 minutes to 6 weeks) are included in the section on Other Clinical Reports (Table 11) later in the report text.

Dermal

Acute dermal toxicity studies on Ammonia were not found in the published literature, nor were these data submitted.

Oral

Either no effects or no serious effects were reported for Ammonia in single oral exposure animal studies. However, when 0.3% Ammonia was administered to rats by gavage (33.3 mg/kg), gastric mucosal lesions were observed within 5 minutes. An acute oral LD_{50} of 350 mg/kg for Ammonia in rats has been reported, and the oral administration of 1 % or 3% (w/w as Ammonium Hydroxide) to rats by gavage has produced severe hemorrhagic lesions.[4,39,40,41,42,43,44,45]

Inhalation

In 10-minute exposure studies involving mice, LC_{50}s of ≤ 10,150 ppm have been reported. In mice exposed to Ammonia (100-800 ppm) for 30 minutes, an RD_{50} (exposure concentration that produced a 50% reduction in respiratory rate) of 303 ppm was reported. The following effects were observed in mice that were exposed to Ammonia at a concentration of

21,400 ppm for 30 minutes: eye irritation, dyspnea, histopathological changes in the lungs (alveolar disruption and loss of septal continuity), coma, and death. Within the range of concentrations tested (3440 ppm to 12,940 ppm) in 1-h exposure studies involving mice, the following effects have been observed: hepatic lesions, congestion, and necrosis; eye irritation; dyspnea; pneumonitis and atelectasis; histopathological changes in the lung (alveolar disruption and loss of septal continuity), and, in some cases, coma and death. Additionally, LC_{50} values of 4837 ppm and 4230 ppm for Ammonia have been reported for 1-h exposures to 3600-5720 ppm and 1190-4860 ppm, respectively.[22,46,47,48,49,50,51,52]

The acute inhalation toxicity of Ammonia was also evaluated in studies involving rats. Exposure durations ranged from 10 minutes (14,170-55,289 ppm) to 1-4 h (3,028-5,053 ppm). For the 10-minute exposure, LC_{50} values were ~ 22,885 ppm (males) and ~31,430 ppm (females) (at highest exposure concentration) and ~14,141 ppm (males) and ~19,769 ppm (females) (at lowest exposure concentration). For the 1-h and 4-h exposures, the LC_{50} were ~17,633 ppm and ~7068 ppm, respectively, and corneal opacity and signs of typical upper respiratory tract irritation were observed. Signs of upper respiratory tract irritation were also associated with exposures ranging from 20 to 45 minutes, which included exposure concentrations up to 35,000 ppm. Reduced body weight was reported for rats exposed to Ammonia at a concentration of 500 ppm. No effects were observed in rats exposed to Ammonia at a concentration of 144 ppm for 5, 15, 30, or 60 minutes. Toxic signs observed in studies in which rabbits were exposed for 1 h to Ammonia at concentrations ranging from 9,800 ppm to 12,800 ppm included congestion of respiratory tract tissues, bronchiolar damage, and alveolar effects (congestion, edema, atelectasis, hemorrhage, and emphysema). At lower concentrations, there was a significant decrease in the rate of respiration (50 ppm and 100 ppm, for 2.5-3 h) and increased respiratory tract fluid output (at 3.5 ppm and 8.7 ppm, for 1 h) in rabbits. Congestion of the respiratory tract/lungs was reported in studies in which cats were exposed to Ammonia for 1 h at concentrations ranging from 5,200 ppm to 12,800 ppm and, for 10 minutes, at a concentration of 1,000 ppm. Gross pathological findings after the 10-minute exposure included varying degrees of congestion, hemorrhage, edema, interstitial emphysema, and lung collapse.[22,4,46,53,54,55,56,57,58,59,60,61]

It has been noted that acute exposure data have demonstrated that injury to respiratory tissues is primarily due to Ammonia's alkaline (i.e., caustic) properties, resulting from the formation of hydroxide ion when Ammonia comes in contact with water and is solubilized.[3] Furthermore, Ammonia readily dissolves in the moisture on mucous membranes, forming Ammonium Hydroxide, which causes liquefactive necrosis of the tissues.

Short-Term Toxicity Studies

Short-term toxicity studies involving animals are summarized in Table 6 (oral and inhalation studies). Human inhalation studies relating to Ammonia (ranging from 5 minutes to 6 weeks) are included in the section on Other Clinical Reports (Table 11) later in the report text.

Dermal

Short-term dermal toxicity data on Ammonia were not found in the published literature, nor were these data submitted.

Oral

Ammonia and Diammonium Phosphate (included as a potentially similar ammonium salt)

Mucosal atrophy in the stomach antrum and enlargement of the proliferative zone in the mucosa of the stomach antrum and body were observed in rats that received Ammonia (0.01% in drinking water) for 8 weeks. A no-observed-adverse effect-level (NOAEL) of 250 mg/kg/day for general toxicity and a lowest-observed-adverse effect-level (LOAEL) of 750 mg/kg/day for general toxicity were reported for diammonium phosphate in rats dosed orally for 5 weeks.[4,62]

Inhalation

Rats were exposed repeatedly to Ammonia at concentrations ranging from 150 ppm (for 75 days) to 1306 ppm (for 42 days). The higher concentration was tolerated for 42 days in rats, and increased thickness of the nasal epithelium was observed at 150 ppm. When rats, rabbits, guinea pigs, monkeys, and dogs were exposed to Ammonia at a concentration of ~ 223 ppm or ~ 1105 ppm, the following effects were observed: focal pneumonitis in 1 of 3 monkeys at 223 ppm; nonspecific lung inflammation in guinea pigs and rats, but not other species at 1105 ppm; and mild to moderate dyspnea in rabbits and dogs during week 1 only at 1105 ppm. Upper respiratory effects (e.g., dyspnea and nasal lesions, irritation, and inflammation) were observed over most of the range of concentrations tested (145 ppm to 1306 ppm) in short-term inhalation toxicity studies on Ammonia involving mice, rats, guinea pigs, pigs, rabbits or dogs. At lower Ammonia concentrations, there were

no treatment-related effects in rats (at 50 or 90 ppm) and there was no increase in the incidence of respiratory diseases in pigs exposed to Ammonia (37 ppm or ~ 14.2 ppm, inhalable dust exposure) for 5 weeks. In other studies, nearly 64% lethality was reported for rats exposed to Ammonia (653 ppm) for 25 days (continuous exposure) and 50 of 51 rats exposed to Ammonia (650 ppm) were dead by day 65 of continuous exposure. A low incidence of carcinoma of the nasal mucosa was observed in mice exposed to Ammonia (12% solution) for 8 weeks, and these results are summarized in more detail in the Carcinogenicity section.[3,22,40, 45,53,63,64,90,65,66,67,94,95,96,68,69,70,71]

Risk Assessment

A minimal risk level (MRL) of 1.7 ppm has been derived for "acute-duration" inhalation exposure (14 days or less) to Ammonia. The study involved 16 subjects exposed to Ammonia (50 ppm, 80 ppm, 110 ppm, or 140 ppm). The MRL is based on a *LOAEL* of 50 ppm for mild irritation to the eyes (6 subjects), nose (20 subjects), and throat (9 subjects) in humans exposed to Ammonia as a gas for 2 hours. The 1.7 ppm MRL was calculated (50 ppm ÷ 30 [uncertainty factor] = 1.7; uncertainty factor = 10 [to protect sensitive individuals] x 3 [for use of a minimal LOAEL] = 30).[72]

It should be noted that The Occupational Safety and Health Administration (OSHA) has established an 8-hour time weighted average exposure limit of 50 ppm (35 mg/m^3) for Ammonia in the workplace.[73] Exposure to Ammonia shall not exceed the 50 ppm limit in any 8-h work shift of a 40-h work week.

Subchronic Toxicity Studies

Dermal

Subchronic dermal toxicity data on Ammonia were not found in the published literature, nor were these data submitted.

Oral

Subchronic oral toxicity data on Ammonia were not found in the published literature, nor were these data submitted.

Inhalation

Subchronic inhalation toxicity studies on Ammonia and Ammonium Hydroxide are summarized in Table 6.

Fatty changes of liver plate cells were seen in rats following continuous exposure to Ammonia (642 ppm) for 90 days. The following results were reported for guinea pigs exposed to ~ 170 ppm Ammonia for 18 weeks: mild congestion of the liver, spleen, and kidneys; degenerative changes in the adrenal glands; hemosiderosis in the spleen; and cloudy swelling in proximal kidney tubules. Damaged tracheal mucosae were observed in rats exposed repeatedly to Ammonia (100 ppm) for 12 weeks. Mild leucocytosis was noted in rats after exposure to 143 ppm, but not 43 ppm, Ammonia repeatedly for 3 months.[46,53, 63,74,75]

A low incidence of mortalities was observed in mice and guinea pigs exposed continuously to 671 ppm Ammonia for 90 days. However, there were no mortalities in rats, guinea pigs, rabbits, monkeys, or dogs exposed continuously to ~57.43 ppm Ammonia for 114 days.[55,85]

Chronic Toxicity Studies

Dermal

Chronic dermal toxicity data on Ammonia were not found in the published literature, nor were these data submitted.

Oral

Enlarged adrenal glands were observed in rabbits that received 124 mg ammonium/kg/day as (w/w/t as Ammonium Hydroxide) by gavage in water for 17 months.[76]

Ammonium Sulfate (included as a potentially similar ammonium salt)

The chronic oral toxicity of ammonium sulfate was evaluated using groups of 10 Fischer 344/DuCrj rats (males and females). Ammonium sulfate was administered in the diet daily at concentrations of 0%, 0.1%, 0.6%, and 3% for 52 weeks. None of the animals died, and there were no macroscopic findings. There was a significant increase in kidney and/or liver weights in males and females of the 3% dietary group, but there were no effects on survival rate, body weights, or hematological, serum biochemical, or histopathological parameters at any concentration. Several non-neoplastic lesions, such as bile duct proliferation in the liver and focal myocarditis in the heart were observed in the control and 3% dietary group, but the difference in results was not statistically significant when the 2 groups were compared.[4] Neoplastic lesions reported in this study are included in Table 8.

Inhalation

Human

Risk Assessment

Chronic occupational exposure (about 14 years) to low levels of airborne Ammonia (12.5 ppm) had no significant effect on pulmonary function or odor sensitivity in a group of workers at a soda ash factory, compared to a control group from the same factory that was not exposed to Ammonia.[77] The ATSDR derived a chronic inhalation minimal risk level (MRL) of 0.1 ppm for Ammonia from this study. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. Derivation of the MRL is described below.

An MRL of 0.1 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to Ammonia. The MRL is based on a NOAEL of 9.2 ppm for sense of smell, prevalence of respiratory symptoms (cough, bronchitis, wheeze, dyspnea, and others), eye and throat irritation, and lung function parameters (forced vital capacity [FVC], forced expiratory volume at end of 1 second of forced expiration [FEV1], FEV1/FVC, forced expiratory flow at 50% of FVC [FEF50], and FEF at 75% of FVC [FEF75]) in humans exposed for an average of 12.2 years in a soda ash plant; no LOAEL was determined.[77] The cohort consisted of 52 workers and 35 controls. The subjects were assessed on two workdays: on the first workday of their workweek and on the last workday of their workweek. Spirometry was performed at the beginning and end of each work shift, so that each worker had four tests done. To determine the exposure levels, exposed and control workers were sampled over one work shift; the average sample collection period was 8.4 hours. All of the participants in the study were males.

Analysis of the results showed no significant differences in the prevalence of reported symptoms, but the exposed workers reported that exposure in the plant aggravated some of their reported symptoms (cough, wheeze, nasal complaints, eye irritation, and throat discomfort). There were no significant differences in baseline lung functions between exposed and control subjects. Analysis of each worker separately showed no significant relationship between the level of Ammonia exposure and changes in lung function. Also, when the workers were divided into groups of individuals that were exposed to low (<6.25 ppm), medium (6.25–12.5 ppm), and high (>12.5 ppm) Ammonia levels, no significant association was found between reporting of symptoms, decline in baseline function, or increasing decline in function over the work shift and exposure to Ammonia. Furthermore, no association was evident between increasing years of exposure and decreasing lung function. However, the power of the indices of both level and length of exposure is low because only eight workers were in areas with relatively high Ammonia exposure. The MRL was calculated by adjusting the mean time-weighted average (TWA) exposure concentration of 9.2 ppm for continuous exposure (8/24 hours x 5/7 days) and dividing by an uncertainty factor of 10 to protect all of the sensitive individuals. A modifying factor of 3 was added for the lack of reproductive and developmental studies.[77]

Based on occupational epidemiology studies, the EPA calculated a chronic inhalation reference concentration (RfC) of 0.5 mg/m^3.[3] The critical effects in these studies were decreased lung function and respiratory symptoms.[78,77,79,80] The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental/reproductive toxicity studies are summarized in Table 7.

Ammonia and Diammonium Phosphate (included as a potentially similar ammonium salt)

A relationship between the duration of exposure and the incidence of exencephaly (concentration-related increase) was observed in an in vitro study in which mouse embryos were cultured with Ammonia (38 to 300 µmol/l) for up to 93 h. In a developmental toxicity study involving pregnant rats exposed to Ammonia in the diet (4293 mg/kg/day; w/w/t as the ammonium ion) from gestation day 1 through day 21 of lactation, body weights of offspring were reduced by 25% (males) and 16% (females). Neither reproductive nor developmental toxicity was reported in a study in which female pigs were exposed (inhalation exposure) to ~7 ppm or ~35 ppm Ammonia from 6 weeks prior to breeding until day 30 of gestation. In a reproductive and developmental toxicity study on diammonium phosphate involving rats, an NOAEL of 1500 mg/kg/day and an LOAEL of >1500 mg/kg/day were reported.[2,4,45,53,81,82,83]

GENOTOXICITY STUDIES

In Vitro

Ammonia was non-genotoxic when tested at concentrations up to 25,000 ppm (with and without metabolic activation) in the following bacterial strains: *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, TA1538, and *Escherichia coli* strain WP2 uvr A.[4,53,45]

Ammonia was non-genotoxic to E. coli strain Sd-4-73 in an in vitro assay without metabolic activation.[45]

In Vivo

Femoral bone marrow cells were examined for polychromatic erythrocytes, and there was no evidence of genotoxicity at the doses administered. Blood samples from 22 workers who had been exposed to Ammonia in a fertilizer factory were compared with samples obtained from 42 unexposed controls. Results (compared to controls) were as follows: increased frequency of chromosomal aberrations, sister chromatid exchanges, and mitotic index, with increasing duration of exposure. However, regarding these results, it has been noted that there are a number of limitations in this study, including gaps in the analysis, small study size, and possible confounding factors such as smoking and exposure to other chemicals.[2,4,19,45,53,84]

Ammonia and Ammonium Chloride (included as a potentially similar ammonium salt)

An increased frequency of micronuclei (compared to controls) was observed in Swiss albino mice that received single intraperitoneal doses of Ammonia (12, 25, or 50 mg/kg). In the micronucleus test, groups of 10 (5 males, 5 females) ddY mice received single intraperitoneal (i.p.) doses of 62.5, 125, 250 and 500 mg/kg ammonium chloride or i.p. doses of 31.3, 62.5, 125, and 250 mg/kg ammonium chloride (4 injections within 24 h).[4]

CARCINOGENICITY STUDIES

Carcinogenicity and tumor promotion studies are summarized in Table 8.

Ammonia and Ammonium Sulfate (included as a potentially similar ammonium salt)

There was no evidence of carcinogenicity in mice dosed orally with Ammonia (dissolved in water; 42 mg /kg/day; w/w/t as the ammonium ion) for 4 weeks. Following the oral dosing of mice (Swiss and C3H) with Ammonia193 mg/kg/day for 2 years, there was no evidence of carcinogenicity and no effect on the spontaneous development of adenocarcinoma of the breast (associated with C3H mouse strain). The life-time oral administration of Ammonia (in drinking water) to Swiss and C3H mice was not associated with any carcinogenic effects. Ammonium sulfate was classified as non-carcinogenic in rats in a study involving dietary concentrations up to 3% daily for 104 weeks. Neoplastic lesions were observed in this study, but were deemed not treatment-related because of the spontaneous occurrence of these lesions in the rat strain (F344/DuCrj) that was tested. Neoplastic lesions were also observed in F344/DuCrj rats after ammonium sulfate was fed in the diet at concentrations up to 3% for 52 weeks.[4,45,53,85,86,87,88,89,90]

Tumor Promotion

A statistically significant increase in the incidence of gastric cancer (70%) was observed in rats dosed orally with the initiator *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) and 0.01% Ammonia, when compared to dosing with MNNG alone.[88] In another study, the size, depth, and metastasis of MNNG-initiated tumors was enhanced in rats dosed orally with Ammonia (~42 mg/kg/day).[89]

OTHER RELEVANT STUDIES

Neurotoxicity

Ammonia is most toxic in the brain, and chronic hyperammonemia may lead to brain damage, especially in children.[8] It has been reported that hyperammonemia is associated with neuronal cell loss and cerebral atrophy that lead to mental retardation and cerebral palsy in pediatric patients.[91] These toxic effects are specific to the developing brain, as neuronal damage is not observed in the brain of adult patients with hyperammonemia due to liver failure.

According to another source, many neurologic disorders are related to congenital or acquired hyperammonemia. Evidence obtained with the use of experimental hyperammonemia models suggests that acute neurotoxic effects of Ammonia are mediated by overactivation of ionotropic glutamate (GLU) receptors, mainly the *N*-methyl-D-aspartate (NMDA) receptors, and, to a lesser degree, the kainic acid [KA]/α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA] receptors.[92] Results from other studies suggest that glutamine is also a mediator of Ammonia neurotoxicity.[93,94]

Toxic levels of Ammonia and alterations in pH, electrolyte disturbances, and membrane potential depolarization are thought to lead to neurological dysfunction, primarily by causing cellular swelling accompanied by brain edema and metabolic dysfunction.[24,95] Studies have suggested that Ammonia is likely to be particularly toxic to astrocytes, as they are the only cells that possess the enzyme glutamine synthetase, responsible for detoxifying Ammonia in the brain through condensation with glutamate.[96,97]

In in vitro studies, it has been demonstrated that acute intoxication with large doses of Ammonia leads to excessive activation of NMDA receptors.[98,99,100,101] Furthermore, excessive activation of NMDA receptors leads to neuronal degeneration and death and is responsible for most of the neuronal damage that is found in brain ischemia.[98]

Cytotoxicity

Lymphocytes separated from peripheral bovine (Holstein-Friesian cows) blood were incubated for 2 h in control medium and test medium with various concentrations of Ammonia (w/v as Ammonium Hydroxide; 0.01 mg/dl, 0.1 mg/dl, 1 mg/dl, and 10 mg/dl).[102] Viability of the lymphocytes, measured by trypan blue exclusion test, was significantly reduced after 2 h of incubation. At a concentration of 0.01 mg/ml, lymphocyte viability was significantly reduced after 24 h and 48 h of incubation. In another experiment, in which lymphocytes were preincubated with Ammonia (w/v as Ammonium Hydroxide; 10 mg/dl) and then washed and resuspended in the fresh medium with Ammonia, the number of viable cells was reduced to 51% ± 8 at 24 h, 40% ± 7 at 48 h, and to 39% ± 6 at 72 h of incubation.

Effect on Mitosis

The ability of Ammonia to affect the mitogenic response of bovine lymphocytes to phytohemagglutinin (PHA) or concanavalin A (Con A) was examined.[102] Lymphocytes from 10 Holstein-Friesian cows were incubated with various concentrations of PHA and Ammonia. Lymphocytes from 6 cows were incubated with Con A and Ammonia. Mitogenic reactivity was measured by the incorporation of methyl-^{3}H-thymidine into the DNA of lymphocytes. Ammonia at concentrations of 0.01 mg/dl (w/V as Ammonium Hydroxide) significantly ($P < 0.01$) suppressed PHA (optimal dose = 0.5 ug/ml) stimulation of lymphocytes from only 1 animal. Other concentrations of Ammonia, at 0.1 mg/dl, 1 mg/dl, and 10 mg/dl (w/V as Ammonium Hydroxide), significantly ($P < 0.01$) reduced the response to PHA of lymphocytes from 5 cows, 9 cows, and from all animals, respectively. These concentrations significantly reduced Con A (optimal dose = 0.5 µg/ml) stimulation of lymphocytes from 1 animal, 5 animals, and all animals, respectively. A significant suppression ($P < 0.01$) of blastogenesis of lymphocytes from 1 cow by 0.01 mg/dl, 6 by 0.1 mg/dl, 14 by 1.0 mg/dl, and from 16 cows by 10.0 mg/dl was observed. The mitogenic response of lymphocytes was reduced when lymphocytes were preincubated with Ammonia for a duration as short as 1 h.

Permeation of Blood Brain Barrier

There is evidence that Ammonia can cross blood-brain barrier (BBB), preferentially by active transport through ion transporters rather than diffusion.[24,103]

Generation of Free Radicals

Elevated concentrations of Ammonia have been shown to generate free radicals in rats and rat cell cultures,[104,105] leading to excessive production of nitric oxide (NO) by stimulating the citrulline-NO cycle.[106]

Immunological Effects

Guinea pigs exposed to 90 ppm Ammonia for 3 weeks developed a significant decrease in the cell-mediated immune response to challenge with a derivative of tuberculin.[107] Furthermore, the response of blood and bronchial lymphocytes to mitogens (phytohemagglutinin, concanavalin A, purified protein derivative of tuberculin) was markedly reduced.

A delayed-type hypersensitivity test was used to evaluate cell-mediated immunity in groups of 8 Hartley guinea pigs.[107] The animals were vaccinated with *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) and exposed to Ammonia (< 15 ppm, 50 ppm, or 90 ppm) for 3 weeks. Exposure to Ammonia was followed by intradermal challenge with a purified protein derivative. Dermal lesion size was reduced in animals that were exposed to Ammonia at a concentration of 90 ppm (Mean diameter of dermal lesion = 8.7 mm, statistically significantly different from control [$p < 0.05$]). Results were not statistically significant in the 2 other exposure groups. Also, blood and bronchial lymphocytes were harvested from guinea pigs exposed to Ammonia, and the cells were then stimulated with the mitogens phytohemagglutinin or concanavalin A. Reduced T cell proliferation was observed. However, bactericidal activity in alveolar macrophages isolated from Ammonia-exposed guinea pigs was not affected. In an *in vitro* experiment in which lymphocytes and macrophages were isolated from unexposed guinea pigs and then treated with Ammonia, reduced proliferation and bactericidal capacity were observed only at concentrations that reduced viability. These results were indicative of nonspecific effects of Ammonia-induced immunosuppression. The authors noted that the data in this study indicate that T cells may be the target of Ammonia exposure, in that specific macrophage effects were not observed.

Neurological Effects

Acute exposure to low levels of Ammonia (100 ppm) has been shown to depress free-access wheel running behavior in rodents.[108]

No overt symptoms of neurological disorders were reported in guinea pigs or monkeys that were exposed to up to 1,105 ppm Ammonia for 6 weeks (Coon et al. 1970).[63]

DERMAL IRRITATION AND SENSITZATION STUDIES

Dermal irritation studies are summarized in Table 9.

Irritation

An undiluted Ammonia solution (as 30% Ammonium Hydroxide) was classified as a corrosive material after topical application to the stratum corneum surface in reconstructed human skin cultures in vitro. At histologic examination of the cultures, epidermal necrosis was observed. The minimum concentration of Ammonia that caused an inflammatory reaction when applied (single application) to the skin of rats and mice (6 per species) was > 25% (rats) and 25% (mice). In a skin irritation study in which groups of 4 rats, guinea pigs, and mice were injected intradermally with Ammonia (0.01 ml), the minimum concentration that caused a positive reaction was 0.05% in rats, mice, and guinea pigs.[109] Ammonia (20% as Ammonium Hydroxide) was corrosive to the skin of rabbits. In another study involving rabbits, 12% aqueous Ammonia was corrosive to the skin, whereas 10% was not. In clinical testing, the application of a saturated aqueous solution of Ammonia to the skin of 16 subjects resulted in blister formation and skin irritation. In a study involving 110 subjects, Ammonia (1:1 aqueous solution) was applied to the skin and minimal blistering time (MBT) served as an indicator of cutaneous irritability. The inflammatory reaction observed was considered slight, and MBT ranged from 3 to 57 minutes. Results from another study in which 50% Ammonia solution was applied to the skin indicated that the time required to produce a full blister was greatly prolonged in the aged, when compared to young adults.[4,19,45,110,109,111,112,113]

Sensitization

Skin sensitization data on Ammonia were not found in the published literature, nor were these data submitted.

OCULAR IRRITATION STUDIES

Ocular irritation studies are summarized in Table 10.

Ammonia (*w* as Ammonium Hydroxide) at 1 mg was classified as an ocular irritant in rabbits. At a concentration of 28.5%, Ammonia induced corneal opacity in rabbits. In a study involving groups of 6 rabbits, Ammonia caused conjunctivitis at concentrations of 1% to 10%, but not 0.3%; the 10% concentration also caused corneal opacities within 1 h of instillation. Conjunctivitis and corneal damage were also observed in a study involving 3 rabbits, whereby 3% Ammonia, 100 µl was instilled into the eyes. Ammonia was classified as a severe ocular irritant in the in vitro ^{51}Cr-release assay involving human corneal endothelial cell cultures.[114]

In a study involving rats, there was no evidence of ocular irritation following exposure to Ammonia at vapor concentrations ranging from 15 to 1157 ppm. It has been reported that Ammonia can penetrate the eye rapidly and that ocular irritation or damage can occur at concentrations as low as 20 ppm.[2,17,22,36, 45,114,115,116,117]

MUCOUS MEMBRANE IRRITATION STUDIES

The stomachs of male Sprague-Dawley rats were exposed (mounted in ex vivo gastric chamber) to 2 ml of Ammonia (15-60 mmol/l, in saline) for 15 minutes (for microscopic study) or for 60 minutes (for macroscopic study), and exposure was followed by examination for mucosal lesions. Microscopic damage to the gastric mucosa was observed.[118]

CLINICAL STUDIES

Case Reports

A 68-yr-old male patient, employed for 18 years, was exposed frequently to anhydrous Ammonia leaks from a microfilm processor camera while on the job. He was diagnosed with interstitial lung disease and severe restrictive lung disease due to Ammonia inhalation. Marked diffuse interstitial fibrosis throughout the lung was observed.[119]

The excessive formation of Ammonia within the brains of Alzheimer's disease patients and its release into the periphery has been demonstrated.[120,121] Furthermore, a higher expression of AMP-deaminase in the brains of Alzheimer's disease patients has been observed, and this finding indicates the existence of a pathologically elevated source of Ammonia within the brain of Alzheimer's disease patients.[120,122]

A male custodian had used Ammonia (28% Ammonium Hydroxide solution) to clean office floors daily for 19 years.[123] He experienced regular episodes of upper airway irritation, coughing, and eye irritation when mixing the chemical in water. An evaluation of the patient revealed a negative rheumatoid factor and positive antinuclear antibody at a 1:320 dilution. The gallium lung scan was normal, but pulmonary function testing indicated a moderate restrictive defect and a formal exercise study indicated ventilator restriction upon attainment of maximum oxygen consumption. The results of a transbronchial lung biopsy with fiberoptic bronchoscopy revealed interstitial fibrosis with chronic inflammation. Granulomata were not present and cultures for tuberculosis and fungal infection were negative. A decrease in the diameter of the hypopharynx, secondary to hypertrophy of the soft tissues in the hypopharynx, was also observed. The opacification of the optic lens capsule, bronchiectasis, and fibrous obliteration of the small airways observed were described as chronic lesions that follow acute exposure to Ammonia.

Other Clinical Reports

Clinical reports relating to inhalation exposure are summarized in Table 11.

In various clinical reports, individuals were exposed to Ammonia at concentrations ranging from 25 ppm to 700 ppm. The periods of exposure ranged from 5 minutes to 6 weeks (5 days per week [2-6 h/day]). Nose, throat, and eye irritation were observed.[46,72,124,125,126,127,128]

EPIDEMIOLOGICAL STUDIES

Non-Cancer Endpoints

A retrospective study was performed to assess the association between petrochemical exposure and spontaneous abortion. Study participants included 2853 non-smoking women who had been pregnant at least once, 96 of whom had been exposed to Ammonia (actual exposure levels unknown). Exposure during the pre-conception period and the first trimester of pregnancy was calculated based on information on perceived Ammonia exposure. Exposure during the first, second, and third trimesters was recorded separately for each pregnancy. Data analyses did not indicate any effect on spontaneous abortion (Odds ratio: 1.2; 95% confidence interval (CI): 0.5-2.60.[4]

SUMMARY

The safety of Ammonia and Ammonium Hydroxide in cosmetics is reviewed in this safety assessment. According to the Dictionary, both ingredients function as pH adjusters in cosmetic products. Additionally, Ammonia functions as an external analgesic and fragrance ingredient and Ammonium Hydroxide functions as a denaturant in cosmetic products. Functioning as an external analgesic is not a cosmetic use and, therefore, the Panel did not evaluate safety in relation to that use in cosmetics. Additionally, the function of fragrance may be excluded from the purview of the Panel, and is not assessed herein.

According to 2017 VCRP data, Ammonia is being used in 599 cosmetic products (mostly rinse-off products) and Ammonium Hydroxide is being used in 1354 cosmetic products (mostly rinse-off products). The results of a concentration of use survey provided by the Council in 2017 indicate that the highest maximum cosmetic use concentration of Ammonia is 4.6 % (in rinse off products [hair dyes and colors]) and the highest maximum cosmetic use concentration of Ammonium Hydroxide is 12.5% (in rinse off products [hair dyes and colors]). Regarding use concentrations in leave-on products, the highest maximum cosmetic use concentrations are 0.73% (Ammonia - in tonics, dressings, and other hair grooming aids) and 1.5% (Ammonium Hydroxide - in face and neck products [not spray]).

These two ingredients are indistinguishable from each other in aqueous formulation. Since the only cosmetic function of Ammonia applicable to this safety assessment is pH adjustor (which by default means aqueous formulations only) and Ammonium Hydroxide does not exist outside of water, regardless of which ingredient is added the final formulations will contain an equilibrium of molecular Ammonia and the ions of Ammonium Hydroxide in water. Thus, whether toxicity data is reported for Ammonia or Ammonium Hydroxide, it is applicable to both (as the test articles would have had this same equilibrium).

An acute oral LD_{50} of 350 mg/kg has been reported in a study involving rats dosed orally with Ammonia dissolved in water. Severe hemorrhagic lesions have been observed in rats dosed orally with 1% or 3% Ammonia (% as Ammonium Hydroxide).

It has been noted that acute exposure data have demonstrated that injury to respiratory tissues is primarily due to Ammonia's alkaline (i.e., caustic) properties from the formation of hydroxide ion when it comes in contact with water and is solubilized. In acute inhalation toxicity studies, Ammonia was tested at concentrations ranging from 3.5 ppm (cats and rabbits, 1-h exposure) to 54,289 ppm (rats, 10-minute exposure). Exposure to the highest concentration resulted in hemorrhagic lungs, and increased respiratory fluid output was noted at the lowest concentration. In 10-minute exposure studies involving mice, LC_{50} of $\leq$ 10,150 ppm have been reported. In mice exposed to Ammonia (100-800 ppm) for 30 minutes, an RD_{50} of 303 ppm was reported. Within the range of concentrations tested (3440 ppm to 12,940 ppm) in 1-h exposure studies involving mice, the following effects have been observed: hepatic lesions, congestion, and necrosis; eye irritation; dyspnea; pneumonitis and atelectasis; histopathological changes in the lung (alveolar disruption and loss of septal continuity), and, in some cases, coma and death.

Exposure durations ranged from 10 minutes (14,170-55,289 ppm) to 1-4 h (3,028-5,053 ppm) in acute inhalation toxicity studies involving rats. For the 10-minute exposure, LC_{50} values were ~ 22,885 ppm (males) and ~31,430 ppm (females) (at highest exposure concentration) and ~14,141 ppm (males) and ~19,769 ppm (females) (at lowest exposure concentration). For the 1-h and 4-h exposures, the LC_{50} were ~17,633 ppm and ~7068 ppm, respectively, and corneal opacity and signs of typical upper respiratory tract irritation were observed.

In short-term oral toxicity studies involving rats, doses of ~ 42 mg/kg/day for 8 weeks resulted in mucosal atrophy in the stomach antrum, and doses up to 1500 mg/kg/day for 35 days resulted in treatment-related changes in body weight, hematological findings, clinical biochemistry findings, and non-neoplastic histopathological findings.

Ammonia was evaluated at concentrations ranging from 0.6 ppm, to 1,306 ppm in short-term inhalation toxicity studies. The results of these studies indicate histopathological changes of respiratory tissues in several animal species (lung inflammation in guinea pigs and rats; focal or interstitial pneumonitis in monkeys, dogs, rabbits, and guinea pigs; pulmonary congestion in mice; thickening of nasal epithelium in rats and pigs; nasal inflammation or lesions in rats and mice) across different dosing regimens. In general, responses in respiratory tissues increased with increasing Ammonia exposure concentration.

Fatty changes of liver plate cells were seen in rats following continuous exposure to Ammonia (642 ppm) for 90 days. Mild congestion/degenerative changes in internal organs were reported for guinea pigs exposed to ~ 170 ppm Ammonia for 18 weeks. Damaged tracheal mucosae were observed in rats exposed repeatedly to Ammonia (100 ppm) for 12 weeks. Mild leucocytosis was noted in rats after exposure to 143 ppm, but not 43 ppm, Ammonia repeatedly for 3 months. A low incidence of mortalities was observed in mice and guinea pigs exposed continuously to 671 ppm Ammonia (reported as Ammonium Hydroxide) for 90 days. However, there were no mortalities in rats, guinea pigs, rabbits, monkeys, or dogs exposed continuously to ~57.43 ppm for 114 days.

Enlarged adrenal glands were observed in rabbits that received 124 mg /kg/day Ammonia (w/w/t as Ammonium Hydroxide) by gavage in water for 17 months.

In a developmental toxicity study involving pregnant rats exposed to Ammonia in the diet (4293 mg/kg/day; w/w/t as the ammonium ion) from gestation day 1 through day 21 of lactation, body weights of male and female offspring were reduced. Neither reproductive nor developmental toxicity were reported in a study in which female pigs were exposed (inhalation exposure) to ~7 ppm or ~35 ppm Ammonia from 6 weeks prior to breeding until day 30 of gestation. In a reproductive and developmental toxicity study on diammonium phosphate involving rats, a NOAEL of 1500 mg/kg/day and an LOAEL of >1500 mg/kg/day were reported.

In the Ames test with and without metabolic activation, Ammonia was non-genotoxic in Salmonella typhimurium strains and in Escherichia coli strain WP2 uvr A. Without metabolic activation, it was nongenotoxic to E. coli strain Sd-4-73. An increased frequency of micronuclei (compared to controls) was observed in Swiss albino mice that received single intraperitoneal doses. Ammonium chloride was non-genotoxic in ddY mice the micronucleus test.

Increased frequencies of chromosomal aberrations, sister chromatid exchanges, and mitotic index, with increasing duration of exposure were reported for workers who had been exposed to Ammonia in a fertilizer factory. However, it was noted that some of the limitations associated with this study include small study size and confounding factors such as smoking and exposure to other chemicals.

Ammonia (whether reported as Ammonia or Ammonium Hydroxide) was not carcinogenic in Swiss and C3H mice dosed orally. A statistically significant increase in the incidence of gastric cancer (70%) was observed in rats dosed orally with MNNG and 0.01% Ammonia, when compared to dosing with MNNG alone. In another study, the size, depth, and metastasis of MNNG-initiated tumors were enhanced in rats dosed orally with Ammonia (~42 mg/kg/day).

It has been reported that hyperammonemia (a metabolic disturbance characterised by an excess of Ammonia in the blood) is associated with neuronal cell loss and cerebral atrophy that lead to mental retardation and cerebral palsy in pediatric patients.

At a concentration of 0.01 mg/ml Ammonia, lymphocyte (from cows) viability was significantly reduced after 24 h and 48 h of incubation. In another study, the mitogenic response of lymphocytes was reduced after preincubation with Ammonia.

Guinea pigs exposed to 90 ppm Ammonia for 3 weeks developed a significant decrease in the cell-mediated immune response to challenge with a derivative of tuberculin.

No overt symptoms of neurological disorders were reported in guinea pigs or monkeys that were exposed to up to 1,105 ppm Ammonia for 6 weeks.

In rabbits, Ammonia (1 mg of Ammonium Hydroxide) was classified as an ocular irritant and 28.5% Ammonia (reported as Ammonium Hydroxide) induced corneal opacity. Additionally, Ammonia caused conjunctivitis in rabbits at concentrations of 1% to 10% (reported as Ammonium Hydroxide), but not 0.3%.

The minimum concentration of Ammonia that caused an inflammatory reaction when applied (single application) to the skin of rats and mice (6 per species) was > 25% (rats) and 25% (mice). In a skin irritation study in which groups of 4

rats, guinea pigs, and mice were injected intradermally with Ammonia (0.01 ml), the minimum concentration that caused a positive reaction was 0.05% in rats, mice, and guinea pigs.[109] Ammonia (reported as Ammonium Hydroxide; 20% and 12%) was corrosive to the skin of rabbits, whereas the 10% concentration was not.

The application of a saturated aqueous solution of Ammonia (reported as Ammonium Hydroxide) to the skin of 16 subjects resulted in blister formation and skin irritation. In a study involving 110 subjects, Ammonia (reported as Ammonium Hydroxide; 1:1 aqueous solution) was applied to the skin and the inflammatory reaction observed was considered slight.

Microscopic damage to the gastric mucosa was observed in the stomachs of male rats exposed (ex vivo) to Ammonia (up to 60 mmol/l of Ammonium Hydroxide) for 15 minutes.

In various clinical reports, ocular, nasal, and throat irritation were observed in human subjects exposed to Ammonia in the 25 ppm to 700 ppm concentration range.

A retrospective study was performed to assess the association between petrochemical exposure and spontaneous abortion. Study participants included 2853 non-smoking women who had been pregnant at least once, 96 of whom had been exposed to unknown Ammonia concentrations. Data analyses did not indicate any effect on spontaneous abortion.

Request for Additional Data

- Dermal absorption data
- Sensitization data

Table 1. Definition, Idealized Structures, and Functions of the Ingredients in this Safety Assessment. [1; CIR Staff]

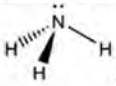
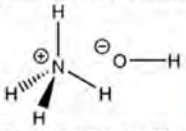
Ingredient CAS No.	Definition & Idealized Structures	Function
Ammonia	Ammonia is an inorganic gas that conforms to the formula:  (See also Ammonium Hydroxide)	External Analgesics; Fragrance Ingredients; pH Adjusters
Ammonium Hydroxide	Ammonium Hydroxide is an inorganic base that conforms to the formula:  [In reality however, the solid, anhydrous salt does not exist. Instead, Ammonium Hydroxide is only present as an aqueous ion pair, the result of hydrolysis (not dissociation of a solid salt), in equilibrium with dissolved ammonia]	Denaturants; pH Adjusters

Table 2. Physical and Chemical Properties of Ammonia and Ammonium Hydroxide

Property	Value	Reference
Ammonia		1
physical form and/or color	Gas at room temperature; colorless	1
molecular weight (Daltons (Da))	17.03	1
water solubility (% w/w at 20°C)	33.1	1
Other solubility (%w/w at 25°C)	10 (absolute ethanol); 16 (methanol); soluble in chloroform and ether	1
density (g/L)	0.7710 (gas);	1
density (g/L at -33.5°C and 1 atm)	0.6818 liquid); 0.7 (liquid)	2,9
vapor density (air = 1)	0.5967	1
specific gravity (g/L at 25°C)	0.747	1
melting point (°C)	-77.7	2,9
boiling point (°C)	-33.35	2,9
autoignition temperature (°C)	650	1
vapor pressure (atm at 20°C)	8.5	1
log K_{ow} (estimated)	0.23	1
Ammonium Hydroxide		
density (g/L at 20°C)	0.89801(28% aqueous)	1
Formula weight (Da)	35.05	9
log K_{ow} (estimated)	-4.37	10

Table 3. Frequency and Concentration of Use According to Duration and Type of Exposure.[14,15]

	Ammonia		Ammonium Hydroxide		
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	
Totals/Conc. Range	599	0.00002-4.6	1354	0.00028-12.5	
Duration of Use					
Leave-On	7	0.00002-0.73	163	0.003-1.5	
Rinse off	592	0.00015-4.6	1191	0.00028-12.5	
Diluted for (bath) Use	NR.	NR.	NR.	NR.	
Exposure Type					
Eye Area	1	NR.	42	0.022-0.58	
Incidental Ingestion	NR.	NR.	NR.	NR.	
Incidental Inhalation- Sprays	3***	0.73*	6*	0.29-1.3*	
Incidental Inhalation- Powders	3***	0.00002-0.14**	NR.	0.45-1.5**	
Dermal Contact	6	0.00002-0.14	159	0.0012-1.7	
Deodorant (underarm)	NR.	NR.	NR.	NR.	
Hair - Non-Coloring	10	0.00006-1.4	72	0.00028-3.6	
Hair-Coloring	582	2.8-4.6	1104	2.5-12.5	
Nail	1	0.00008-0.00075	3	0.003-1.2	
Mucous Membrane	NR.	NR.	1	NR.	
Baby Products	NR.	NR.	NR.	NR.	

NR. = Not Reported; Totals = Rinse-off + Leave-on + Diluted for Bath Product Uses.
*It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.
**It is possible that these products may be powders, but it is not specified whether the reported uses are powders.
***Not specified whether a powder or spray, so this information is captured for both categories of incidental inhalation.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 4. Acute Oral Toxicity Studies

Ingredient	Animals	Protocol	Results
Ammonia (0.3%)	Rats.	Administered by gavage (dose = 33.3 mg/kg)	Gastric mucosal lesions produced within 5 minutes.[42]
Ammonia (dissolved in water)	Male Wistar rats (groups of 10)	Administered by gavage according to Organization for Economic Co-operation and Development (OECD) Guideline 401. Dosing followed by 14-day observation period	LD_{50} (calculated) = 350 mg/kg.[4,43,45]
Ammonium Hydroxide (1% or 3%)	Rats	Administered by gavage	Severe hemorrhagic lesions produced.[44]

Table 5. Acute Inhalation Toxicity

Ingredient	Animals/Protocol	Results
Ammonia (21,400 ppm)	Mice. 30-minute exposure	Signs and symptoms included eye irritation (blinking and scratching), dyspnea, frothing, convulsions, excitation/escape behavior, coma, and death. Histopathology of the lungs of mice that died showed alveolar disruption and loss of septal continuity.[22,47]
Ammonia (8,770-12,940 ppm)	Mice (groups of 20). 10-minute exposure	LC_{50}=10,150 ppm.[46,48,53]
Ammonia (8,723-12,870 ppm)	Mice. 10-minute exposure	At 8,723 ppm, 25% of the animals died. At 12,870 ppm, and 80% of the animals died. LC_{50} = 10,096 ppm.[22,48]
Ammonia (3,600-5,720 ppm)	Mice. 1-h exposure	Nasal and eye irritation, followed by labored breathing, in all groups. Gross examination of surviving mice showed mild congestion of the liver at the intermediate (4550 ppm) and high (5720 ppm) concentrations. LC_{50} = 4837 ppm (95% CI = 4409–5305 ppm).[22,50,53]
Ammonia (1,190-4,860 ppm)	ICR male mice (groups of 12). 1-h exposure	In animals that survived 14-day observation period, pathologic lesions included mild-to-moderate pneumonitis (dose-related severity), focal atelectasis in the lungs (4,860 ppm), and degenerative hepatic lesions (dose-related severity, 3,440–4,860 ppm). LC_{50} = 4,230 ppm.[22,48,53]
Ammonia (4,840 ppm)	Mice. 1-h exposure	Signs and symptoms included eye irritation (blinking and scratching), dyspnea, frothing, convulsions, excitation/escape behavior, coma, and death. Histopathology of the lungs of mice that died showed alveolar disruption and loss of septal continuity.[22,51]
Ammonia (3,440 ppm)	Mice. 1-h exposure	Liver necrosis.[49]
Ammonia (92 mg/m^3 [~132 ppm] to 1243 mg/m^3 [~1785 ppm])	SPF mice of the OF1-ICO strain. Nose-only exposure for 45 minutes	Mice appeared more susceptible to ammonia in presence of dry air (RD_{50} (exposure concentration producing a 50% decrease in respiratory rate) = 582 [407 ppm] and 732 mg/m^3 [547 ppm] in dry and wet air, respectively).[22,58]
Ammonia (100-800 ppm)	Male Swiss-Webster mice. 30-minute exposure	RD_{50} = 303 ppm (95% confidence limits = 188–490 ppm).[22,52,53]
Ammonia (9,870 mg/m^3 [14,170 ppm] to 37,820 mg/m^3 [54,289 ppm])	SPF-bred Wistar rats (5 males, 5 females/group). 10-minute exposure to 54, 289 ppm and 60-minute exposure to 14,170 ppm	LC_{50} (higher concentration) = 15,940 mg/m^3 (~22,885 ppm) (males) and 31,430 mg/m^3 (~45,124 ppm) (females). LC_{50} (lower concentration) = 9,850 mg/m^3 (~14,141 ppm) (males) and 13,770 mg/m^3 (~19,769 ppm) (females). Hemorrhagic lungs in animals that died.[4,54]
Ammonia (9,000-35,000 ppm)	Male Sprague-Dawley rats: 4 groups of 6 (9,000 to 26,000 ppm), 1 group of 8 (30,000 ppm), and 1 group of 4 (35,000 ppm). Exposure for 20 minutes in head-out exposure system	Lung edema increased in all groups. Dose-dependent increases in ocular irritation, lacrimation, and labored breathing. LC_{50} (determined by probit analysis) = 23,672 ppm.[55]

Table 5. Acute Inhalation Toxicity

Ingredient	Animals/Protocol	Results
Ammonia (9,000 to 23,000 ppm)	Groups of 6 male Sprague-Dawley rats. Exposure for 20 minutes in head-only exposure system for 20 minutes	Peak inspiratory and expiratory flow decreased after exposure to 20,000 and 23,000 ppm. Weight loss, and increased total blood cell counts (white blood cells, neutrophils, and platelets) after exposure to 20,000 ppm. Morphological changes at histopathologic examination of lungs and trachea: alveolar, bronchial, and tracheal edema; epithelial necrosis, and exudate at 20,000 ppm.[96]
Ammonia (3028-14,044 ppm)	Male and female SPF-bred Wistar rats (Hsd Cpb:WU strain; 5 males, 5 females). Nose-only exposure to 9,222-14,044 ppm for 1 h and 3,028-5,053 ppm for 4 h.	Signs typical of upper respiratory tract irritation. No gross abnormalities in any organ or nasal passages were found at necropsy of surviving rats (2 weeks post-exposure). Rats that died had corneal opacity, collapsed lungs, nasal discharge, reddened larynx, and tracheal epithelial desquamation. LC_{50} (1-h exposure) = = 12,303 mg/m^3 [~17,633 ppm]). LC_{50} (4-h exposure = 4,923 mg/m^3 [~7068 ppm]).[97] -
Ammonia (6210-9840 ppm)	Groups of 10 male CFE rats. 1-h exposure	Signs of eye and nasal irritation observed immediately, followed by labored breathing and gasping. Surviving animals exposed to the low concentration weighed less than controls on day 14, and gross examination showed mottling of the liver and fatty changes at the two highest concentrations. LC_{50} = 7338 ppm (95% CI = 6822–7893 ppm).[22,50-53]
Ammonia (431, 1436, and 4307 ppm)	Rats. Inhalation exposure	Decrease in static muscular tension and other sublethal effects.[53]
Ammonia (1436, 4307, and 6814 ppm)	White rats. Inhalation exposure	Dyspnea, irritation of respiratory tract and eyes, cyanosis of extremities, and increased excitability.[53]
Ammonia (92 mg/m^3 [~132 ppm] to 1243 mg/m^3 [~1785 ppm])	Groups of 4 male specific pathogen free (SPF) Wistar rats of the Hsd Cpb:WU (SPF) strain. Nose-only exposure for 45 minutes	RD_{50} = 972 and 905 mg/m^3 (corresponding to ~1306 and ~1299 ppm, respectively) in rats in dry and wet air, respectively.[22,98]
Ammonia (500 ppm)	Rats. Inhalation exposure	Reduced body weight.[99]
Ammonia (144 ppm)	Rats. Inhalation exposure for 5, 10, 15, 30, or 60 minutes	No effects.[53]
Ammonia (5,200-12,800 ppm)	Rabbits. 1-h exposure	Average survival: 18 h (gassed after cannulation), 33 h (gassed before cannulation). 2- to 3-fold increase in production of respiratory tract fluid. No change in water content of lungs. Increased blood hemoglobin. Increased plasma lipids.[22]
Ammonia (10,360 ppm, average)	Rabbits. 1-h exposure	Congestion of respiratory tract tissues.[22]
Ammonia (50 ppm and 100 ppm)	16 New Zealand White rabbits. Inhalation Exposure for 2.5 h to 3 h	Significant decrease in rate of respiration.[53]
Ammonia (3.5 ppm and 8.7 ppm)	54 rabbits. Exposure for 1 h	Increased respiratory tract fluid output by 2- to 3-fold. No appreciable effect on water content of respiratory tract tissues. Transient decrease in blood hemoglobin. Lipemia also observed.[53]

Table 5. Acute Inhalation Toxicity

Ingredient	Animals/Protocol	Results
Ammonia (5,200-12,800 ppm)	Cats. 1-h exposure	Average survival: 18 h (gassed after cannulation), 33 h (gassed before cannulation). 2- to 3-fold increase in production of respiratory tract fluid. No change in water content of lungs. Increased blood hemoglobin. Increased plasma lipids.[46,60]
Ammonia (10,360 ppm, average)	Cats. 1-h exposure	Congestion of respiratory tract tissues.[46,60] –
Ammonia (1,000 ppm)	20 cats. 10-minute exposure	Biphasic course of respiratory pathology Effects at 24 h post-exposure included severe dyspnea, anorexia, and dehydration; rhonchi and coarse rales evident upon auscultation. Gross pathology revealed varying degrees of congestion, hemorrhage, edema, interstitial emphysema, and collapse of the lungs at all time points. Pulmonary resistance increased throughout the study.[53,61]
Ammonia (3.5 ppm and 8.7 ppm)	18 cats. Exposure for 1 h	Increased respiratory tract fluid output by 2- to 3-fold. No appreciable effect on water content of respiratory tract tissues. Transient decrease in blood hemoglobin.[62]

Table 6. Short-Term and Subchronic Toxicity Studies

Ingredient	Animals	Protocol	Results
Short-term Oral Studies			
Ammonia (0.01% in drinking water)	Rats	~ 42 mg/kg/day for 8 weeks	Mucosal atrophy in stomach antrum and enlargement of proliferative zone in antral and body mucosa. [62]
diammonium phosphate (17.9% NH_4 and 46.86% P_2O_5 equivalent)	Groups of Crj: CD(SD) rats (5 males, 5 female/group)	Administered by gavage daily (doses of 0, 250, 750, and 1500 mg/kg/day, 7 days/week) for 35 days	Clinical signs were not observed, and none of the animals died. However, there were treatment-related changes in body weight, hematological findings, clinical biochemistry findings, and non-neoplastic histopathological findings. Histological examination of stomachs revealed some submucosal inflammation at all doses, but this change was not dose-dependent and was not statistically significant at the low dose. LOAEL for general toxicity = 750 mg/kg/day.[4,33,45]
Short-term Inhalation Studies			
Ammonia (~1,306 ppm)	Rats	5 days/week (8 h/day)	Exposure tolerated for 42 days. [63]
Ammonia (~223 ppm or ~1105 ppm)	Sprague-Dawley and Long-Evans rats (males and females, groups of 15); Male New Zealand albino rabbits (groups of 3); Princeton-derived guinea pigs (males and females, groups of 15); Male squirrel monkeys (Saimiri sciureus, groups of 3); Beagle dogs (groups of 2)	Exposure 5 days per week (8 h/day) for 6 weeks	Lung effects: Gross necropsies normal. Focal pneumonitis in 1 of 3 monkeys at 223 ppm. Nonspecific lung inflammation in guinea pigs and rats, but not in other species at 1105 ppm. Upper respiratory tract effects: mild to moderate dyspnea in rabbits and dogs exposed to 1105 ppm during week 1 only; no indication of irritation after week 1. Nasal turbinates not examined for gross or histopathologic changes[3,40,63]
Ammonia (1,086 ppm)	Rats, squirrel monkeys, and guinea pigs	Inhalation exposure 5 days per week (8 h/day) for 6 weeks	No fatty changes of liver plate cells. No pathological changes in kidney.[63]
Ammonia (653 ppm)	Rats	Continuous inhalation exposure for 25 days	Nearly 64% lethality.[62]
Ammonia (~653 ppm)	Sprague-Dawley or Long-Evans rats (males and females, 15 to 51/group)	Inhalation exposure for 65 days	Lung effects: Focal or diffuse interstitial pneumonitis in all animals. Upper respiratory tract effects: Dyspnea and nasal irritation/discharge.[3,63]
Ammonia (650 ppm; Ct [product of concentration and exposure time (ppm-h)] =1,014,000)	51 rats	Continuously for 65 days	32 of 51 rats dead by day 25 (390,000 ppm-h); 50 of 51 rats dead by day 65 (1,014,000 ppm-h).[46,63]
Ammonia (500 ppm)	27 male rats	Continuous inhalation exposure for up to 8 weeks	After 3 weeks, nasal irritation and inflammation of upper respiratory tract, but no effects observed in bronchioles and alveoli. No lesions observed at 8 weeks.[53,59]

Table 6. Short-Term and Subchronic Toxicity Studies

Ingredient	Animals	Protocol	Results
Ammonia (250 ppm)	F344 rats (6/sex/group)	Exposure in inhalation chamber for 35 days	Increased thickness of nasal epithelium (3 to 4 times) and nasal lesions at 150 ppm.[3,64]
Ammonia (221 ppm; Ct [ppm-h] = 53,040)	Rats, guinea pigs, rabbits, squirrel monkeys, and beagle dogs	5 days per week (8 h per day) for 6 weeks	No effect.[46,63]
Ammonia (10 or 150 ppm)	Sherman rats (5/sex/group)	Inhalation exposure from bedding for 75 days	Increased thickness of nasal epithelium (3 to 4 times) and nasal lesions at 150 ppm.[3,33,64]
Ammonia (50 or 90 ppm)	Male Wistar rats (8-14 per group)	Inhalation exposure continuously for 50 days	None of the animals died and there were no treatment-related effects.[53,70]
Ammonia (12% solution)	50 maleWhite albino mice	Vapor exposure 6 days per week (15 minutes/day) for 4, 5, 6, 7, or 8 weeks	Nasal mucosa adversely affected. Histological changes progressed from weeks 4–8 from crowding of cells forming crypts and irregular arrangements to epithelial hyperplasia, patches of squamous metaplasia, loss of cilia, and dysplasia of the nasal epithelium. One animal that had loss of polarity of the epithelium, hyperchromatism, and mitotic figures with an intact basement membrane also had a carcinoma *in situ* in one nostril. At week 8, one mouse had an invasive adenocarcinoma of the nasal mucosa. Histochemical results were also abnormal.[3,53]
Ammonia (78 ppm, 271 ppm, and 711 ppm)	Groups of 10 male Swiss mice	Exposure for 4, 9,or 14 days (6 h/day)	No clinical signs of toxicity were noted for mice exposed to ammonia. Rhinitis and pathologic lesions with metaplasia and necrosis were seen only in the respiratory epithelium of the nasal cavity of mice inhaling 711 ppm, the severity of the lesions increased with duration of exposure, ranging from moderate on day 4, severe on day 9, to very severe on day 14. No lesions were seen in the controls or in mice inhaling the 78 ppm. No effects were seen at 271 ppm, even after 9 days of exposure.[22,65]
Ammonia (303 ppm)	Groups of 16 to 24 male Swiss Webster mice	Exposure for 5 days (6 h/day)	Histopathological findings, which were confined to the respiratory epithelium of the nasal cavity, included minimal exfoliation, erosion, ulceration, and necrosis; moderate inflammatory changes; and slight squamous metaplasia.[22,65]
Ammonia (20 ppm)	Swiss albino mice (males and females, groups of 4)	Exposure for 7, 14, 21, 28, or 42 days	Lung congestion, edema, and hemorrhage observed after 42 days.[3,67]
Ammonia (170 ppm; Ct [ppm-h] =30,600 to 91,800)	Guinea pigs	5 days per week (6 h per day) for 6 weeks	No histopathologic changes.[46,74]

Table 6. Short-Term and Subchronic Toxicity Studies

Ingredient	Animals	Protocol	Results
Ammonia (50 ppm)	Guinea pigs (males and females, groups of 6)	Exposure for 42 days	Lung congestion, edema, and hemorrhage.[3,67]
Ammonia (20 ppm)	Guinea pigs (males and females, groups of 2)	Exposure for 7, 14, 21, 28, or 42 days	Lung congestion, edema, and hemorrhage after 42 days. [3,67]
Ammonia (100 ppm [average range = 20 to 203 ppm; Ct [ppm-h] =100,800) alone and with corn starch dust	Yorkshire-Landrace pigs (groups of 6)	Continuously for 6 weeks	Tracheal damage (thickened tracheal epithelium [50 to 100% increase] and goblet cells reduced) at end of week 2 in animals exposed to 100 ppm (33,600 ppm-h) without dust. Changes more prominent by week 6. Conjunctival irritation more severe in pigs exposed to ammonia and corn starch dust, persisting for 2 weeks.[3, 46,120]
Ammonia (10 ppm and 50 to 150 ppm; Ct [ppm-h] = 42,000 to 126,000)	Duroc Pigs (groups of 36)	Continuously for 5 weeks	Excessive nasal, lacrimal and mouth secretions at 50, 100, and 150 ppm; more pronounced at 100 and 150 ppm, gradually diminishing over 1-2 weeks. No histopathologic changes in nasal turbinates or lung.[4,46,71]
Ammonia (12, 61, 103, or 145 ppm)	Duroc pigs (males and females, groups of 9)	Exposure for 5 weeks	Excessive nasal, lacrimal, and mouth secretions, and increased frequency of cough at 103 and 145 ppm.[3,71]
Ammonia (5 ppm [range = 0 to 7 ppm] to 100 ppm [range = 90 to 112 ppm])	Belgian Landrace pigs (groups of 7)	Nasal lavage technique. 6-day exposure in chamber	No-observed-effect value for Ammonia-induced somatic growth inhibition < 25 ppm. Nasal irritation down to 25 ppm. Conjunctival irritation observed in 4 pigs exposed to 100 ppm. Lethargy in groups exposed to 25, 50 and 100 ppm for 2 to 3 days after placement in chamber.[68]
Ammonia (0.6, 10, 18.8, or 37 ppm)	Pigs (different breeds, groups of 24)	Inhalable dust exposure for 5 weeks	No increase in incidence of respiratory diseases.[3, 69]
Ammonia (~1.8, ~3.9, ~7.3, or ~14.2 ppm)	Pigs (different breeds, groups of 24)	Inhalable dust exposure for 5 weeks	No increase in incidence of respiratory diseases.[3, 69]
		Subchronic Inhalation Studies	
Ammonia (642 ppm)	Rats	Continuous exposure for 90 days	Fatty changes of liver plate cells.[63]
Ammonia (43 ppm or 143 ppm)	White rats	Inhalation exposure for 3 months (25- or 60-minute exposures every 48 h)	Mild leukocytosis after exposure to 143 ppm. No adverse effects after exposure to 43 ppm.[53]
Ammonia (100 ppm)	Rats	Inhalation exposure 5 days per week (5 h/day) for 12 weeks	Damaged tracheal mucosae.

Table 6. Short-Term and Subchronic Toxicity Studies

Ingredient	Animals	Protocol	Results
Ammonia (~170 ppm)	12 male guinea pigs (additional 6 were controls)	Inhalation exposure 5 days per week (6 h/day) for 18 weeks	No significant findings after 6 and 12 weeks of exposure. Results at 18 weeks were: relatively mild congestion of the liver, spleen, and kidneys; degenerative changes in adrenal glands; hemosiderosis in spleen (indicative of hepatotoxicity); and cloudy swelling in epithelium of proximal kidney tubules, with albumin precipitation in lumen
Ammonium Hydroxide (671 ppm)	515 rats and 15 guinea pigs	Inhalation exposure continuously for 90 days	13 rats and 4 guinea pigs died.[10,69]
Ammonium Hydroxide (~57.43 ppm)	Sprague-Dawley rats (males and females), Long-Evans rats (males and females), Princeton-derived guinea pigs (males and females), male New Zealand albino rabbits, male squirrel monkeys, and purebred male beagle dogs	Inhalation exposure continuously for 114 days	No mortalities or signs of toxicity. Necropsy observations were normal and there were no treatment-related histopathological findings.

Table 7. Developmental and Reproductive Toxicity Studies

Ingredient	Animals/Embryos	Protocol	Results
In Vitro Study			
Ammonium ion (38 to 300 µmol/l)	Mouse embryos (conceived in vivo)	Embryos cultured in modified mouse tubal fluid medium (mMTF) or mMTF supplemented with 300 µmol/L ammonium ion for 48, 69, or 93 h before being transferred to pseudo-pregnant mouse dams	Examination on gestational day 15 showed apparent relationship between the duration of exposure and the incidence of exencephaly. Increased incidence of exencephaly with increased ammonium concentration (38–300 µmol/L) and decreased percentage of implantation sites with increased ammonium concentration.[82]
Oral Studies			
ammonium ion	Pregnant rats	Feeding with ammonium ion in the diet (4293 mg ammonium/kg/day) from gestation day 1 through day 21 of lactation	Body weights of offspring reduced by 25% (males) and 16% (females).[180]
diammonium phosphate (17.9% NH_4 and 46.86% P_2O_5 equivalent)	Groups of Crj: CD(SD) rats (5 males, 10 females [reproductive subgroup])	Administered by gavage daily (doses of 0, 250, 750, and 1500 mg/kg/day) for, at most, 28 days (males) and 53 days (females).	No treatment-related deaths and no signs of overt clinical toxicity. Body weight gain was reduced during the first week of gestation (82% of control) in females dosed with 1500 mg/kg/day, but returned to control levels for remainder of study. Mating performance and fertility were unaffected by treatment, and parental treatment had no apparent effect on the offspring to day 4 of age. NOAEL for reproductive and developmental toxicity = 1500 mg/kg/day; LOAEL = > 1500 mg/kg/day.[4,45]
diammonium phosphate	Groups of 10 (5 males, 5 females) Crj: CD(SD) rats	Administered by gavage daily for, at most, 28 days (males) and 53 days (females). Doses of 0, 250, 750, and 1500 mg/kg/day.	Mating performance and fertility unaffected by dosing. Also, dosing had no apparent effect on offspring up to 4 days of age. NOAEL (for reproductive and developmental toxicity) = 1500 mg/kg/day; LOAEL = 1500 mg/kg/day.[4,53]
Inhalation Study			
Ammonia (7 ppm or 35 ppm)	Female pigs	Exposure for 6 weeks (7 ppm or 35 ppm). Exposure to ~7 ppm or ~35 ppm from 6 weeks prior to breeding until day 30 of gestation	No statistically significant differences in ovarian or uterine weights after 6 weeks of exposure. After exposure from 6 weeks prior to breeding until day 30 of gestation, no statistically significant differences in age at puberty, number of live fetuses, fetal length, or fetus-to-corpus luteum ratio compared to pigs exposed to only about 7 ppm . No unexposed controls were included in this study.[81]

Table 8. Carcinogenicity and Tumor Promotion Studies

Ingredient	Animals	Protocol	Results
		Oral Studies	
Ammonia (dissolved in water)	Mice	Dose of 42 mg ammonium/kg/day by gavage for 4 weeks.	No evidence of carcinogenic effect.[85]
Ammonium Hydroxide	Swiss and C3H mice	Exposure of mice to 193 mg ammonium/kg/day, as Ammonium Hydroxide (in drinking water), for 2 years	No carcinogenic effects, and did not affect spontaneous development of breast cancer (adenocarcinoma), which is common to C3H female mice.[45, 53,86]
Ammonium (combined with pyrocarbonate)	16 mice	Gavage	Lung tumors in 9 of 16 mice. It was noted that the Ammonia and pyrocarbonate may have reacted in vivo to form the carcinogen, urethane.[87]
Ammonium ion (and diethyl pyrocarbonate)	Pregnant mice	Exposure (by gavage) during pregnancy and lactation	No lung tumors.[87]
Ammonium Sulfate	Groups of 10 F344/DuCrj rats (male and female)	Dietary concentrations of 0%, 1.5%, 3% daily for 104 weeks	Survival rates of control, 1.5%, and 3% groups were 88%, 78%, and 76%, respectively, for males, and 76%, 80%, and 80%, respectively, for females. Neoplastic lesions (not treatment-related; occur spontaneously in rats of this strain): C-cell adenomas/adenocarcinomas in the thyroids, fibroadenomas/adenomas/adeno-carcinomas in mammary glands, adenomas/adenocarcinomas in pituitary glands, interstitial cell tumors in testes, and endometrial stromal polyps in uteri. The only macroscopic finding at necropsy was massive, nodular or focal lesions suggesting neoplastic change. Ammonium Sulfate classified as non-carcinogenic.[4]
Ammonium Sulfate	Groups of 10 F344/DuCrj rats (male and female)	Dietary concentrations of 0%, 0.1%, 0.6%, and 3% for 52 weeks	Neoplastic lesions reported included malignant pheochromocytoma of the adrenal gland in males of the 3% dietary group, 2 adenomas in the anterior pituitary of females of the 3% dietary group, and uterine endometrial stromal polyp in a female control rat.[4]

Inhalation Study			
Ammonia (12% solution)	10 male mice	Vapor exposure 6 days per week (15 minutes/day) for 4, 5, 6, 7, or 8 weeks	Histological changes progressed from (weeks 4 to 8) from crowding of cells forming crypts and irregular arrangements to epithelial hyperplasia, patches of squamous metaplasia, loss of cilia, and dysplasia of the nasal epithelium. One mouse had a carcinoma *in situ* in 1 nostril. At week 8, 1 mouse with invasive adenocarcinoma of the nasal mucosa. Authors noted that prolonged exposure to Ammonia may interfere with normal protective reflexes of the respiratory nasal mucosa, resulting in the accumulation of particulate matter initiating or promoting a neoplastic process.[86]
Tumor Promotion			
Ammonia (dissolved in water)	Rats	Rats pretreated with the initiator *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) in drinking water for 4 weeks, prior to receiving 0.01% Ammonia solution in drinking water for 24 weeks	Statistically significantly greater incidence of gastric cancer (70% of rats) and number of tumors per tumor-bearing rat (2.1) than rats that received only MNNG and tap water (31% and 1.3 tumors/rat).[33,88]
Ammonia	Rats	Rats pretreated with MNNG prior to dosing with Ammonia (~ 42 mg/kg/day)	The size, depth, and metastasis of the MNNG-initiated tumors enhanced in rats dosed with Ammonia.[89]

Table 9. Dermal Irritation Studies

Ingredient	Animals/Subjects/Cells	Protocol	Results
Skin Irritation Studies			
In Vitro Studies			
Undiluted Ammonium Hydroxide (30% active material in neat substance)	Reconstructed human skin cultures	Test substance applied topically to stratum corneum surface of cultures. Skin culture damage or cytotoxicity measured as decreased 3-[4,5-dimethylthiazol-2- yl] 2,5-diphenyltetrazolium bromide (MTT) vital dye metabolism. In time-course experiments, the time (in minutes) of test material exposure eliciting a 50% reduction of MTT metabolism (i.e., t50 value) was calculated.	Histologic examination of the cultures indicated gradations of epidermal necrosis quantitated using a specially designed grading scale, which correlated well with the corrosivity of treatment chemicals and cytotoxicity measurements. Ammonium Hydroxide (30% active in neat substance) was classified as corrosive (t50 = 0.90 minutes).[110]
Animal Studies			
Ammonia	Wistar rats (3 males, 3 females) and ddY mice (3 males, 3 females)	Test solutions (1 ml/kg or 1 g/kg) applied once, unoccluded, to shaved skin of the back. Area of application was 3 x 4 cm for rats and 1 x 2 cm for mice. Distilled water control. Test sites observed for inflammatory reactions for 1 week after application.	Minimum concentration of Ammonia that caused a positive reaction was >25% (minimum amount = >250 mg/kg) in rats and 25% (minimum amount = 250 mg/kg) in mice.[109]
Ammonia	Wistar rats (4), Hartley guinea pigs (4), and ddY mice (4)	Injected intradermally with test solutions (0.01 ml) at 4 spots on shaved dorsal skin. Saline served as the control. The test sites were evaluated for skin irritation for up to 1 week after application.	The minimum concentration that resulted in a positive reaction was 0.05% in rats (minimum amount = 25 µg/kg), mice (minimum amount = 250 µg/kg), and guinea pigs (minimum amount = 12.5 µg/kg).[109]
Ammonium Hydroxide (10% and 20%)	Groups of 3 New Zealand Albino rabbits	Each concentration (0.5 ml) applied to the skin (2 replicates at each dose)	Results positive for skin corrosion at 20% concentration. Negative results at 10% concentratyion.[10,63]
Ammonium Hydroxide (10% and 12% aqueous)	Female Albino New Zealand White rabbits	Each solution (0.1 ml) applied, under an occlusive patch ("1 x 1"), to the skin for 4 h. There were 3 rabbits per dose, with 2 replicates per rabbit at each concentration.	The 12% solution was corrosive to the skin, but the 10% solution was not.[4]
Human Studies			
Ammonium Hydroxide (saturated aqueous solution)	16 subjects (10 men, 6 women)	Applied (via a chamber) to middle of ventral aspect of forearm	Formation of a well-defined, sub-epidermal blister (positive reaction) observed within a few minutes of chamber application; skin irritation observed in all subjects.[111]

Table 9. Dermal Irritation Studies

Ingredient	Animals/Subjects/Cells	Protocol	Results
Ammonium Hydroxide (1:1aqueous solution)	110 subjects	Test substance (0.5 ml) placed in 8 mm well drilled in acrylic plastic block (3 x 3 x 1 cm) that was strapped to the skin. Block (used to measure minimal blistering time [MBT, indicator of cutaneous irritability, defined as total exposure in well that results in a single bulla, occupying the total area of contact]).	MBT ranged from 3 to 57 minutes. Inflammatory reaction considered slight; healing was rapid and without scarring. Intensity of the dermatitis provoked by a 24-h exposure to sodium lauryl sulfate was strongly correlated with the MBT.[112]
Ammonium Hydroxide solution (50% solution)	Young adults and older adults	Blistering response measured	Mild discomfort during procedure. The initial response, characterized by the appearance of tiny follicular vesicles, occurred more quickly in older adults. The time required to produce a full blister was greatly prolonged in the aged.[119]

Table 10. Ocular Irritation Studies

Ingredient	Animals/Cells	Test Protocol	Results
In Vitro			
Ammonium Hydroxide	Human corneal endothelial cell cultures	^{51}Cr-release assay. Performed by loading the cells with isotope, incubating the cells with Ammonium Hydroxide, and measuring the isotope that was recovered in the medium.	Severe ocular irritant (ED_{50} = 3.9 x 10^{-3} M).[114]
Animal			
Ammonia	Not available	Not available	Ammonia can penetrate the eye rapidly. Ocular irritation or damage can occur at concentrations beginning at 20 ppm.[17]
Ammonia (15, 32, 310, or 1157 ppm vapor concentrations)	Rats	Exposure for 24 h	No clinical signs or evidence of irritation to the eyes or mucous membranes.[22,36]
Ammonium Hydroxide	Rabbits	Instillation of test substance (1 mg) followed by ocular rinsing	Ocular irritant.[45]
Ammonium Hydroxide (28.5%)	Rabbits	Brief exposures (2 seconds)	Corneal opacity.[2,111]
Ammonium Hydroxide (0.3%, 1%, 2.5%, and 10%)	New Zealand albino rabbits (groups of 6)	Draize test. Test substance (0.1 ml) instilled into the eye. In 1 group, eyes rinsed after instillation	Conjunctivitis (at 1% to 10%, but not at 0.3%). Ammonium Hydroxide (10%) produced pannus in 5/6 unwashed rabbit eyes and 2.5% produced pannus in 1/6 unwashed and 6/6 washed eyes. Ammonium Hydroxide at 1% produced pannus in 3/6 washed eyes. Keratoconus was produced by 10% Ammonium Hydroxide in 4/6 unwashed eyes and 2/6 washed eyes and 2.5% produced keratoconus in 2/6 unwashed eyes. Ammonium Hydroxide (10%) caused corneal opacities within 1 h of instillation.[116]
Ammonium Hydroxide (prepared with 3% Ammonia)	3 New Zealand White Albino Rabbits	Draize test. Test substance (100 µl) instilled into eye	Conjunctivitis (score = 3 at 96 h; mean maximum Draize score = 3), chemosis (score = 3 at 96 h; mean maximum score = 4), iritis (score = 1; mean maximum Draize score = 2), corneal opacity (score = 4; mean maximum Draize score = 4), and mean surface of corneal damage (70% corneal damage; mean maximum Draize value = 100%). Risk of serious damage to the eyes.[117]

Table 11. Other Clinical Reports

Ingredient	Number of Subjects	Protocol	Results
		Inhalation Exposure	
Ammonia (700 ppm)	Number of subjects not available	Not available	Eye irritation.[124]
Ammonia (500 ppm)	Number of subjects not available	30-minute exposure	Variable lacrimation.[124]
Ammonia (500 ppm)	Number of subjects not available	30-minute exposure	Increased blood pressure and pulse rate.[124]
Ammonia (500 pm)	Number of subjects not available	30-minute exposure	Nasal and throat irritation, increased minute volume, and cyclic pattern of hyperpnea.[124]
Ammonia (500 ppm)	7 men	30-minute exposure	Increase in ventilation minute volume of 50-250%, accompanied by cyclic increase in respiratory rate. Irritation of the nose and throat. No significant change in nitrogen or urea in blood and urine. No significant change in serum nonprotein nitrogen.[125]
Ammonia (500 ppm)	7 subjects	30-minute exposure via face mask	Ventilation minute volume increased 50 to 250% over pre-exposure values. Respiratory minute volumes fell below pre-exposure levels at termination of exposure.[46,125]
Ammonia (101 to 335 ppm)	Number of subjects not available	20-minute exposure	Decrease in exercise ventilation minute volume at 151-335 ppm, related either to a decrease in respiratory rate (at 151 ppm) or tidal volume (at 205 and 335 ppm); no significant effects at 101 ppm.[46,126]
Ammonia (50 to 140 ppm)	16 subjects	2-h exposure. Testing repeated after a 1-week interval.	110 ppm tolerable for all subjects. 140 ppm intolerable at 1 h (4 subjects) and at 2 h (4 subjects). No significant increase in vital capacity, forced expiratory volume at end of 1 second of forced expiration (FEV_1), or forced inspiratory volume inhaled at end of 1st second of forced inspiration (FIV_1). Lowest-observed-adverse-effect level (LOAEL) of 50 ppm for mild irritation to the eyes (6 subjects), nose (20 subjects), and throat (9 subjects). LOAEL divided by uncertainty factor of 30 (10 to protect sensitive individuals and 3 for the use of a minimal LOAEL)[72]
Ammonia (135 ppm)	6 subjects	5-minute exposure	Chest irritation in 1 of 6 subjects.[124]
Ammonia (135 ppm)	Number of subjects not available	5-minute exposure	Nose and throat irritation.[124]
Ammonia (135 ppm)	Number of subjects not available	5-minute exposure	Eye irritation with lacrimation.[124]

Table 11. Other Clinical Reports

Ingredient	Number of Subjects	Protocol	Results
Ammonia (25, 50, and 100 ppm)	6 subjects	Exposure: 5 days per week (2 to 6 h per day) for 6 weeks	Mild to moderate irritation of the eyes, nose and throat: 16/54 (30%) of observations on 6 subjects in week 2; 12/90 (13%) in week 3; 2/60 (3%) in week 4; 0/78 in week 5; and 5/78 (6%) in week 6. No apparent effects on pulse, respiration rate, blood pressure, FVC, or FEV_1.[127]
Ammonia (25-100 ppm)	Not available	Exposure to varying concentrations for varying periods (2-6 h) 5 days/week for 6 weeks	Decreasing signs of irritation of the mucous membranes of the eyes, nose and throat over the 6-week observation period were reported, and there was no evidence of adverse health effects.[46,127]
Ammonia (72 ppm)	Number of subjects not available	5-minute exposure	Eye irritation with lacrimation.[124]
Ammonia (50 ppm)	Number of subjects not available	5-minute exposure	Eye irritation with lacrimation.[124]
Ammonia (50 ppm)	Number of subjects not available	120-minute exposure	Eye irritation.[124]
Ammonia (50 ppm)	Number of subjects not available	120-minute exposure	Nose and throat irritation. Urge to cough.[124]
Ammonia (30 and 50 ppm)	6 subjects	10-minute exposure	Barely perceptible irritant effects (nose and eye) in 2 of 6 subjects (30 ppm). Faint to moderate irritation (nose and eye) in 5 of 6 subjects (50 ppm).[51]
Ammonia (30 ppm and 50 ppm)	6 subjects	10-minute exposure	Moderate irritation of nose and eyes at 50 ppm (4 of 6 subjects), but not at 30 ppm.[51]
Ammonia (32 ppm)	Number of subjects not available	5-minute exposure	Eye irritation with lacrimation.[124]
Ammonia (> 30 ppm)	Not available	Not available	Immediate irritation of the nose and throat.[51,128,72]
Ammonia	Not available	Not available	Tolerance appears to develop with repeated exposure.[128,72]

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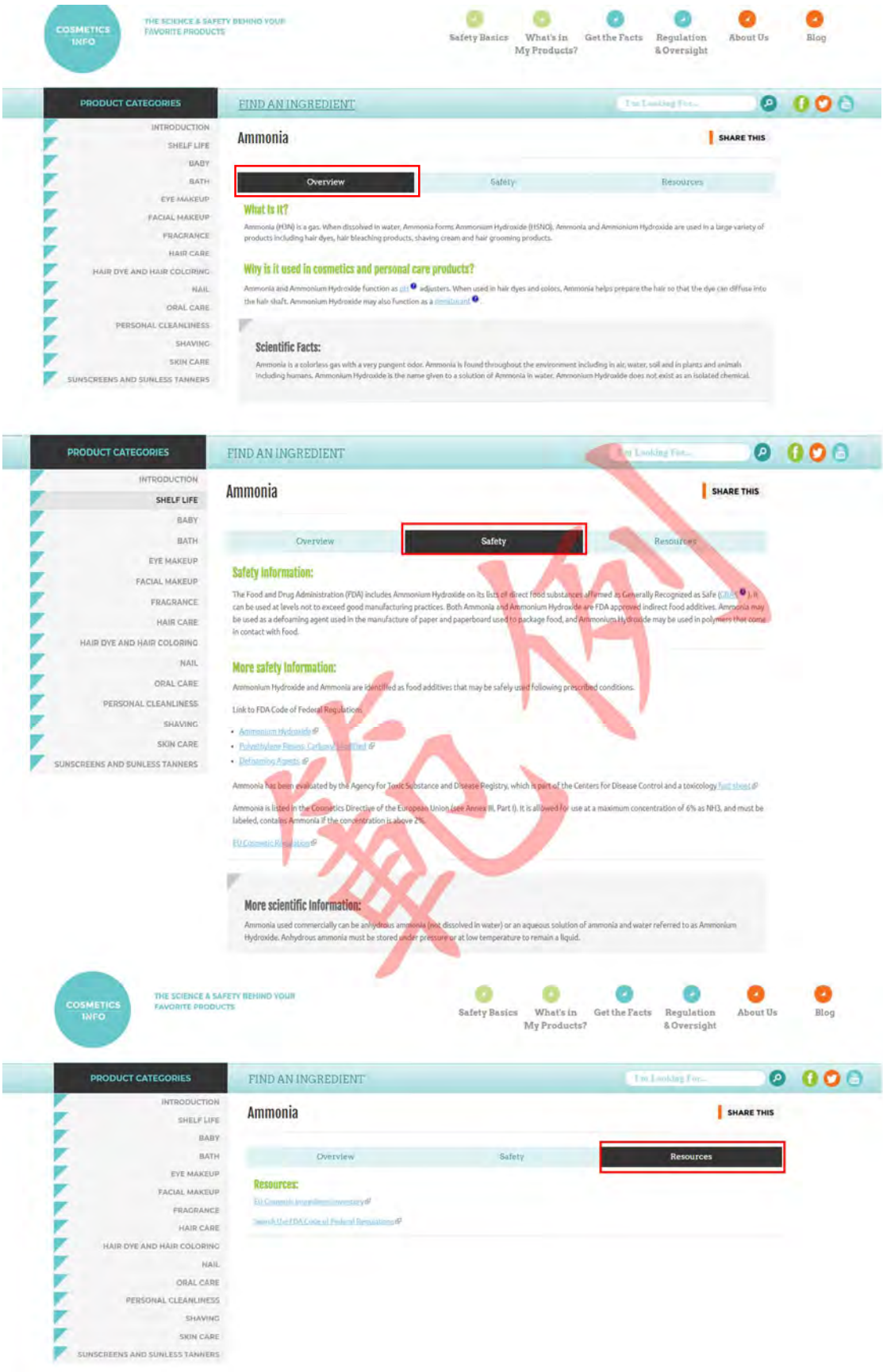


附錄 3　Fragrance IFRA 符合性聲明

CERTIFICATE OF CONFORMITY

This Certificate assesses the conformity of the fragrance mixture with IFRA Standards and provides restrictions for use as necessary. It is based only on those materials subject to IFRA Standards for the toxicity endpoints described in each Standard. It also provides information on any restrictions due to the EU Cosmetic Regulation. This Certificate does therefore not replace a comprehensive safety assessment of the fragrance mixture.

CERTIFYING PARTY:

CERTIFICATE DELIVERED TO:
GRACEFRUIT LTD

SCOPE OF THE CERTIFICATE:
FIG & VANILLA FRAGRANCE 454155

COMPULSORY INFORMATION:

Implementation of the 49th Amendment is as follows:-
10th May, 2021: Entry into force for new formulations
10th May, 2022: Compliance of existing formulations created before 10th May 2021

We certify that the above mixture is in compliance with the Standards of the INTERNATIONAL FRAGRANCE ASSOCIATION (IFRA), up to and including the 49th Amendment to the IFRA Code of Practice (published January 2020) and the European Cosmetic Regulation (EC) 1223/2009 & its modifications, provided it is used in the following categories at a maximum concentration level of:

IFRA Categories [see Annex 1 below for details]	Maximum Level of use (%)
IFRA Category 1	Not approved
IFRA Category 2	0.92%
IFRA Category 3	2.73%
IFRA Category 4	17.20%
IFRA Category 5A	4.40%
IFRA Category 5B	3.66%
IFRA Category 5C	4.40%
IFRA Category 5D	1.20%
IFRA Category 6	Not approved
IFRA Category 7A	3.66%
IFRA Category 7B	3.66%
IFRA Category 8	1.20%
IFRA Category 9	10.83%
IFRA Category 10A	10.83%
IFRA Category 10B	35.00%
IFRA Category 11A	1.20%
IFRA Category 11B	1.20%
IFRA Category 12	Not limited

For other kinds of application or use at higher concentration levels, a new evaluation can be needed; please contact Fragrance Oils (International) Limited

EU COSMETIC INFORMATION:

We certify that the above mixture is in compliance with the EU Cosmetic Regulation 1223/2009 and its amendments, provided it is used in the following applications at a maximum concentration level of:

Cosmetic Application	Maximum Level of use (%)
Fine Fragrance	8.00%
Eau de Toilette	8.00%
Fragrancing cream	8.00%
Rinse off cosmetic products	8.00%
Other leave-on cosmetic products	8.00%
Oral products	Not approved

Regulatory Affairs Department

ANNEX 1

Below is an extract of information provided by IFRA in relation to types of application present in each IFRA Category. Additional information about IFRA Categories can be found in the Guidance to IFRA Standards, issued by IFRA.

IFRA Category	Product Type
IFRA Category 1	Products applied to the lips: Lip products e.g. lipstick, lip balm; Childrens toys
IFRA Category 2	Products applied to the axillae: Deodorant and antiperspirant products of all types; Body sprays/mists
IFRA Category 3	Products applied to the face/body using fingertips: Eye products e.g. eye make-up, eye moisturizer; Facial make-up; Make-up remover; Nose pore strips; Wipes for face, neck, hands, body; Facial masks; Body and face paint
IFRA Category 4	Products related to fine fragrance: Hydroalcoholic and non-hydroalcoholic fine fragrance of all types e.g. Eau de Toilette, Parfum, Cologne, solid perfume, fragrancing cream, aftershaves of all types; Ingredients of perfume and fragrance mixtures for cosmetic kits; Scent pads; Scent strips
IFRA Category 5A	Body lotion products applied to the body using the hands (palms), primarily leave on: Foot care products e.g. creams, powders; Insect repellent for application to the skin; All powders and talc (excluding baby powders and talc)
IFRA Category 5B	Face moisturizer products applied to the face using the hands (palms), primarily leave on: Facial toner; Facial moisturizers and creams
IFRA Category 5C	Hand cream products applied to the hands using the hands (palms), primarily leave on: Hand cream; Nail care products including cuticle creams; Hand sanitizers
IFRA Category 5D	Baby creams, baby oils and baby talc: Baby cream/lotion, baby oil, baby powders and talc
IFRA Category 6	Products with oral and lip exposure: Toothpaste; Mouthwash, including breath sprays; Toothpowder, strips, mouthwash tablets
IFRA Category 7A	Rinse-off products applied to the hair with some hand contact: Hair permanent or other hair chemical treatments (rinse-off) e.g. relaxers, including rinse-off hair dyes
IFRA Category 7B	Leave-on products applied to the hair with some hand contact: Hair sprays of all types e.g. pumps, aerosol sprays; Hair styling aids non sprays e.g. mousse, leave- on conditioners; Hair permanent or other hair chemical treatments (leave-on) e.g. relaxers, including leave-on hair dyes; Shampoo - Dry (waterless shampoo); Hair deodorizer
IFRA Category 8	Products with significant anogenital exposure: Intimate wipes; Tampons; Baby wipes; Toilet paper (wet)
IFRA Category 9	Products with body and hand exposure, primarily rinse off: Bar soap; Liquid soap; Shampoo of all type; Conditioner (rinse-off); Body washes and shower gels of all types; Baby wash, bath, shampoo; Bath gels, foams, mousses, salts, oils and other products added to bathwater; Cleanser for face (rinse-off); Shaving creams of all types e.g. stick, gels, foams; All depilatories (including facial) and waxes for mechanical hair removal; Foot care products (feet are placed in a bath for soaking); Shampoos for pets
IFRA Category 10A	Household care excluding aerosol / spray products: Hand wash laundry detergent; Laundry pre-treatment of all types e.g. paste, sprays, sticks; Machine laundry detergents with skin contact e.g. liquids, powders; Fabric softeners of all types including fabric softener sheets; Ironing water; Hand dishwashing detergent; Hard surface cleaners of all types e.g. bathroom, kitchen cleansers, furniture polish; Toilet seat wipes; Household cleaning products, other types including fabric cleaners, carpet cleaners, furniture polishes sprays and wipes, stain removers, treatment products for textiles e.g. starch sprays; Floor wax; Dry cleaning kits; Fragranced oil for lamp ring, reed diffusers, pot-pourri, liquid refills for air fresheners (non-cartridge systems), etc.
IFRA Category 10B	Household aerosol/spray products: Animal sprays applied to animals; Air freshener sprays, manual, including aerosol and pump; Aerosol/spray insecticides
IFRA Category 11A	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate without UV exposure: Feminine hygiene conventional pads, liners, interlabial pads; Diapers (baby and adult); Adult incontinence pant, pad; Toilet paper (dry)
IFRA Category 11B	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate with potential UV exposure: Tights with moisturizers; Scented socks, gloves; Facial tissues (dry tissues); Napkins; Paper towels; Wheat bags; Facial masks (paper/protective) e.g. surgical masks not used as medical device; Fertilizers, solid (pellet or powder)
IFRA Category 12	Products not intended for direct skin contact, minimal or insignificant transfer to skin: Candles of all types ; Laundry detergents for machine wash with minimal skin contact (e.g. Liquid tabs, pods); Automated air fresheners and fragrancing of all types e.g. concentrated aerosol with metered doses, plug-ins, electrical, incense, liquid refills (cartridge); Air delivery systems; Cat litter; Cell phone cases; Deodorizers/maskers not intended for skin contact e.g. fabric drying machine deodorizers, carpet powders; Fuels; Insecticides e.g. mosquito coil, paper, electrical, for clothing, excluding aerosols/sprays; Joss sticks or incense sticks; Dishwash detergent and deodorizers - for machine wash; Olfactive board games; Paints; Plastic articles (excluding toys); Scratch and sniff; Scent pack; Scent delivery system (using dry air technology); Shoe polishes; Rim blocks (Toilet)

IFRA CONFORMITY CERTIFICATE

Product: **FIG & VANILLA FRAGRANCE 454155**

We certify that the above item is in compliance with the Standards of the INTERNATIONAL FRAGRANCE ASSOCIATION (IFRA - 48th Amendment / published June 2015), provided it is used in the following classes at a maximum concentration level of:

IFRA classes [see annex for detail]	Maximum level of use (%)
IFRA Class 1 Limit	Not approved
IFRA Class 2 Limit	1.6%
IFRA Class 3.A Limit	8%
IFRA Class 3.B Limit	8%
IFRA Class 3.C Limit	8%
IFRA Class 3.D Limit	8%
IFRA Class 4.A Limit	8%
IFRA Class 4.B Limit	8%
IFRA Class 4.C Limit	8%
IFRA Class 4.D Limit	8%
IFRA Class 5 Limit	8%
IFRA Class 6 Limit	Not approved
IFRA Class 7.A Limit	3.2%
IFRA Class 7.B Limit	3.2%
IFRA Class 8.A Limit	8%
IFRA Class 8.B Limit	8%
IFRA Class 9.A Limit	8%
IFRA Class 9.B Limit	8%
IFRA Class 9.C Limit	8%
IFRA Class 10.A Limit	8%
IFRA Class 10.B Limit	8%
IFRA Class 11 Limit	100%

化粧品產品資訊檔案(範例)

<燙髮劑 1 號>

＜PIF **無特定之格式**，本範例**僅提供參考用**＞

中華民國 111 年 7 月

目　錄

頁 次

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)	燙髮劑 1 號(第一劑、第二劑) Waving Solution No.1 (First dose、Second dose)
產品類別	頭髮用化粧品類
產品劑型	第一劑-液劑、第二劑-液劑
用途	燙髮
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：oo 市 oo 路 oo 段 XX 號 公司負責人：李○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：0123XXXXTEST2000000000


產品基本資訊
全成分
如需多筆要件資料匯入請至[產品基本資訊]頁籤，使用多筆匯入功能。
全成分匯入
選擇組合式產品：
燙髮劑第二劑
產品類型：
單一產品
產品型號：
燙髮劑1號
燙髮劑第二劑-成分資訊 * -單位：
%(W/W)
序號
* 成分名稱
* 含量
限量成分用途
*公告限量成分才需填寫
提醒事項
1
AQUA
查詢
適量
2
Sodium Bromate
查詢
標誌量
7.0000000000000
燙髮劑
用途：燙髮劑,限量
0.0000%~11.5000%
3
Disodium Phosphate
查詢
適量

(3) 全成分名稱及其各別含量

第一劑

	INCI Name	Cas No.	w/w%	功能
1	Aqua	7732-18-5	84.3	溶劑
2	Ammonium Thioglycolate (50% Solution)	5421-46-5	10.0	還原劑
3	Polysorbate 80	9005-65-6	2.0	界面活性劑-乳化
4	Ammonia (28% Solution)	7664-41-7	1.6	鹼劑
5	Sorbitan Stearate	1338-41-6	1.0	界面活性劑-乳化
6	Paraffinum Liquidum	8012-95-1 / 8042-47-5	0.6	皮膚調理-潤膚
7	Lanolin Wax	68201-49-0	0.5	皮膚調理-潤膚
TOTAL			100	

第二劑

	INCI Name	Cas No.	w/w%	功能
1	Aqua	7732-18-5	89.5	溶劑
2	Sodium Bromate	7789-38-0	7.0	氧化劑
3	Disodium Phosphate	7558-79-4 / 7782-85-6	3.5	緩衝劑
TOTAL			100	

(4) 產品標籤、仿單、外包裝或容器

項目	資料
內包裝/容器第一劑(正反面)	
內包裝/容器第二劑(正反面)	

標籤/仿單	 燙髮劑1號 Waving Solution NO.1 第 1 劑 40 ml 製造廠商名稱/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2021.07.05，有效期間3年 批號：IT1007AC 1  燙髮劑1號 Waving Solution NO.1 第 2 劑 40 ml 製造廠商名稱/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2021.07.05，有效期間3年 批號：IT1007AC 2
外盒	 燙髮劑1號 Waving Solution NO.1 製造廠商名稱/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2021.07.05，有效期間3年 批號：IT1007AC

標籤、仿單	內容物：燙髮劑(第一劑、第二劑) 品名：燙髮 1 號 (第一劑、第二劑) 用途：燙髮 用法： (1)燙髮前請先將頭髮洗淨擦拭擦乾後上捲，並以棉條或毛巾做好保護額頭、頸部及耳背後之防護工作。 (2)頭髮上捲完成後，將第一劑適量均勻塗抹在髮捲上，並停留 10~15 分鐘，最長不超過 20 分鐘。 (3)完成(2)靜置並檢視頭髮捲度，若可則再上第二劑適量均勻塗抹在髮捲上，並停留 10~15 分鐘。 (4)完成(3)靜置後，請徹底將頭髮上燙髮劑沖洗乾淨，並將髮絲吹整至乾燥。 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 2021.07.05、有效期間 3 年 批號：IT1007AC 容量：第一劑 40 ml /第二劑 40 ml 全成分-第一劑： 特定用途成分含量：Ammonia (28%)...1.6%、Ammonium Thioglycolate (50%)...10.0% 其他成分：Aqua、Polysorbate 80、Sorbitan Stearate、Paraffinum Liquidum、Lanolin Wax。 全成分-第二劑： 特定用途成分含量：Sodium Bromate...7.0% 其他成分：Aqua、Disodium Phosphate。 使用注意事項：限美髮專業技術人士使用。 (依規定「燙髮劑之標籤、仿單或包裝應標示事項」刊載。) 一、使用前請詳閱說明書，並依據使用方法正確使用。 二、不得使用於眉毛、睫毛等頭髮以外之毛髮。 三、燙髮一星期前後，不建議進行染髮。 四、燙髮操作時應戴手套。 五、應避免燙髮劑接觸臉部或頸部，若不慎接觸時，應立即沖洗。 六、應避免燙髮劑於操作及沖洗時接觸眼睛、口腔及鼻子，若不慎接觸時，應立即以大量清水沖洗，並迅速就醫。 七、燙髮後若皮膚有任何異常現象，應迅速就醫。

	八、因使用燙髮劑(不限本產品)，曾引發過敏反應或身體不適等症狀者應避免使用，(另如哮喘或支氣管敏感患者建議使用前先諮詢醫師)。 九、頭皮、頸、臉部有腫脹、受傷、過敏、發炎狀態、皮膚疾病或身體有特殊情況(如患病、病後恢復、生理期及懷孕期間等)者，應避免使用。 十、本產品應放置於孩童伸手不及之場所儲存。

(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：

製造廠（場所）地址：

核定劑型及作業項目：

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)

符合化粧品優良製造準則聲明書(**範例**)

符合化粧品優良製造準則聲明書

Declaration of Conformity

本業者／本人(製造或輸入)之化粧品符合中華民國之化粧品優良製造準則，產品資料如下：

I hereby declare that the products described below manufactured in conformity with Cosmetic Good Manufacturing Practice

一、製造廠名稱：

Manufacturer's Name

二、製造廠地址：

Manufacturer's Address

三、製造劑型：

Product forms

四、作業項目：

The process of operations

以上聲明書所保證之內容，如有造假不實或違背相關法規等情事，本業者／本人願自行負擔法律上一切責任。

Where violations of this declaration occur, I agree to take the legal responsibilities.

立聲明書人：　(Signature)

Applicant

負責人/代表人：　(Signature)

Person in charge

統一編號或身分證字號：

Company Tax ID No. / ID Number

地址：

Address:

申請廠商蓋公司章

負責人或代表人章

中 華 民 國　年　月　日

Date　year　month　day

(6) 製造方法、流程

第一劑

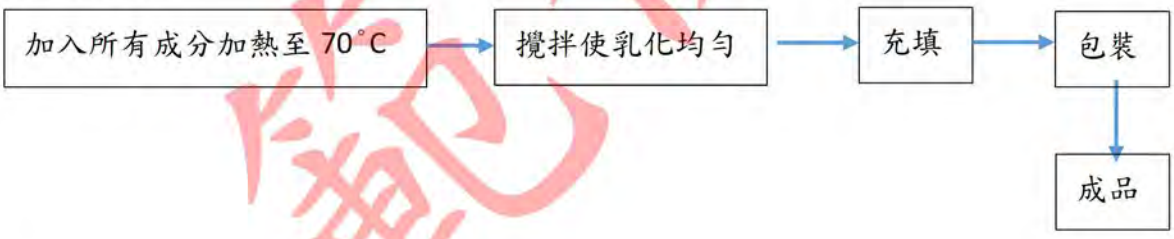
	INCI Name	Cas No.	w/w%
1	Aqua	7732-18-5	84.3
2	Ammonium Thioglycolate (50% Solution)	5421-46-5	10.0
3	Polysorbate 80	9005-65-6	2.0
4	Ammonia (28% Solution)	7664-41-7	1.6
5	Sorbitan Stearate	1338-41-6	1.0
6	Paraffinum Liquidum	8012-95-1 / 8042-47-5	0.6
7	Lanolin Wax	68201-49-0	0.5

* Ammonium Thioglycolate (50%)相當於含 Thioglycolate Acid 5%。

製造方法：

1.加入第一劑所有成分加熱至 70°C，攪拌使其乳化均勻，冷卻至室溫即可。

製程流程圖：



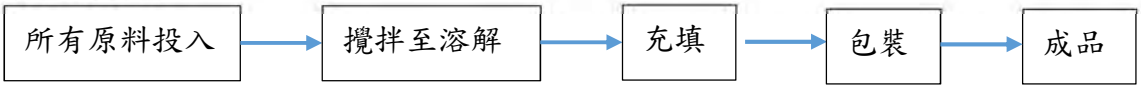
第二劑

	INCI Name	Cas No.	w/w%
1	Aqua	7732-18-5	89.5
2	Sodium Bromate	7789-38-0	7.0
3	Disodium Phosphate	7558-79-4 / 7782-85-6	3.5

製造方法：

1.依序將 1~3 項，攪拌至溶解即可。

製程流程圖：



(7) 使用方法、部位、用量、頻率及族群

使用方法：

(1)燙髮前：請先將頭髮洗淨擦拭，濕度呈半乾燥狀態。

(2)頭髮上捲完成後，將第一劑均勻塗抹在頭髮上，並停留 10~15 分鐘。

(3)完成(2)靜置後再上第二劑，並停留 10~15 分鐘。

(4)完成(3)靜置後，請徹底將頭髮上燙髮劑沖洗乾淨，並將髮絲吹整至乾燥。

使用部位：頭髮。

用量：每次燙髮使用第一劑 40 ml、使用第二劑 40 ml。

使用族群：適用於頭髮及頭皮無受損之成年人。

使用頻率：每 3 個月 1 次 (每次燙髮至少間隔 3 個月) 。

(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立即更新於本產品資訊檔案，並及時提供給安全資料簽署人員。

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

第一劑

燙髮劑 1 號第一劑成品 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	乳白色不透明	乳白色不透明	目視
氣味	"氨"刺激氣味	有刺激氣味	嗅覺
pH	9.5 ± 0.5	9.57	使用已校正之 pH meter 依 pH meter 檢測方法測定
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； 綠膿桿菌 陰性； 金黃色葡萄球菌 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 公布建議檢驗方法-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)	

第二劑

燙髮劑 1 號第二劑成品 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	乳白色微透明	乳白色微透明	目視
氣味	無	無添加香精	嗅覺
pH	5.5 ± 0.5	5.61	使用已校正之 pH meter 依 pH meter 檢測方法測定
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； 綠膿桿菌 陰性； 金黃色葡萄球菌 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 公布建議檢驗方法-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	6.0~8.5	6.85	使用已校正之線上(on line) pH meter 測定
導電度	<20 µS/cm	17.5 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)	

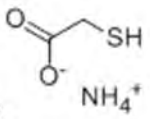
INCI name：Ammonium Thioglycolate (50% Solution)

CAS No.: 5421-46-5

Molecular Formula: $C_2H_7NO_2S$

Molecular Fomula:109.15

Chemical Structure:



AMMONIUM THIOGLYCOLATE Typical Properties

Item	Specifications	Results
Appearance	colorless or lavender pink	colorless
Activity %min	≥50.0%	50.4%
Specific gravity (ρ20, g/cm3)	1.24(25℃)	1.24(25℃)
PH	6.0-6.8(25℃)	6.2
Conclusion	The results conforms with Enterprise standards	

INCI name：Polysorbate 80

Certificate of Analysis

Product Name:TWEEN® 80

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：Ammonia (28% Solution)

Product Name: AMMONIA 28% Solution AR

Alternate Name(s) Ammonium hydroxide; aqua ammonia; ammonium hydrate.

Description

Solution in water of flammable, toxic gas with a pungent odour. Suffocating smell. Extremely dangerous to the eyes.

Properties

Chemical Formula:

Molecular Weight: 35.05

Product Code: AA005

CAS No.: 1336-21-6

General Information:

Corrosive to Cu, Ni, Zn & Sn and their alloys such as brass.

Hazard and Safety Data

UN Group:	III
Class:	8
UN Number:	2672
Hazchem code:	2R
CS MSDS Code:	1CH0U
Poison schedule:	S6
Emergency Procedure Guide No.:	37

Quality Specification

Typical Assay: 28.0 - 30.0 % w/w

Specific Properties and Impurities [Typical levels]:

Appearance	Passes test
Residue after ignition	≤ 0.002%
Carbon dioxide (CO2)	≤ 0.002%
Chloride (Cl)	≤ 0.00005%
Nitrate (NO3)	≤ 0.0002%
Phosphate (PO4)	≤ 0.0002%
Sulfate (SO4)	≤ 0.0002%
Heavy metals (as Pb)	≤ 0.00005%
Substances reducing permanganate	Passes test
Aluminium (Al)	≤ 0.0001%
Barium (Ba)	≤ 0.00001%
Boron (B)	≤ 0.00002%
Cadmium (Cd)	≤ 0.000005%
Calcium (Ca)	≤ 0.0001%
Chromium (Cr)	≤ 0.000002%
Cobalt (Co)	≤ 0.000002%
Copper (Cu)	≤ 0.000002%
Iron (Fe)	≤ 0.00005%
Lead (Pb)	≤ 0.000005%
Lithium (Li)	≤ 0.000002%
Magnesium (Mg)	≤ 0.0001%
Manganese (Mn)	≤ 0.000002%
Molybdenum (Mo)	≤ 0.000002%

INCI name：Sorbitan Stearate

Certificate of Analysis

(Representative Sample Certificate)

Product Name:	Sorbitan Stearate
INCI Name:	Sorbitan Monostearate
CAS Number:	1338-41-6
Lot Number:	Not available (data may vary slightly with different lots or batches)
Expiration Date:	12 months from production date

Characteristic	Specifications	Values
Acid value, MG KOH/G	5-10	5.9
Hydroxyl Value MG KOH/G	235-260	239
Saponification Value MG KOH/G	147-157	155
Moisture KF, %	<=1.5	0.5
Arsenic	<3ppm	Pass
Heavy Metals	<10ppm	Pass
Color, Garner	6 max	Pass

INCI name：Paraffinum Liquidum

Certificate of Analysis

(Representative Sample Certificate)

Product Name:	Mineral Oil
INCI Name:	Mineral Oil (Paraffinum Liquidum)
CAS Number:	8012-95-1, 8020-83-5, 8042-47-5
Lot Number:	Not available (data may vary slightly with different lots or batches)
Expiration Date:	24 months from production date

Property	Specification	Analysis
Apperance	Bright and Clear	Pass
Neutrality	Neutral	Pass
Specific Gravity @ 60 F	0.820-0.880	0.838
Color Saybolt	+30 Min	30+
Viscosity SUS @ 100 F	65-80	72.0

INCI name：Lanolin Wax

Certificate of Analysis

(Representative Sample Certificate)

Product Name: Lanolin Wax
INCI Name: Lanolin Wax
CAS Number: 68201-49-0
Lot Number: Not available (data may vary slightly with different lots or batches)
Expiration Date: 24 months from production date

Characteristic	Specifications	Lab Values	Final Results
Appearance (Method Visual)	Waxy Solid	Pass	Pass
Free Fatty Acid Value as Oleic (mg KOH/1g sample)	0.56 Max	0.18	Pass
*Color Gardner Method 008.01	10 max	8	Pass
Percent Loss On Drying (%) Method 014.01	0.3 Max	0.25	Pass
Melting Point (Class II) (C) Method 012.01	45-55	48	Pass
Iodine Value (Hanus) (g Iodine/100g sample)	18-36	26.2	Pass
Hydroxyl Value (mg KOH/1g sample) Method 009.01	20-35	33.25	Pass
Saponification Value (mg KOH/1g sample)	85-100	99.15	Pass

INCI name：Sodium Bromate

Product	32769 - Sodium Bromate extrapure AR, 99% - [7789-38-0]
Batch No	6843689
Molecular Formula	NaBrO3
Molecular Weight	150.89

Test Parameters	Standards	Actual Results
Appearance (Colour)	White	White
Appearance (Form)	Crystalline powder	Crystalline powder
Solubility (Turbidity) 5% aq. solution	Clear	Clear
Solubility (Colour) 5% aq. solution	Colourless	Colourless
Assay	min.99%	99.9%
Iron (Fe)	max. 0.0005%	Passes
Heavy Metals (Pb)	max. 0.0005%	Passes

INCI name：Disodium Phosphate

INCI:	Disodium Phosphate		
CHEMICAL COMPOSITION:	**Chemical name**	**CAS NO.**	**Chem. Formula**
	Disodium hydrogen phosphate	7558-79-4	Na_2HPO_4
APPEARANCE:	White crystalline solid		
ODOR:	Odorless		
STORAGE:	Tightly closed. Dry. Store at +5 °C to +30 °C Note: RonaCare® Di-Sodium Hydrogen Phosphate is hygroscopic		
SHELF LIFE:	Minimum 2 years		
TECHNICAL ASPECTS: pH value (1% in water) Solubility Temperature stability	 8.7 – 9.3 (at 20 °C) water soluble (77 g/l at 20 °C) stable		
FUNCTIONS:	pH adjusting and buffering agent Masking agent Fragrance ingredient		
APPLICATIONS:	Skin care Oral care (mouthwash, toothpaste) Hair care (shampoo, hair colorants) Shaving preparations Shower and bath products		

(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之各個成分毒理資料，另存放於燙髮劑 1 號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：Ammonium Thioglycolate (50% Solution)

- 急性毒性：根據 OECD 423 在雄性和雌性大鼠中測試巰基乙酸銨(Ammonium Thioglycolate)和巰基乙酸銨鈉(Sodium Thioglycolate)的經口急性毒性。在 Sprague-Dawley 大鼠中，71%銨鹽水溶液 LD_{50} 介於 50 ~ 200 mg/kg bw（或以活性成分表示時 LD50 介於 35 ~ 142 mg/kg bw）之間 (Hönack, 1996)。另一項根據 OECD 401 使用 Ammonium Thioglycolate 在 Wistar 大鼠進行的研究結果顯示 LD_{50} 介於 25 ~200 mg a.i./kg bw 之間(Heusener, 1998)。巰基乙酸(Thioglycolic acid)及其銨鹽和鈉鹽與皮膚接觸是有害的。在一項急性皮膚毒性研究中，每組每性別各 2 隻紐西蘭大白兔分別施予巰基乙酸（純度 98.2%）250、500、1000 或 2000 mg/kg bw。暴露 14 天後觀察動物的死亡率和臨床症狀，第一天的死亡率為 0/4、1/4、2/4 和 4/4。除了施用部位的皮膚刺激性外，未有其他影響之報告，LD_{50} 為 848 mg/kg bw (Rampy,1973)。在根據 OECD 402 對 Sprague-Dawley 大鼠進行的研究中，在皮膚施用 71%巰基乙酸銨水溶液 2000 mg/kg bw 後未觀察到死亡，臨床症狀僅限於施用部位的中度皮膚刺激性 (Klein, 2003a)。[1]
- 經皮吸收：根據一項依 OECD 428 研究，在永久性燙髮配方（配方中 13%，pH 9.5），以[^{14}C]-放射性標記的巰基乙酸銨，測試後皮膚吸收率為 16.74 μg/cm^2。[1]
- 皮腐蝕性和刺激性：巰基乙酸和巰基乙酸銨是皮膚刺激物；在高濃度下，可能具有腐蝕性。根據歐盟化學物質及混合物之分類、標示及包裝法規(Classification, Labelling and Packaging, CLP)，巰基乙酸被歸類為皮膚腐蝕劑 1B；H314（可能導致嚴重的皮膚灼傷和眼睛損傷）。[1]
- 皮膚致敏性：巰基乙酸銨為致敏劑，但接觸性過敏皮膚炎的發生率較低。[1]
- 重複劑量毒性：使用含有 7.0% Ammonium Thioglycolate 的冷燙溶液

(pH 9.0~9.5)的皮膚毒性。分別將 0.5、1.0、2.0 和 4.0 ml/kg 四種劑量冷燙溶液塗在白兔皮膚上 90 天。18 隻白兔在劑量為 4.0 ml/kg 的條件下有 11 隻死亡；17 隻白兔在劑量為 2.0 ml/kg 條件下有 2 隻死亡；15 隻白兔在劑量為 1.0 ml/kg 條件下沒有死亡發生。在對約 50 隻動物的皮膚切片進行顯微鏡檢查時觀察到輕度皮膚發炎現象。在國家毒理學計劃(National Toxicology Program, NTP)對大鼠反覆皮膚毒性研究中，系統性 NOAEL 為 180 mg/kg bw/day，局部 LOAEL 為 11.25 mg/kg bw/day。歐盟消費者安全科學委員會(Scientific Committee on Consumer Safety, SCCS)使用系統性 NOAEL（每週 5 天校正值：180 x 5/7 = 129 mg/kg bw/day）計算 MoS。[1,2]

- 致突變性/遺傳毒性：根據 OECD 476 進行 Ammonium Thioglycolate 小鼠淋巴瘤正向突變分析測試。在使用的實驗條件下，Ammonium Thioglycolate 以 tk 基因作為報告基因的小鼠淋巴瘤試驗中顯現非致突變性。[1]
- 致癌性：根據目前的實驗，沒有任何關於巰基乙酸及其鹽可能致癌作用的相關數據。[1]
- 生殖毒性：透過餵食法給藥，用於孕婦和胚胎胎兒毒性 NOAELs 分別為 15 和 75 mg/kg bw/day。在所有研究中均觀察到無致畸胎作用。[1]
- 毒物動力學：沒有關於巰基乙酸和/或其鹽透過吸入或口服暴露吸收的數據。然而，巰基乙酸鹽具有極低 $\log K_{ow}$ (ECHA, 2008)的可電離水溶性小分子的物理化學性質以及由急性經口和吸入毒性數據顯示，巰基乙酸和/或其鹽可經由吸入和口服途徑吸收。[1]
- 人體數據：14 名哮喘患者（13~60 歲）吸入以下 Ammonium Thioglycolate 稀釋液的霧氣分別為：1：10、1：100、1：10,000 和 1：100,000。經暴露後，有 13 位患者出現以下症狀：哮喘、無法控制的陣發性咳嗽、咽部和鼻腔刺激(UCLA, 1985)。咽部刺激持續 0.5 到 2 小時，具體取決於患者的敏感程度。8 名對照患者（非哮喘和非特應性）對受試物質沒有陽性反應，已知會在敏感人群中產生皮膚刺激性。另對患有職業性鼻炎的美髮師進行鼻刺激測試(Prowis，1976)，結果顯示 31 名患者中有 1 名患者對 pH 7.0 的 0.6% Ammonium Thioglycolate 溶液呈陽性反應(Hytonen, 1997)。Cosmetics Europe 進行上市後監督之報告顯示，兩種產品 Ammonium Thioglycolate 最高濃度分別為 4.5%和 4.95%，銷售 100 萬個產品在

5 年和 18 個月的使用中，發生與皮膚有關的皮膚刺激事件約為 1 次（分別為 1.2 和 0.94）。[1,3]

- 其他安全資料：依據美國化粧品成分審查(Cosmetic Ingredient Review, CIR)專家小組指出用於燙髮劑，濃度高達 15.2%（作為巰基乙酸）使用濃度下，巰基乙酸及其鹽和酯在急性單次口服和皮膚接觸中僅具有輕微毒性。對這些巰基乙酸鹽的刺激性和致敏性的皮膚測試結果取決於所用測試系統的類型。在封閉式貼片測試下，數據顯示這些成分是累積性刺激物，可能是弱致敏劑，但在半封閉式測試條件下則否。在主要是美髮師臨床患者中，硫醇乙酸甘油酯(Glyceryl Monothioglycolate)在濃度低至 0.25% 時會引起過敏反應。CIR 專家小組得出結論認為，巰基乙酸銨可安全用於頭髮直髮劑、燙髮劑、美髮產品、以及濃度高達 15.2%（以巰基乙酸計）的染髮劑。美髮師應避免皮膚接觸，並儘量減少消費者皮膚接觸。加拿大衛生部允許在燙髮和直髮產品中使用硫乙醇酸及其鹽，其濃度≤8%，pH 值為 7~ 9.5，用於專業用途的燙髮和直髮產品中，濃度≤11%，pH 值為 7 ~9.5。[4]
- 參考資料：

1. SCCS OPINION ON Thioglycolic acid and its salts (TGA), SCCS/1520/13, 11 November, 2013.
2. The Toxicity Studies of Sodium Thioglycolate (casrn 367-51-1) administered dermally to F344/N Rats and B6C3F1/N mice. NTP Technical Report, May, 2016.
3. Final Amended Report on the Safety Assessment of Ammonium Thioglycolate, Butyl Thioglycolate, Calcium Thioglycolate, Ethanolamine Thioglycolate, Ethyl Thioglycolate, Glyceryl Thioglycolate, Isooctyl Thioglycolate, Isopropyl Thioglycolate, Magnesium Thioglycolate, Methyl Thioglycolate, Potassium Thioglycolate, Sodium Thioglycolate, and Thioglycolic Acid. CIR, 1991.
4. Cosmetics Info 網站：https://www.cosmeticsinfo.org/ingredients/ammonium-thioglycolate/

2. 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。由於聚乙二醇(Polyethylene glycol, PEG)是環氧乙烷與水的縮合產物，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 1,4-二噁烷不純物（乙氧基化的副產物）。1,4-二噁烷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 1,4-二噁烷的含量，根據化粧品行業報告顯示已知 1,4-二噁烷可能是 PEG 中的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> 20 000 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 Polysorbate 80（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畸形的差異。[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]
- 細胞/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（在乙醇中），無論在有或沒有代謝活化的情況下，均無遺傳毒性，對照均達到預期的結果。[1]
- 皮膚刺激性：無 Polysorbate 80 之數據，而在人體刺激性研究中，類似的聚山梨酯類成分乙氧基化的 Polysorbate 60 (100%)，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]
- 毒物動力學：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 13(7) 4152, 2015.

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

3. INCI name：Ammonia

- 不純物：根據美國藥典的規定，強氨溶液的限制包括，重金屬限度為 0.0013%、不揮發殘留物不超過 5 mg (0.05%)、易氧化的物質經反應後，其粉紅色在 10 分鐘內不能完全消失。[1]
- 毒物動力學：氨(Ammonia)是氨基酸代謝的主要副產物，肝臟是氨代謝的主要器官。氨是由腸道中的含氮物質分解以及在小腸中使用谷氨酰胺作為新陳代謝的燃料而產生的。經由肝臟吸收後，轉化成毒性較低的尿素。大量代謝產生的氨被吸收到腸道中及血液，並通過門靜脈進入肝臟進行代謝。由於氨具有劇毒，因此會在許多組織中轉化為谷氨酰胺和丙氨酸，以運輸到肝臟。然後，氨通過肝臟中的尿素循環轉化為尿素，尿素從尿中排出。有證據顯示氨可以穿過血腦屏障 (Blood-Brain Barrier, BBB)，主要是通過離子轉運蛋白，而不是經由氣態氨的被動擴散。[1]
- 急性毒性：已發表的文獻中未發現氨的急性經皮毒性研究，也未有數據提交。在單次口服動物實驗中，對氨氣沒有影響或沒有嚴重影響的報導。但是，當透過管飼法(33.3 mg/kg）向大鼠施用 0.3%的氨水時，在 5 分鐘內觀察到胃粘膜損傷。據報導，大鼠對氨的急性口服 LD_{50} 為 350 mg/kg，透過管飼法向大鼠口服 1%或 3%（w/w 為氫氧化銨）會產生嚴重的出血性病變。
- 重複劑量毒性：在接受飲用水中添加 0.01%氨水大鼠試驗 8 週中，觀察到胃竇的粘膜萎縮以及胃竇和身體的粘膜增生區擴大，磷酸二銨的一般毒性的 NOAEL 為 250 mg/kg bw/day。在大鼠口服 5 週試驗中一般毒性的 LOAEL 為 750 mg/kg bw/day。[1]
- 皮膚致敏性：在公開的文獻中未找到關於氨的皮膚致敏性數據。[1]

- 眼睛刺激性：據報導氨可以迅速滲透到眼睛中，並且在低至 20 ppm 的濃度下會引起眼睛刺激或損害。[1]
- 致突變性/遺傳毒性：在沒有代謝激活的體外測定中，氨對大腸桿菌 Sd-4-73 株無遺傳毒性。[1]
- 致癌性：當 10 隻小鼠反覆吸入接觸 12%氨溶液蒸氣 8 週時，2 隻小鼠觀察到鼻粘膜癌。小鼠口服氨(溶解於水；42 mg/kg bw/day) 4 週後，沒有致癌性的證據。小鼠(Swiss 和 C3H)以氨 193 mg/kg bw/day 的劑量口服服藥 2 年後，沒有致癌性的證據，也沒有對乳腺腺癌(與 C3H 小鼠品係有關)的自然發展產生影響。[1]
- 生殖毒性：在一項生殖毒性研究中，從懷孕第 1 天到哺乳第 21 天，妊娠大鼠中飲食中暴露於 293 mg/kg bw/day 氨水，後代的雄性體重降低 25%和雌性體重降低 16%。在繁殖前 6 週到妊娠第 30 天，母豬吸入暴露於～7 ppm 或～35 ppm 的氨中，此研究沒有發現生殖或發育毒性。在涉及大鼠的磷酸二銨的生殖和發育毒性研究中，據研究結果顯示 NOAEL 為 1500 mg/kg bw/day，LOAEL 為>1500 mg/kg bw/day。[1]
- 人體數據：對於氨來說"急性"吸入（14 天或更短）吸入的最低風險水平(Minimum risk level, MRL)為 1.7 ppm。該研究涉及 16 位暴露於氨氣(50 ppm、80 ppm、110 ppm 或 140 ppm)的受試者。MRL 基於 50 ppm LOAEL，暴露於氨氣中 2 小時的受試者中有 6 名受試者眼睛產生輕微刺激，有 20 名受試者鼻子產生輕微刺激和有 9 名受試者喉嚨產生輕微刺激。一名工作了 18 年的 68 歲男性患者，在工作中經常暴露於縮微膠卷相機的無水氨洩漏，他因吸入氨觀察到整個肺部明顯的瀰漫性間質纖維化，被診斷為間質性肺病和嚴重的限制性肺病。[1]
- 其他安全資料：氨(NH_3)是一種氣體，當溶解在水中時，氨形成氫氧化銨(NH_4OH)。氨和氫氧化銨用於多種產品，包括染髮劑、頭髮脫色產品、剃鬚膏和美髮產品。氨被列入歐盟化粧品指令（附件三）。允許氨的最高使用濃度為 6%，如果濃度高於 2%，則產品必須標明含有氨。[2]
- 參考資料：

1. Safety Assessment of Ammonia and Ammonium Hydroxide as Used in Cosmetics, CIR, 2017.
2. Cosmetics Info 網站：https://cosmeticsinfo.org/ingredient/ammonia

4. INCI name：Sorbitan Stearate

- 毒物動力學：脫水山梨糖醇硬脂酸酯(Sorbitan Stearate)在攝入時水解為硬脂酸(stearic acid)和山梨糖醇酐(sorbitol)。當以油溶液餵給大鼠時，大約 90%的脫水山梨糖醇硬脂酸酯被吸收和水解，當以水乳劑的形式給予時，50%的脫水山梨糖醇硬脂酸酯被吸收和水解。脫水山梨糖醇硬脂酸酯不會在大鼠身體的脂肪儲存中積累。[1]
- 急性毒性：在 20 項山梨糖醇酯(Sorbitan ester)研究中，大鼠的脫水山梨糖醇硬脂酸酯最低致死劑量 LD_{50} 為 31 g/kg。[1]
- 皮膚刺激性：對動物進行的大量皮膚刺激性研究顯示，山梨糖醇類物質(Sorbitans)是微至輕度刺激物。在人類 21 天累積刺激性研究中，發現含有 2%~4%脫水山梨糖醇硬脂酸酯的產品是輕度刺激物。[1]
- 眼睛刺激性：一項關於 30%脫水山梨糖醇硬脂酸酯對兔子眼部的研究刺激性結果為陰性，而含有 4%硬脂酸鈉(Sodium stearate)的乳膏產品會引起兔子眼睛輕微的結膜刺激。[1]
- 重複劑量毒性：30 隻雄性大鼠餵食 5%脫水山梨糖醇硬脂酸酯（相當於 5000 mg/kg bw/day）的飲食 2 年，以肉眼或微觀觀察對臨床體徵、死亡率、體重、飼料消耗、血液學、臨床化學病變或病理，未發現不良反應。[1]
- 皮膚致敏性：經 420 名受試者重複進行的三次人類反覆刺激斑貼試驗(Human Repeat-Insult Patch Test, HRIPT)結果顯示，高達 4%脫水山梨糖醇硬脂酸酯不是致敏劑。[1]
- 致癌性：根據專家判斷，沒有證據顯示山梨糖醇酐脂肪酸酯(Sorbitan fatty acid esters)會致癌。[1,2]
- 生殖毒性：妊娠雌性 Wistar 大鼠（每組 20 隻）在妊娠第 0 至 20 天透過管飼法每天一次給藥 0、500 或 1,000 mg/kg bw/day 脫水山梨糖醇硬脂酸酯，然後犧牲動物，母體毒性和致畸性的 NOAEL 為 1000 mg/kg bw/day，未有與試驗品相關的胚胎毒性結果。每天一次對每組 12 隻雄性和 12 隻雌性 Sprague-Dawley 大鼠進行強制餵食，分別在水中加入 0、40、200 或 1000 mg/kg bw/day 的脫水山梨醇硬脂酸酯。20 隻雌性在交配前 2 週服用，直到第 4 天，哺乳期雄性被給藥 42 天，結果顯示沒有毒性跡象，對死亡率、體重或體重增加沒有影響，也沒有觀察到肉眼可見或微觀病變。[1]
- 光毒性/光敏感性：對脫水山梨糖醇硬脂酸酯或脫水山梨糖醇油酸

酯(Sorbitan oleate)的產品進行光敏性評估，結果顯示這兩種產品為無光毒性和無光敏感性。[1]

- 其他安全資料：依據 CIR 專家小組評估了科學數據並得出結論，在目前的濃度和使用條件下，脫水山梨糖醇硬脂酸酯作為化粧品成分是安全的。CIR 專家小組指出，脫水山梨糖醇硬脂酸酯通常是溫和的皮膚刺激物，但不致敏，也不是光敏劑，且在致癌性研究中呈陰性。[3]
- 參考資料：

1. Safety Assessment of Sorbitan Esters as Used in Cosmetics, CIR, 2019.
2. Sorbitan stearate, registration dossier. Administrative data, Key value for chemical safety assessment. ECHA https://echa.europa.eu/registration-dossier/-/registered-dossier/15165/7/6/1
3. Cosmetics Info 網站：https://www.cosmeticsinfo.org/ingredients/sorbitan-stearate/

5. INCI name：Paraffinum Liquidum

- 不純物：殘留溶劑和多環芳烴應符合歐洲藥典的規定，重金屬：砷、鉛、鎳、鎘和汞，每種不純物殘留量不超過 1 mg/kg。[1]
- 急性毒性：在文獻中沒有發現急性口服毒性相關研究。專家小組認為鑑於微晶蠟(microcrystalline the wax)的惰性和缺乏腸道吸收，可以假設此物質具有非常低的急性毒性。[4]
- 皮膚刺激性：非皮膚刺激性物質。[1]
- 眼睛刺激性：用 50%石蠟配製的產品對眼睛有輕微刺激。[1]
- 重複劑量毒性:在大鼠 90 天 P-70 油試驗中，測試最高劑量，NOAEL 為 2100 mg/kg bw/day。在一項為期 2 年的長期研究中，對 F344 大鼠測試高黏度(P-100)和 I 類中黏度(P-70)白油。NOAEL 為 1200 mg/kg bw/day，是兩種油的測試最高劑量。[1,3]
- 皮膚致敏性：沒有相關研究數據，但 Paraffinum Liquidum 不太可能是致敏劑，因為其分子量>500 Da，皮膚吸收率低。[1]
- 生殖毒性：沒有關於高黏度礦物油的具體生殖或發育毒性相關研究。然而，根據現有的關於低黏度白礦物油的研究為生殖和發育

影響提供證據並推論，高或中黏度礦物油不會產生生殖或發育毒性。[1]

- 致癌性：對於高度精煉的白色礦物油和蠟，來自動物研究或流行病學研究皆未有致癌性的證據。[2]
- 參考資料：

1. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS); Scientific Opinion on the use of high viscosity white mineral oils as a food additive on request from the European Commission. EFSA Journal, 7(11), 1387, [39 pp.], doi:10.2903/j.efsa, 2009.
2. Critical Reviews in Toxicology Mineral oil in food, cosmetic products, and in products regulated by other legislations Mineral oil in food, cosmetic products, and in products regulated by other legislations, Critical Reviews in Toxicology. January, 2020.
3. Mineral Hydrocarbons In Cosmetic LIP Care Products., COSMETICS EUROPE RECOMMENDATION N°14, 17-09, 2018.
4. Scientific opinion on the safety assessment of medium viscosity white mineral oils with a kinematic viscosity between 8.5~11 mm^2/s at 100 °C for the proposed uses as a food additive. EFSA Journal, 2013.

6. INCI name：Lanolin Wax

- 急性毒性：九種羊毛脂(Lanolin)成分中已在大鼠中進行了急性經口毒性測試，均表現出低口服毒性。含 50%羊毛脂蠟(Lanolin Wax)玉米油急性口服 LD_{50}>32 g/kg。[1,2]
- 皮膚刺激性：羊毛脂成分對實驗動物的皮膚無刺激性或至多有輕微刺激性。在對未稀釋的羊毛脂酸進行的測試中，主要刺激指數(Primary Irritation Index, PII)範圍為 0.78~2.2（最大值為 8），羊毛脂蠟獲得的最高 PII 值為 0.67。[1,2]
- 眼睛刺激性：所有羊毛脂成分對實驗動物的眼睛無刺激性，或至多有輕微刺激性。[1,2]
- 重複劑量毒性：依照 OECD 408，RccHanTM: WIST 大鼠每天餵食懸浮於玉米油中的羊毛脂，濃度分別為：100, 300, 1000 mg/kg bw/day，

每個濃度分別餵食 10 隻雄性及雌性 WIST 大鼠。所有動物在第 13 週後犧牲進行大體屍檢及組織病理學檢查。在任何劑量濃度下都沒有發現與測試項目相關的差異或變化，NOAEL 評估為≥1000 mg/kg bw/day。[3]

- 皮膚致敏性：用懸浮在玉米油中的羊毛脂蠟對天竺鼠(n = 10)進行皮膚致敏研究。每週進行十次皮內注射，兩週後再進行挑戰性注射 1 次，測試結果平均得分為 0.95（0.1 和 2.0 之間的分數為輕度致敏劑），顯示羊毛脂蠟是一種輕度皮膚致敏劑。[1]
- 人體數據：使用羊毛脂和相關化粧品成分對志願者進行了許多人類反覆刺激斑貼試驗。未經稀釋的羊毛脂 250 多個受試者中均未顯示出原發性刺激或致敏的跡象。羊毛脂油已經在 300 多個受試者中進行了皮膚測試，沒有不良反應發生。未稀釋的羊毛脂蠟顯示極低的刺激性，在 200 多名受試者中沒有致敏的跡象。[1,2]
- 其他安全資料：FDA 允許將羊毛脂用於保護皮膚的非處方藥物和保護肛門直腸區域的非處方藥中。羊毛脂和羊毛脂衍生成分的安全性，經 CIR 專家小組評估科學數據並得出結論：羊毛脂、羊毛脂油(Lanolin Oil)、羊毛脂蠟、羊毛脂醇(Lanolin Tocopherol)可安全用於化粧品和個人護理產品。然而，根據研究指出含有羊毛脂和相關材料的化粧品和個人護理產品會產生粉刺效應或形成粉刺。[4]
- 參考資料：

1. CIR Safety Assessment of Polyether Lanolins as Used in Cosmetics. CIR, 2012.
2. Final report of the safety assessment for Acetylated Lanolin Alcohol and related compounds. CIR, JEPT 4(4):63-92, 1980.
3. ECHA Fatty acids, lanolin, registration dossier. Repeated dose toxicity: Oral, https://echa.europa.eu/registration-dossier/-/registered-dossier/13395/7/6/2
4. Cosmetics Info 網站：https://www.cosmeticsinfo.org/ingredients/lanolin-wax/

7. INCI name：Sodium Bromate

- 急性毒性：使用溴酸鈉(Sodium Bromate)進行試驗非常少，大多數研究都以溴酸鉀(Potassium Bromate)為主。在大鼠中，溴酸鉀的口服 LD_{50} 為 200~400 mg，導致 100%死亡率的口服致死劑量為 700 mg/kg。在小鼠中，口服 LD_{50} 為 400 mg/kg。在一次胃內給予溴酸鉀後，大鼠、小鼠和倉鼠的 LD_{50} 超過 3700 mg/kg。這些物種的 LD_{50} 值在 300~500 mg/kg 的範圍內。[1]
- 重複劑量毒性：用溴酸鉀進行研究。由對溴酸鈉的研究並參照結果顯示，這兩種物質會都在水中解離，且鈉(Na+)和鉀(K+)離子都是天然存在的物質。Kurokawa 等人評估溴酸鹽的亞慢性效應（1990 年），它們在水中以 0、150、300、600、1250、2500、5000 或 10000 ppm 的濃度，並對 F344 大鼠組（10 隻/性別/組）施用溴酸鉀 13 週。假設平均默認飲用水消耗量為 0.4 L/day，平均默認體重為 0.3 kg，研究顯示與這些濃度相對應的劑量約為 0、16、32、63、140、270、650 或 1080 mg BrO^{3-} /Kg/day。所有暴露於>1,250 ppm 的動物均在 7 週內死亡。觀察到的毒性跡象包括在≥600ppm 雄性大鼠體重減少和雄性及雌性大鼠血清鉀濃度顯著下降，觀察到腎小管的再生變化，該研究將 LOAEL 值確定為 63 mg BrO^{3-} /Kg bw/day，但提供的數據未足以確定在較低劑量下是否會發生影響。中野(1989)等人將雄性 Wistar 大鼠餵食 0.04%溴酸鉀飲用水，在 0.1 L/kg/day 的攝入量下，對應約為 30 mg BrO^{3-}/kg bw/day 的劑量下，長達 15 個月。發現動物的體重增加明顯受到抑制，7~11 週時的腎臟組織學檢查顯示腎內部存在異常變化。15 個月後發現 BUN 增加，皮質小管明顯結構異常。基於體重增加減少和腎臟影響，本研究確定可觀察到不良反應最低劑量(LOAEL)為 30 mg BrO^{3-} /kg bw/day，但無法確定未觀察到不良反應劑量 (NOAEL)。[3]
- 皮膚刺激性：針對天竺鼠刺激性研究發現，溴酸鈉具有刺激性。[1]
- 經皮吸收：在一些動物研究中發現，將溴酸鈉施用於切下的天竺鼠皮膚，通過測量總溴化物(Bromide)而不是溴酸鹽(Bromate)以確定溴酸鹽吸收量。如發生溴酸鹽吸收，則吸收速度很慢（30 分鐘內為 0.12%）。當將溴酸鈉施用在天竺鼠的皮膚上時，血液中沒有檢測到溴酸鹽。[1]

- 人類數據：據研究顯示人類意外或自殺性攝入永久性燙髮劑中和溶液後出現了幾例急性溴酸鹽中毒案例。這些產品通常含有 2%的溴酸鉀或 10%的溴酸鈉。最常見的急性症狀是嚴重的胃腸道刺激（嘔吐、疼痛和腹瀉）和中樞神經系統抑鬱（嗜睡、低血壓和喪失反射反應），血管內溶血也可能導致貧血。這些影響通常是可逆的。後來的後遺症（通常在幾天內）包括明顯的腎損傷和聽力損失，但如果治療不成功，可能會導致腎衰竭死亡。如果治療成功，腎功能通常在 5~10 天後恢復。發生聽力損失通常是不可逆轉的。這些病例的估計劑量範圍為 20~1000 g BrO^{3-}/kg。[2]
- 其他安全資料：在幾項體內和體外研究中，發現溴酸鹽很難通過皮膚吸收。在哺乳動物細胞試驗和測試的三種細菌菌株中發現溴酸鉀具有致突變性。用於皮膚或皮下注射的溴酸鉀不會致癌，但這與口服給藥後觀察到的陽性結果相反，推測這些氧化劑的高反應性和較差的皮膚吸收，被認為是暴露途徑之間結果差異所造成之結果。根據 CIR 報告數據得出的結論是，溴酸鈉和溴酸鉀可以以不超過 10.17%的濃度（以溴酸鈉計）用於化粧品用燙髮配方。[4]
- 參考資料：

1. Final Report on the Safety Assessment of Sodium Bromate and Potassium Bromate, CIR, 1994.
2. Toxicological Review of Bromate. EPA, EPA/635/R-01/002, 2001.
3. ECHA Sodium bromate, registration dossier. Repeated dose toxicity: Oral , https://echa.europa.eu/registration-dossier/-/registered-dossier/14239/7/6/2
4. Cosmetics Info 網站：https://www.cosmeticsinfo.org/ingredients/sodium-bromate/

8. INCI name：Disodium Phosphate

- 急性毒性：據報導，磷酸鈉鹽(Sodium alts of phosphoric acid)的兔子皮膚單次劑量急性毒性 LD_{50} 範圍> 300 mg/kg ~ > 7940 mg/kg。在急性口服毒性研究中，給大鼠、小鼠、倉鼠和天竺鼠服用磷酸鈉鹽，LD_{50} 範圍為 1300 mg/kg（焦磷酸四鈉 Tetrasodium

Pyrophosphate［小鼠］）至 10600 mg/kg（三偏磷酸鈉 Sodium Trimetaphosphate［大鼠］）。磷酸鈉鹽、鉀鹽和鈣鹽具有較低的吸入毒性。[1]

- 眼睛刺激性：磷酸(Phosphoric Acid)在 70% ~ 85%的濃度範圍對兔子的眼睛有腐蝕性，但在 10%~17%的濃度範圍無刺激性。沒有一種磷酸鹽對兔子的眼睛有腐蝕性。[1]
- 重複劑量毒性：對大鼠餵食（飲食中最多 5%）磷酸二鈉(Disodium Phosphate)或焦磷酸二鈉(Disodium Pyrophosphate) 100 天的研究根據腎組織病理學結果推算出磷酸二鈉之 LOAEL< 2571 mg/kg/d。當將磷酸二鈉、三磷酸五鈉(Pentasodium Triphosphate)或焦磷酸四鈉(Tetrasodium Pyrophosphate)在飲食中以高達 5%的濃度給予大鼠 39 週時，報告得到的 LOAEL 為 495 mg/kg bw/day。在大鼠研究中，每天在飲食中餵食濃度高達 0.75%的磷酸(Phosphoric Acid)，持續時間> 52 週確定的最高 NOAEL 為 338 mg/kg bw/day。
- 皮膚刺激性：磷酸二鈉(Disodium Phosphate)具中度刺激性。[1]
- 皮膚致敏性：磷酸在人類受試者中不致敏，而磷酸鈉（在丙二醇中為 10%）在局部淋巴結試驗亦顯現不致敏。[1]
- 致癌性：非致癌性。[1]
- 遺傳毒性：磷酸及其銨鹽、鈉鹽、鉀鹽和鈣鹽在體外或體內遺傳毒性試驗為陰性。[1]
- 毒物動力學：磷酸鹽從胃腸道吸收，腸道管腔的運輸是一個依賴能量的過程。維生素 D 刺激磷酸鹽吸收。在生理 pH 7.4 下，細胞外磷酸鹽主要以磷酸二鈉鹽和磷酸鈉鹽(4:1)的形式存在。磷酸鹽一旦吸收，就會與鈣結合形成骨骼和牙齒中的磷酸氫鈣。游離正磷酸鹽是膳食吸收的主要形式，攝入大量的磷酸根離子後，腸中大部分的磷酸根離子吸收便會消除。根據另一種來源，成年人中約三分之二的磷酸根吸收是透過胃腸道吸收的，吸收的磷酸根幾乎全部釋放至尿液中。[1]
- 人體數據：依據FDA研究報告指出在確定的使用磷酸鈉片劑的178例患者（佔女性的 71%）中，每年與片劑製備相關的腎臟不良藥物反應的數量不斷增加。2006 年，研究 74 例腎臟不良藥物反應(renal adverse drug reactions, ADRs)中有 9 例(12%來自攝入片劑。片劑製劑中患有腎臟併發症的女性的平均體重為 68.57±1.78 kg，遠低於全國健康和營養檢查調查中同一年齡組的全國平均體重

74±0.5 kg (P = 0.003)。結論是，平均體重低於全國平均體重的女性中，磷酸鈉片引起的腎臟不良藥物反應更為常見。

◆ 其他安全資料：

FDA 將磷酸鈉（單鹼基、二鹼基和三鹼基）列入公認安全(Generally Recognized As Safe, GRAS)的物質中，可用作多用途食品物質、營養劑和作為螯合劑。磷酸鈉（一元和二元）也被批准用於作為非處方瀉藥產品的成分。FDA 的 GRAS 物質特別委員會(Select Committee on GRAS Substances, SCOGS) 得出結論，在有關磷酸鈉（單鹼基、二鹼基和三鹼基）的可用資訊中，沒有證據顯示或有合理理由懷疑它對公眾造成危害。[2]

◆ 參考資料：

1. Safety Assessment of Phosphoric Acid and Simple Salts as Used in Cosmetics, CIR, 2016.
2. Cosmetics Info 網站：https://www.cosmeticsinfo.org/ingredients/disodium-phosphate/

(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、微生物檢測、包材外觀結果項目進行 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	燙髮劑 1 號第一劑			
包裝材質	PVC			
試驗時間 / 試驗項目	第 0 個月 40 ℃ 75 %RH	第 1 個月 40 ℃ 75 %RH	第 3 個月 40 ℃ 75 %RH	第 6 個月 40 ℃ 75 %RH
外觀	流動液體	流動液體	流動液體	流動液體
顏色	乳白色不透明	乳白色不透明	乳白色不透明	乳白色不透明
氣味	有刺激氣味	有刺激氣味	有刺激氣味	有刺激氣味
pH	9.57	9.46	9.79	9.65
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)

產品名稱	燙髮劑 1 號第二劑			
包裝材質	PVC			
試驗時間 / 試驗項目	第 0 個月 40 ℃ 75 %RH	第 1 個月 40 ℃ 75 %RH	第 3 個月 40 ℃ 75 %RH	第 6 個月 40 ℃ 75 %RH
外觀	流動液體	流動液體	流動液體	流動液體
顏色	乳白色微透明	乳白色微透明	乳白色微透明	乳白色微透明
氣味	無	無	無	無
pH	5.61	5.73	5.58	5.42
微生物檢測結果	未檢出	未檢出	未檢出	未檢出
包材外觀	無變形、變色、腐蝕及脆裂之現象	無變形、變色、腐蝕及脆裂之現象	無變形、變色、腐蝕及脆裂之現象	無變形、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

燙髮劑1號第一劑雖然含氨0.448%，未符合ISO 29621: 2017微生物低風險性含氨≥0.5%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。

產品名稱	燙髮劑 1 號-第一劑		
產品批號	IT1007AC2		
產品製造日期	110.07.05		
包裝材質	PVC	試驗日期	110.07.08
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 公布建議檢驗方法-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)		

產品名稱	燙髮劑 1 號-第二劑		
產品批號	IT1007AC2		
產品製造日期	110.07.05		
包裝材質	PVC	試驗日期	110.07.08
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 公布建議檢驗方法-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

燙髮劑1號第一劑雖然含氨0.448%，未符合ISO 29621: 2017微生物低風險性含氨≥0.5%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)	燙髮劑 1 號第一劑				
測試日期(Date Tested): 110/06/01~110/06/30					
試驗參考方法(Method Code): ISO 11930:2019					
測試菌種 (Organism)					
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	8.4×10^5	9.8×10^5	9.3×10^5	8.9×10^4	9.1×10^4
第 7 天	<10	<10	<10	$6.3X10^2$	$3.5X10^3$
第 14 天	<10	<10	<10	<10	$1.3X10^2$
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）				

樣品名稱 (Sample Name)	燙髮劑 1 號第二劑

測試日期(Date Tested): 110/06/01~110/06/30

試驗參考方法(Method Code): ISO 11930:2019

測試菌種 (Organism)

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	8.8×10^5	9.2×10^5	9.4×10^5	8.6×10^4	9.7×10^4
第 7 天	<10	<10	<10	$3.7X10^2$	$2.6X10^3$
第 14 天	<10	<10	<10	<10	$1.4X10^2$
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

燙髮劑相關功能性測定，如燙髮捲度試驗等。

(15) 與產品接觸之包裝材質資料

包裝材料	材質	產品容量
燙髮劑1號第一劑-瓶身	PVC	40 ml
燙髮劑1號第一劑-瓶蓋	PVC	40 ml
燙髮劑1號第二劑-瓶身	PVC	40 ml
燙髮劑1號第二劑-瓶蓋	PVC	40 ml

III. 安全評估資料

(16) 產品安全資料

燙髮劑 1 號每日皮膚暴露量計算

參考 2021 年 3 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 11 版(SCCS/1628/21)，並依據使用用途、部位、頻率進行安全性評估計算。

基本數據	
平均體重(K)	60 kg
接觸部位	頭皮和手部
接觸種類	駐留產品
日常每日使用劑量(GBC)	4.0 g/day
保留因子(RBC)	0.1
相對每日暴露量(Eproduct)	5.74 mg/kg bw/day
每日皮膚暴露量（Edermal） Edermal =（GBC* RBC）/ K	
(4.0×0.1)/60 = 0.00667 g/Kg bw/day = 6.67 mg/kg bw/day	

燙髮劑 1 號各個成分 MoS 值計算

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

SED= Edermal (每日皮膚暴露量)× C/100(配方百分比)× DAp/100(皮膚吸收率)

MoS*= PODsys/*SED

PODsys 可以是 BMDL 或者是 NOAEL、LOAEL。

SCCS 化粧品成分測試及其安全性評估指引第 11 版 (SCCS/1628/21) 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 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:

第一劑

INCI name	配方百分比 C (%)	皮膚吸收率 DAp(%)	NOAEL (mg /kg bw/day)	SED (mg /kg bw/day)	MoS
Aqua	84.3	-	-	-	>100
Ammonium Thioglycolate (50% Solution)	10.0	1.09	129	0.0036	35833
Polysorbate 80	2.0	100	730	0.1334	5472
Ammonia (28% Solution)	1.6	100	77	0.0299	2575
Sorbitan Stearate	1.0	100	2500	0.0667	37481
Paraffinum Liquidum	0.6	10	600	0.0040	150000
Lanolin Wax	0.5	100	500	0.0334	14970

第二劑

INCI name	配方百分比 C (%)	皮膚吸收率 DAp(%)	NOAEL (mg /kg bw/day)	SED (mg /kg bw/day)	MoS
Aqua	89.5	-	-	-	>100
Sodium Bromate	7.0	10	5	0.0467	107
Disodium Phosphate	3.5	100	82.5	0.2335	353

INCI name	NOAEL 校正說明
Ammonium Thioglycolate (50% Solution)	對大鼠13週反覆皮膚毒性研究中，系統性NOAEL為180 mg/kg bw/day，考慮每週只進行5天試驗不確定因子，將180*5/7 =129 mg/kg bw/day。
Polysorbate 80	大鼠膳食亞慢性研究(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。
Ammonia (28% Solution)	參照在飲用水中添加0.01%氨水大鼠試驗8週中，磷酸二銨NOAEL為250 mg/kg bw/day，考慮口服生物可用率50%及試驗天數(8週)之不確定因子，將250*50%*8/13=77 mg/kg bw/day。
Sorbitan Stearate	雄性大鼠餵食5%脫水山梨糖醇硬脂酸酯2年NOAEL為5000 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，將5000*50% =2500 mg/kg bw/day。
Paraffinum Liquidum	在一項為期2年長期研究中，F344大鼠口服高黏度(P-100)和I類中黏度(P-70)白油，NOAEL為1200 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，將1200*50%=600 mg/kg bw/day。
Lanolin Wax	13週大鼠口服毒性得知NOAEL約為1000 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，將1000*50% =500 mg/kg bw/day。
Sodium Bromate	長達15個月Wistar大鼠餵食0.04%溴酸鉀飲用水，確定可觀察到不良反應最低劑量(LOAEL)為30 mg /kg bw/day，考慮LOAEL轉換成NOAEL及口服生物可用率50%之不確定因子，將30/3*50% =5 mg/kg bw/day。
Disodium Phosphate	大鼠口服5%磷酸二鈉39週，報告得到的LOAEL為495 mg/kg bw/day，考慮LOAEL轉換成NOAEL及口服生物可用率50%之不確定因子，495/3*50% =82.5 mg/kg bw/day。

燙髮劑 1 號安全評估結論

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據以結論，推定燙髮劑 1 號在預期正常合理使用條件下，本產品為可安全使用之產品，不致對人體健康造成傷害。

標籤警語和使用說明

燙髮劑 1 號產品的包裝材料/標籤上已刊載使用說明，且使用注意事項已依「燙髮劑之標籤、仿單或包裝應標示事項」規定刊載。

由於產品標籤和產品的一般描述足以定義產品作為燙髮劑的用途，產品中之每種成分沒有使用到會因其毒理學和/或物理性質或由於它們在成品中的濃度比例需要額外指示或加註標示警語注意事項，因此不需要另外加註標示警語注意事項和使用說明，但建議可於包裝外盒上使用注意事項加註「建議每 3 個月使用 1 次(每次燙髮至少間隔 3 個月)」提醒消費者。

安全評估理由

燙髮劑 1 號的安全性評估基於每種成分的毒理學特性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. 由於該產品含有濃度 7% Sodium Bromate 強氧化劑成分，根據 CIR 研究數據，CIR 專家小組得出的結論是，溴酸鈉可以不超過 10.17%的濃度用於化粧品用燙髮配方，我國特定用途化粧品成分名稱及使用限制表溴酸鈉限制使用濃度標準為 11.5%，燙髮劑 1 號添加 7% Sodium Bromate 是合乎規範且安全的。
3. 根據本產品「燙髮劑 1 號」之物理/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評估，結果由數據顯示產品符合規格特性，證實「燙髮劑 1 號」產品配方具有足夠安定性及微生物安全性。
4. 燙髮劑 1 號第一劑經評估非屬於低微生物風險產品，故仍需進行防腐效能試驗及微生物檢測。燙髮劑 1 號第一劑及第二劑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通過 ISO 11930:2019 Criteria A 之標準。

Table B.1 — Evaluation criteria

Log reduction values ($R_x = \lg N_0 - \lg N_x$) required[a]								
Micro organisms	Bacteria			*C. albicans*			*A. brasiliensis*	
Sampling time	T7	T14	T28	T7	T14	T28	T14	T28
Criteria A	≥ 3	≥ 3 and NI[b]	≥ 3 and NI	≥ 1	≥ 1 and NI	≥ 1 and NI	≥ 0[c]	≥ 1 and NI
Criteria B	Not performed	≥ 3	≥ 3 and NI	Not performed	≥ 1	≥ 1 and NI	≥ 0	≥ 0 and NI

a In this test, an acceptable range of deviation of 0,5 log is accepted (see 5.7).

b NI: no increase in the count from the previous contact time.

c $R_x = 0$ when $\lg N_0 = \lg N_x$ (no increase from the initial count).

5. 本產品使用之包裝材質為 PVC，根據過去類似配方及此包材之使用經驗，評估此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 11 版”，計算化粧品中產品和每種成分的暴露程度。對於暴露計算，以正常合理的可預見方式作為燙髮劑，使用保留因子 0.1（10%）計算。針對此款燙髮劑中包含的每種原料成分，計算各別之安全邊際值（MoS）皆高於 100，成品中的所有原材料和成分被評估為在產品中作為化粧品成分使用是安全的，支持此產品的安全性。此燙髮劑 1 號無添加香精及防腐劑，降低致敏風險。
7. 目前此產品在市面上尚未出現不良影響和嚴重的不良影響，如有不良影響和嚴重不良影響的相關資訊會立即更新，並及時提供給安全資料簽署人員，以重新評估此產品之安全性。

(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(亦須包含 Fragrance 內含成分)之品質規格或各成分之檢驗報告(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：Ammonia

SAFETY DATA SHEET

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name : Ammonia solution 28-30% for analysis EMSURE® ACS,Reag. Ph Eur

1.2 Other means of identification

No data available

1.3 Relevant identified uses of the substance or mixture and uses advised against

Identified uses : Reagent for analysis, Chemical production

1.4 Details of the supplier of the safety data sheet

1.5 Emergency telephone

SECTION 2: Hazards identification

2.1 GHS Classification

Skin corrosion/irritation (Category 1), H314
Serious eye damage/eye irritation (Category 1), H318
Specific target organ toxicity - single exposure (Category 3), Respiratory system, H335
Short-term (acute) aquatic hazard (Category 1), H400

Long-term (chronic) aquatic hazard (Category 2), H411

For the full text of the H-Statements mentioned in this Section, see Section 16.

2.2 GHS Label elements, including precautionary statements

Pictogram

Signal word: Danger

Hazard statement(s)

H314	Causes severe skin burns and eye damage.
H335	May cause respiratory irritation.
H400	Very toxic to aquatic life.
H411	Toxic to aquatic life with long lasting effects.

Precautionary statement(s)

Prevention

P261	Avoid breathing dust/ fume/ gas/ mist/ vapors/ spray.
P264	Wash skin thoroughly after handling.
P271	Use only outdoors or in a well-ventilated area.
P273	Avoid release to the environment.
P280	Wear protective gloves/ protective clothing/ eye protection/ face protection.

Response

P301 + P330 + P331	IF SWALLOWED: Rinse mouth. Do NOT induce vomiting.
P303 + P361 + P353	IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water/ shower.
P304 + P340 + P310	IF INHALED: Remove person to fresh air and keep comfortable for breathing. Immediately call a POISON CENTER/ doctor.
P305 + P351 + P338 + P310	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/ doctor.
P363	Wash contaminated clothing before reuse.
P391	Collect spillage.

Storage

P403 + P233	Store in a well-ventilated place. Keep container tightly closed.
P405	Store locked up.

Disposal

P501	Dispose of contents/ container to an approved waste disposal plant.

2.3 Other hazards - none

SECTION 3: Composition/information on ingredients

Substance / Mixture : Mixture

3.2 Mixtures

Hazardous ingredients

Component		Classification	Concentration
ammonia solution			
CAS-No. EC-No.	1336-21-6 215-647-6	1B; 1; STOT SE 3; Aquatic Acute 1; Aquatic	>= 25 - < 30 %

Index-No.	007-001-01-2	Chronic 2; H314, H318, H335, H400, H411 Concentration limits: >= 5 %: STOT SE 3, H335; M-Factor - Aquatic Acute: 10	

For the full text of the H-Statements mentioned in this Section, see Section 16.

SECTION 4: First aid measures

4.1 Description of first-aid measures

General advice
First aiders need to protect themselves.

If inhaled
After inhalation: fresh air. Call in physician.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower. Call a physician immediately.

In case of eye contact
After eye contact: rinse out with plenty of water. Immediately call in ophthalmologist. Remove contact lenses.

If swallowed
After swallowing: make victim drink water (two glasses at most), avoid vomiting (risk of perforation). Call a physician immediately. Do not attempt to neutralise.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Use extinguishing measures that are appropriate to local circumstances and the surrounding environment.

Unsuitable extinguishing media
For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture
Nitrogen oxides (NOx)
Not combustible.
Ammonia solution itself is not flammable, but can form an ignitable ammonia/air-mixture by outgassing.
Ambient fire may liberate hazardous vapours.
Fire may cause evolution of:
nitrogen oxides

5.3 Advice for firefighters
Stay in danger area only with self-contained breathing apparatus. Prevent skin contact by keeping a safe distance or by wearing suitable protective clothing.

5.4 Further information
Cool closed containers exposed to fire with water spray. Suppress (knock down) gases/vapors/mists with a water spray jet. Prevent fire extinguishing water from contaminating surface water or the ground water system.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures
Advice for non-emergency personnel: Do not breathe vapors, aerosols. Avoid substance contact. Ensure adequate ventilation. Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions
Do not empty into drains.

6.3 Methods and materials for containment and cleaning up
Cover drains. Collect, bind, and pump off spills.Observe possible material restrictions (see sections 7 and 10).Take up with liquid-absorbent and neutralising material (e.g. Chemizorb® OH^-, Merck Art. No. 101596). Dispose of properly. Clean up affected area.

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling

Advice on safe handling
Observe label precautions.

Hygiene measures
Immediately change contaminated clothing. Apply preventive skin protection. Wash hands and face after working with substance.
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
No metal or light-weight-metal containers.
Tightly closed.

Recommended storage temperature see product label.

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

Appropriate engineering controls
Immediately change contaminated clothing. Apply preventive skin protection. Wash hands and face after working with substance.

Personal protective equipment

Eye/face protection
Tightly fitting safety goggles

Skin protection
This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Full contact
Material: butyl-rubber
Minimum layer thickness: 0.7 mm
Break through time: 480 min
Material tested:Butoject® (KCL 898)

This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).
Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0.40 mm
Break through time: 240 min
Material tested:Camatril® (KCL 730 / Aldrich Z677442, Size M)

Body Protection
protective clothing

Respiratory protection
required when vapours/aerosols are generated.

Control of environmental exposure
Do not empty into drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: liquid Color: colorless
b)	Odor	stinging, ammoniacal
c)	Odor Threshold	0.03 - 0.05 ppm - Ammonia
d)	pH	> 12 at 20 °C strongly alkaline

e)	Melting point/freezing point	Melting point: ca.-72 °C
f)	Initial boiling point and boiling range	ca.32 °C
g)	Flash point	Not applicable
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	No data available
j)	Upper/lower flammability or explosive limits	Upper explosion limit: 33.6 %(V) Lower explosion limit: 15.4 %(V)
k)	Vapor pressure	635 hPa at 20 °C
l)	Vapor density	No data available
m)	Relative density	No data available
n)	Water solubility	at 20 °C soluble
o)	Partition coefficient: n-octanol/water	log Pow: -1.38 - (anhydrous substance), Bioaccumulation is not expected.
p)	Autoignition temperature	No data available
q)	Decomposition temperature	No data available
r)	Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: No data available
s)	Explosive properties	No data available
t)	Oxidizing properties	No data available

9.2 Other safety information

Minimum ignition energy	380 - 680 mJ

SECTION 10: Stability and reactivity

10.1 Reactivity

No data available

10.2 Chemical stability

Ammonia solution itself is not flammable, but can form an ignitable ammonia/air-mixture by outgassing.

10.3 Possibility of hazardous reactions

A risk of explosion and/or of toxic gas formation exists with the following substances:
Oxidizing agents
Mercury
Oxygen
silver compounds
nitrogen trichloride
hydrogen peroxide
silver
antimony hydride

Halogens
Acids
Calcium
Chlorine
Chlorites
auric salts
perchlorates
sodium hypochlorite
mercury compounds
halogen oxides
Heavy metals
Heavy metal salts
Acid chlorides
Acid anhydrides
Risk of ignition or formation of inflammable gases or vapours with:
Boranes
Boron
Oxides of phosphorus
Nitric acid
silicon compounds
chromium(VI) oxide
chromyl chloride
Exothermic reaction with:
Acetaldehyde
Acrolein
Barium
boron compounds
Bromine
halogen-halogen compounds
hydrogen bromide
silane
Hydrogen chloride gas
halogen compounds
dimethylsulfate
nitrogen oxides
Fluorine
Hydrogen fluoride
chlorates
carbon dioxide
Ethylene oxide
polymerisable

10.4 Conditions to avoid
Heating.

10.5 Incompatible materials
Aluminum, Lead, Nickel, silver, Zinc, Copper, metal alloys, various metals

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Mixture

Acute toxicity
Oral: No data available
Symptoms: mucosal irritations, Cough, Shortness of breath, bronchitis, Possible damages:, damage of respiratory tract
Dermal: No data available

Skin corrosion/irritation
Skin - Rabbit
Result: Severe irritations
Remarks: (29% solution)
(RTECS)
Dermatitis Necrosis

Serious eye damage/eye irritation
Eyes - Rabbit
Result: Severe irritations
Remarks: (29% solution)
(RTECS)
Mixture causes serious eye damage. Risk of blindness!

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
No data available

Carcinogenicity
No data available

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
Mixture may cause respiratory irritation. - Respiratory system

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information

Cough
Shortness of breath
bronchitis
gastric pain
Bloody vomiting
Nausea
collapse
shock
Unconsciousness

Other dangerous properties can not be excluded.
Handle in accordance with good industrial hygiene and safety practice.

Components

ammonia solution

Acute toxicity
Oral: No data available
Inhalation: Material is extremely destructive to the tissue of the mucous membranes and upper respiratory tract.
Dermal: No data available

Skin corrosion/irritation
Causes skin burns.

Serious eye damage/eye irritation
Causes serious eye damage.

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
No data available

Carcinogenicity
No data available

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
May cause respiratory irritation.

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

SECTION 12: Ecological information

12.1 Toxicity

Mixture
No data available

12.2 Persistence and degradability
Biodegradability Remarks: No data available

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
PBT/vPvB assessment not available as chemical safety assessment not required/not conducted

12.6 Other adverse effects
Biological effects:
Harmful effect due to pH shift.
Forms toxic and corrosive mixtures with water even if diluted.

Discharge into the environment must be avoided.
No data available

Components

ammonia solution

Toxicity to fish	flow-through test LC50 - Pimephales promelas (fathead minnow) - 0.068 mg/l - 96 h Remarks: (in analogy to similar products) (ECHA) The value is given in analogy to the following substances: ammonium sulphate
Toxicity to daphnia and other aquatic invertebrates	static test LC50 - Daphnia magna (Water flea) - 101 mg/l - 48 h Remarks: (ECHA) anhydrous

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product

Waste material must be disposed of in accordance with the national and local regulations. Leave chemicals in original containers. No mixing with other waste. Handle uncleaned containers like the product itself. See www.retrologistik.com for processes regarding the return of chemicals and containers, or contact us there if you have further questions. The chemical must be disposed or recycled in accordance with Waste Disposal Act. See www.epa.gov.tw for the information of chemical waste disposal companies and their contacts.

SECTION 14: Transport information

14.1 UN number

ADR/RID: 2672 IMDG: 2672 IATA-DGR: 2672

14.2 UN proper shipping name

ADR/RID: AMMONIA SOLUTION
IMDG: AMMONIA SOLUTION
IATA-DGR: Ammonia solution

14.3 Transport hazard class(es)

ADR/RID: 8 IMDG: 8 IATA-DGR: 8

14.4 Packaging group

ADR/RID: III IMDG: III IATA-DGR: III

14.5 Environmental hazards

ADR/RID: yes IMDG Marine pollutant: yes IATA-DGR: no

14.6 Special precautions for user

None

14.7 Incompatible materials

Aluminum, Lead, Nickel, silver, Zinc, Copper, metal alloys, various metals

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture

No data available

SECTION 16: Other information

Training advice Provide adequate information, instruction and training for operators.

Full text of H-Statements referred to under sections 2 and 3.

H314	Causes severe skin burns and eye damage.
H318	Causes serious eye damage.
H335	May cause respiratory irritation.
H400	Very toxic to aquatic life.
H411	Toxic to aquatic life with long lasting effects.

The branding on the header and/or footer of this document may temporarily not visually match the product purchased as we transition our branding. However, all of the information in the document regarding the product remains unchanged and matches the product ordered. For further information please contact mlsbranding@sial.com.

Literature references	About detail information, please refer to each section The information contained herein is based on the present state of our knowledge. It characterises the product with regard to the appropriate safety precautions. It does not represent a guarantee of any properties of the product.		
Organization that prepared the SDS	Name:Merck KGaA LS-QH		
	Address/Telephone number:64271 Darmstadt Germany/+49 6151 72-0		
Date that the SDS was prepared	01.07.2021	Print Date	26. 10. 2021

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：Ammonia

1. Safety Assessment of Ammonia and Ammonium Hydroxide as Used in Cosmetics. CIR, 2017.

Safety Assessment of
Ammonia and Ammonium Hydroxide as Used in Cosmetics

Status: Scientific Literature Review for Public Comment
Release Date: July 7, 2017
Panel Date: September 11-12, 2017

All interested persons are provided 60 days from the above date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Interim Director, Dr. Bart Heldreth.

The 2017 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Interim Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, and Ivan Boyer, Ph.D., Toxicologist.

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INTRODUCTION

The safety of Ammonia and Ammonium Hydroxide in cosmetics is reviewed in this Cosmetic Ingredient Review (CIR) safety assessment. According to the *International Cosmetic Ingredient Dictionary and Handbook*, both ingredients are reported to function as pH adjusters in cosmetic products.[1] Additionally, Ammonia is reported to function as an external analgesic and fragrance ingredient and Ammonium Hydroxide is reported to function as adenaturant in cosmetic products. Functioning as an external analgesic is not a cosmetic use and, therefore, the Panel will not evaluate safety in relation to that use in cosmetics. Additionally, the function of fragrance may be excluded from the purview of the Panel, and is not assessed herein.

An Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile for Ammonia was published in 2004, and many of the toxicity studies summarized in this document are also included in this CIR safety assessment.[2] Pertinent information (e.g., number of animals tested and study details) that is missing from some of the study summaries in this safety assessment is being sought.

More recently, an Environmental Protection Agency (EPA) toxicological review that covers gaseous Ammonia (NH_3) and Ammonia dissolved in water (Ammonium Hydroxide, NH_4OH) was published in 2016.[3] It should be noted that portions of the EPA review are adapted from the toxicological profile for Ammonia that was developed by the ATSDR, and that this CIR safety assessment also includes toxicity data on Ammonia/Ammonium Hydroxide that have become available since the ATSDR and EPA documents were published.

In addition to the safety test data on Ammonia and Ammonium Hydroxide that are included in this safety assessment, the following data on surrogate chemicals are also included: data on ammonium ion (reproductive and developmental toxicity, genotoxicity, and carcinogenicity data) that are included in the ATSDR toxicological profile for Ammonia; diammonium phosphate (repeated dose (short-term) oral toxicity and reproductive and developmental toxicity data); ammonium chloride (genotoxicity data [micronucleus test]); ammonium sulfate (oral carcinogenicity and chronic oral toxicity data); and diammonium phosphate (reproductive toxicity data). The European Chemicals Agency (ECHA) registration dossier on Ammonia is the source of the safety test data on diammonium phosphate, ammonium chloride, ammonium sulfate, and ammonium sulfate.[4] The CIR Expert Panel will determine whether or not these data on surrogate chemicals are useful in evaluating the safety of Ammonia and Ammonium Hydroxide in cosmetic products.

Furthermore, in addition to the ASTDR and EPA reports on Ammonia, an expert assessment, prepared by a 14-member task group, of the effects on human health and the environment posed by Ammonia is available.[5] This assessment was published under the joint sponsorship of the United Nations Environment Program, the International Labor Organization, and the World Health Organization.

CHEMISTRY

Definition and General Characterization

Ammonia, ammonia gas, anhydrous ammonia, and liquid ammonia are terms that are often used interchangeably to refer to the ingredient, Ammonia, in either its liquid or gaseous state.[6] Ammonia dissolved in water is referred to as aqueous ammonia, ammonia solution, and the ingredient name, Ammonium Hydroxide. In an aqueous formulation, these two ingredients will each comprise at least some of the other.

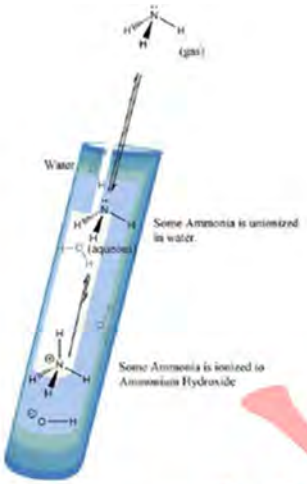


Figure 1. The aqueous relationship of Ammonia and Ammonium Hydroxide

Most inorganic hydroxides are alkaline salts formed by treating oxides with water, or via decomposing salts by adding other soluble hydroxides to a solution thereof. However, some Ammonium Hydroxide is formed simply by the hydrolysis of Ammonia. Regardless of whether the ingredient is named Ammonia or Ammonium Hydroxide, if the formulation or test article is aqueous, both are present due to an equilibrium. At or near neutral pH, more than 99% is in the form of dissolved (i.e. molecular) Ammonia, and less than 1% is Ammonium Hydroxide. In more alkaline (i.e. higher pH) solutions, the Ammonium Hydroxide concentration can be significantly higher though (e.g., at pH 9.25 the ratio of Ammonia to Ammonium Hydroxide is about 1:1; pK_b ~4.8 at room temperature). Accordingly, the ratio of dissolved molecular Ammonia versus the ions of Ammonium Hydroxide is dependent, *inter alia*, on the pH of the formulation. Saturation in water, at room temperature and atmospheric pressure, is approximately 34%.[7]

Application of ammonia gas (i.e., anhydrous ammonia) to cosmetics, without addition to water seems unlikely, unless some other reaction product is desired. Since the functions of external analgesic and fragrance may be excluded from the purview of the CIR Expert Panel, the only function of Ammonia under review herein is pH adjuster. The term "pH" refers to a ratio of hydroxide and hydronium ions in water. Accordingly, any ingredient that functions as a pH adjuster must do so in an aqueous formation. *Ipso facto*, this assessment addresses only the safety of the ingredient, Ammonia, as used in aqueous formulations. And, Ammonium Hydroxide does not exist outside of an aqueous solution. Therefore, whether Ammonia or Ammonium Hydroxide is on the cosmetic ingredient label, the chemical moieties contained therein are the same.

The definitions, structures, and functions in cosmetics of these ingredients are presented in Table 1.

Chemical and Physical Properties

Ammonia is a small nitrogenous compound with a molecular weight of 17, that is a gas at standard temperature and pressure.[8] It is a weak base that exists in equilibrium with the Ammonium Hydroxide as shown in Figure 1. Ammonium Hydroxide is a salt, formed by hydrolysis of Ammonia,that essentially does not exist outside of aqueous solution.

Chemical and physical properties of Ammonia and Ammonium Hydroxide are presented in Table 2.[2,9,10]

Method of Manufacture

Ammonia can be formed from water gas and producer gas via the Haber-Bosch process.[7]

Ammonium Hydroxide can be produced by passing Ammonia gas into water.[11]

Composition

According to the *Food Chemicals Codex*, Ammonium Hydroxide contains not less than 27% and not more than 30% by weight NH_3.[12] The monograph on strong Ammonia solution in the *United States Pharmacopoeia* states that this is a solution of NH_3, containing not less than 27% and not more that 31 % (w/w) NH_3.[13]

Impurities

According to the *Food Chemicals Codex*, the acceptance criteria for Ammonium Hydroxide include: lead (not more than 0.5 mg/kg), nonvolatile residue (not more than 0.02%), and readily oxidizable substances (pink color does not completely disappear within 10 minutes).[12] Similarly, according to the *United States Pharmacopoeia*, the limitations on strong Ammonia solution include: heavy metals (0.0013% limit), nonvolatile residue (not more than 5 mg of residue remains [0.05%]), and readily oxidizable substances (pink color does not completely disappear within 10 minutes).[13]

USE

Cosmetic

The safety of Ammonia and Ammonium Hydroxide is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database.[14] Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.[15]

According to 2017 VCRP data, Ammonia is being used in 599 cosmetic products (mostly rinse-off products) and Ammonium Hydroxide is being used in 1354 cosmetic products (mostly rinse-off products) (Table 3).[14] The results of a concentration of use survey provided by the Council in 2017 indicate that the highest maximum cosmetic use concentration of Ammonia is 4.6 % (in rinse-off products [hair dyes and colors]) and that the highest maximum cosmetic use concentration of Ammonium Hydroxide is 12.5% (in rinse-off products [hair dyes and colors]) (Table 3).[15] Regarding use concentrations in leave-on products, the highest maximum cosmetic use concentrations are 0.73% (Ammonia - in tonics, dressings, and other hair grooming aids) and 1.5% (Ammonium Hydroxide - in face and neck products [not spray]).

Cosmetic products containing Ammonia or Ammonium Hydroxide may be applied to the skin and hair or, incidentally, may come in contact with the eyes (at maximum use concentrations up to 0.58% [Ammonium Hydroxide] in eye area) and mucous membranes (Ammonium Hydroxide, in bath soaps and detergents). Products containing Ammonia or Ammonium Hydroxide may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Ammonia is on the European Union's list of substances that cosmetics must not contain, except when subject to the following restriction: maximum concentration in ready for use preparation (6% [as NH_3]).[16] Furthermore, the following phrase appears in the "wording of conditions of use and warnings" category: Above 2%: contains Ammonia. Ammonium Hydroxide does not appear on the European Union's list of substances that cosmetics must not contain.

Noncosmetic

Ammonia is a common industrial, and naturally formed, chemical with diverse uses, such as fertilizer and as a refrigerant.[17] It is also used in production of dyes, plastics, synthetic fibers, pesticides, and the purification of water, explosives, refrigerants, and pharmaceuticals.[6]

Ammonium Hydroxide is affirmed as generally recognized as safe (GRAS) as a direct human food ingredient.[11] This designation also means that Ammonium Hydroxide meets the specifications of the *Food Chemicals Codex* (see Impurities section).[12] Anhydrous Ammonia is used or intended for use as a source of nonprotein nitrogen in cattle feed.[18]

In Australia, Ammonia and Ammonium Hydroxide are listed in the *Poisons Standard*, the standard for the uniform scheduling of medicines and poisons (SUSMP) in schedules 5 and 6.[19] Under schedule 5, Ammonia and Ammonium Hydroxide are permitted in preparations containing $\leq$ 5% Ammonia, with the following exceptions: in preparations for human internal therapeutic use; in preparations for inhalation when absorbed in an inert solid material; or in preparations containing $\leq$ 0.5% free Ammonia. Schedule 5 chemicals are defined as substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label; schedule 5 chemicals are labeled with "Caution".

Ammonia, as an intravenously-injected prescription drug, is included on the list of FDA-approved drug products.[20] Ammonia solution has been classified as an over-the-counter (OTC) drug active ingredient as a skin protectant and external analgesic, and the same is true for Ammonium Hydroxide as a skin protectant. However, FDA has determined that there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses.[21]

TOXICOKINETIC STUDIES

Because of the equilibrium nature of these two ingredients, the studies that follow will simply recite "Ammonia" for most cases, regardless of whether Ammonia or Ammonium Hydroxide was reported.

Absorption, Distribution, Metabolism, and Excretion

Ammonia is the principle byproduct of amino acid metabolism, and the liver is the central organ of Ammonia metabolism.[8] It is generated from the breakdown of nitrogenous substances in the gut and from the use of glutamine as a metabolic fuel in the small intestine, and is taken up by the liver where it is detoxified by conversion to urea and, to a lesser extent, glutamine.[22,23] The main source of Ammonia generation occurs in the intestines, from lysis of blood-borne urea and also from protein digestion/deamination by urease-positive bacteria and microbial deaminase.[24,25] A large amount of metabolically-generated Ammonia is absorbed into the blood and, via the portal vein, is detoxified by the liver.[24,26,27] The normal concentration of Ammonia in the portal blood varies from 300 to 600 µM, but in the blood leaving the liver, the concentration is reduced to 20–60 µM. This indicates that the liver occupies a central position in the regulation of Ammonia levels in the organism.[28,29]

The substrates from which Ammonia may be formed in the gut comprise derivatives of ingested nitrogenous material, epithelial and bacterial debris, and compounds secreted from the circulation to the mucosal cells and lumen (e.g., certain peptides, amino acids, and smaller diffusible substances such as urea).[30] Both the gut and kidneys generate substantial amounts of Ammonia from the deamidation of glutamine.[8] The glutamine-glutamate cycle in the body works in conjunction with the glucose alanine cycle to shuttle Ammonia from peripheral to visceral organs.

Ammonia in aqueous solution (e.g., in the blood) is present as NH_3 and NH_4OH (Ammonia and Ammonium Hydroxide, respectively), with the ratio NH_3/NH_4OH depending on the pH, as defined by the Henderson-Hasselbach equation. However, contrary to expectations of simple solution phase kinetics, under physiological conditions with a blood pH of 7.4, more than 98% is in the form of NH_4OH.[24,31] Renal regulation of acid-base balance involves the formation and excretion of NH_3 to buffer hydrogen ions that are excreted in the urine. Approximately two-thirds of urinary NH_4OH is derived from the amide nitrogen of glutamine, a reaction that is catalyzed by the glutaminase enzyme in renal tubular cells.[8]

The urea cycle, a cycle of biochemical reactions that produces urea from Ammonia, is the major pathway for Ammonia detoxification in terrestrial mammals.[32] In the liver, the urea cycle is essential to the conversion of excess nitrogen from Ammonia and aspartate into urea.[33] When the supply of Ammonia in mammals exceeds the capacity for its detoxification, the excretion of orotic acid in the urine increases.[32] Orotic acid (from the urea cycle) is an intermediate product in the biosynthesis of pyrimidines.

Animal

Inhalation

Brain glutamine levels have been shown to increase in rats that inhaled 25 or 300 ppm Ammonia vapor for 6 hours/day for 5 days, which is likely a result of Ammonia metabolism by the astrocytic glutamate-glutamine cycle .[34,35]

Continuous exposure of rats for 24 h to concentrations up to 32 ppm Ammonia resulted in significant increase in blood Ammonia levels.[36] Exposures to 310 - 1157 ppm led to significantly increased blood concentrations of Ammonia within 8 h of exposure initiation, but blood Ammonia returned to pre-exposure values within 12 hours of continuous exposure and did not change over the remainder of the 24-hour exposure period.

Parenteral

Following the administration of [^{13}N]Ammonia to rats [via either the carotid artery or cerebrospinal fluid], most metabolized label was in glutamine (amide) and little was in glutamate (plus aspartate).[37]

Human

Oral

The first step in the degradation of most amino acids is the removal of an α-amino residue, and an amino residue is transferred to α-ketoglutaric acid to produce glutamate.[38] Glutamate dehydrogenase converts glutamate to α- ketoglutarate and Ammonia. Since Ammonia is highly toxic, it is converted to glutamine and alanine in a number of tissues for transportation to the liver. Ammonia is then converted to urea via the urea cycle in the liver, and urea is excreted in the urine.

TOXICOLOGICAL STUDIES

Because of the equilibrium nature of these two ingredients, the studies that follow will simply recite "Ammonia" for most cases, regardless of whether Ammonia or Ammonium Hydroxide was reported.

Acute Toxicity Studies

Acute toxicity studies (animal studies) are summarized in Table 4 (oral studies) and in Table 5 (inhalation studies). Human inhalation studies relating to Ammonia (ranging from 5 minutes to 6 weeks) are included in the section on Other Clinical Reports (Table 11) later in the report text.

Dermal

Acute dermal toxicity studies on Ammonia were not found in the published literature, nor were these data submitted.

Oral

Either no effects or no serious effects were reported for Ammonia in single oral exposure animal studies. However, when 0.3% Ammonia was administered to rats by gavage (33.3 mg/kg), gastric mucosal lesions were observed within 5 minutes. An acute oral LD_{50} of 350 mg/kg for Ammonia in rats has been reported, and the oral administration of 1 % or 3% (w/w as Ammonium Hydroxide) to rats by gavage has produced severe hemorrhagic lesions.[4,39,40,41,42,43,44,45]

Inhalation

In 10-minute exposure studies involving mice, LC_{50s} of $\leq$ 10,150 ppm have been reported. In mice exposed to Ammonia (100-800 ppm) for 30 minutes, an RD_{50} (exposure concentration that produced a 50% reduction in respiratory rate) of 303 ppm was reported. The following effects were observed in mice that were exposed to Ammonia at a concentration of

21,400 ppm for 30 minutes: eye irritation, dyspnea, histopathological changes in the lungs (alveolar disruption and loss of septal continuity), coma, and death. Within the range of concentrations tested (3440 ppm to 12,940 ppm) in 1-h exposure studies involving mice, the following effects have been observed: hepatic lesions, congestion, and necrosis; eye irritation; dyspnea; pneumonitis and atelectasis; histopathological changes in the lung (alveolar disruption and loss of septal continuity), and, in some cases, coma and death. Additionally, LC_{50} values of 4837 ppm and 4230 ppm for Ammonia have been reported for 1-h exposures to 3600-5720 ppm and 1190-4860 ppm, respectively.[22,46,47,48,49,50,51,52]

The acute inhalation toxicity of Ammonia was also evaluated in studies involving rats. Exposure durations ranged from 10 minutes (14,170-55,289 ppm) to 1-4 h (3,028-5,053 ppm). For the 10-minute exposure, LC_{50} values were ~ 22,885 ppm (males) and ~31,430 ppm (females) (at highest exposure concentration) and ~14,141 ppm (males) and ~19,769 ppm (females) (at lowest exposure concentration). For the 1-h and 4-h exposures, the LC_{50} were ~17,633 ppm and ~7068 ppm, respectively, and corneal opacity and signs of typical upper respiratory tract irritation were observed. Signs of upper respiratory tract irritation were also associated with exposures ranging from 20 to 45 minutes, which included exposure concentrations up to 35,000 ppm. Reduced body weight was reported for rats exposed to Ammonia at a concentration of 500 ppm. No effects were observed in rats exposed to Ammonia at a concentration of 144 ppm for 5, 15, 30, or 60 minutes. Toxic signs observed in studies in which rabbits were exposed for 1 h to Ammonia at concentrations ranging from 9,800 ppm to 12,800 ppm included congestion of respiratory tract tissues, bronchiolar damage, and alveolar effects (congestion, edema, atelectasis, hemorrhage, and emphysema). At lower concentrations, there was a significant decrease in the rate of respiration (50 ppm and 100 ppm, for 2.5-3 h) and increased respiratory tract fluid output (at 3.5 ppm and 8.7 ppm, for 1 h) in rabbits. Congestion of the respiratory tract/lungs was reported in studies in which cats were exposed to Ammonia for 1 h at concentrations ranging from 5,200 ppm to 12,800 ppm and, for 10 minutes, at a concentration of 1,000 ppm. Gross pathological findings after the 10-minute exposure included varying degrees of congestion, hemorrhage, edema, interstitial emphysema, and lung collapse.[22,4,46,53,54,55,56,57,58,59,60,61]

It has been noted that acute exposure data have demonstrated that injury to respiratory tissues is primarily due to Ammonia's alkaline (i.e., caustic) properties, resulting from the formation of hydroxide ion when Ammonia comes in contact with water and is solubilized.[3] Furthermore, Ammonia readily dissolves in the moisture on mucous membranes, forming Ammonium Hydroxide, which causes liquefactive necrosis of the tissues.

Short-Term Toxicity Studies

Short-term toxicity studies involving animals are summarized in Table 6 (oral and inhalation studies). Human inhalation studies relating to Ammonia (ranging from 5 minutes to 6 weeks) are included in the section on Other Clinical Reports (Table 11) later in the report text.

Dermal

Short-term dermal toxicity data on Ammonia were not found in the published literature, nor were these data submitted.

Oral

Ammonia and Diammonium Phosphate (included as a potentially similar ammonium salt)

Mucosal atrophy in the stomach antrum and enlargement of the proliferative zone in the mucosa of the stomach antrum and body were observed in rats that received Ammonia (0.01% in drinking water) for 8 weeks. A no-observed-adverse effect-level (NOAEL) of 250 mg/kg/day for general toxicity and a lowest-observed-adverse effect-level (LOAEL) of 750 mg/kg/day for general toxicity were reported for diammonium phosphate in rats dosed orally for 5 weeks.[4,62]

Inhalation

Rats were exposed repeatedly to Ammonia at concentrations ranging from 150 ppm (for 75 days) to 1306 ppm (for 42 days). The higher concentration was tolerated for 42 days in rats, and increased thickness of the nasal epithelium was observed at 150 ppm. When rats, rabbits, guinea pigs, monkeys, and dogs were exposed to Ammonia at a concentration of ~ 223 ppm or ~ 1105 ppm, the following effects were observed: focal pneumonitis in 1 of 3 monkeys at 223 ppm; nonspecific lung inflammation in guinea pigs and rats, but not other species at 1105 ppm; and mild to moderate dyspnea in rabbits and dogs during week 1 only at 1105 ppm. Upper respiratory effects (e.g., dyspnea and nasal lesions, irritation, and inflammation) were observed over most of the range of concentrations tested (145 ppm to 1306 ppm) in short-term inhalation toxicity studies on Ammonia involving mice, rats, guinea pigs, pigs, rabbits or dogs. At lower Ammonia concentrations, there were

no treatment-related effects in rats (at 50 or 90 ppm) and there was no increase in the incidence of respiratory diseases in pigs exposed to Ammonia (37 ppm or ~ 14.2 ppm, inhalable dust exposure) for 5 weeks. In other studies, nearly 64% lethality was reported for rats exposed to Ammonia (653 ppm) for 25 days (continuous exposure) and 50 of 51 rats exposed to Ammonia (650 ppm) were dead by day 65 of continuous exposure. A low incidence of carcinoma of the nasal mucosa was observed in mice exposed to Ammonia (12% solution) for 8 weeks, and these results are summarized in more detail in the Carcinogenicity section.[3,22,40, 45,53,63,64,90,65,66,67,94,95,96,68,69,70,73]

Risk Assessment

A minimal risk level (MRL) of 1.7 ppm has been derived for "acute-duration" inhalation exposure (14 days or less) to Ammonia. The study involved 16 subjects exposed to Ammonia (50 ppm, 80 ppm, 110 ppm, or 140 ppm). The MRL is based on a LOAEL of 50 ppm for mild irritation to the eyes (6 subjects), nose (20 subjects), and throat (9 subjects) in humans exposed to Ammonia as a gas for 2 hours. The 1.7 ppm MRL was calculated (50 ppm ÷ 30 [uncertainty factor] = 1.7; uncertainty factor = 10 [to protect sensitive individuals] x 3 [for use of a minimal LOAEL] = 30).[72]

It should be noted that The Occupational Safety and Health Administration (OSHA) has established an 8-hour time weighted average exposure limit of 50 ppm (35 mg/m^3) for Ammonia in the workplace.[73] Exposure to Ammonia shall not exceed the 50 ppm limit in any 8-h work shift of a 40-h work week.

Subchronic Toxicity Studies

Dermal

Subchronic dermal toxicity data on Ammonia were not found in the published literature, nor were these data submitted.

Oral

Subchronic oral toxicity data on Ammonia were not found in the published literature, nor were these data submitted.

Inhalation

Subchronic inhalation toxicity studies on Ammonia and Ammonium Hydroxide are summarized in Table 6.

Fatty changes of liver plate cells were seen in rats following continuous exposure to Ammonia (642 ppm) for 90 days. The following results were reported for guinea pigs exposed to ~ 170 ppm Ammonia for 18 weeks: mild congestion of the liver, spleen, and kidneys; degenerative changes in the adrenal glands; hemosiderosis in the spleen; and cloudy swelling in proximal kidney tubules. Damaged tracheal mucosae were observed in rats exposed repeatedly to Ammonia (100 ppm) for 12 weeks. Mild leucocytosis was noted in rats after exposure to 143 ppm, but not 43 ppm, Ammonia repeatedly for 3 months.[46,53, 63,74,75]

A low incidence of mortalities was observed in mice and guinea pigs exposed continuously to 671 ppm Ammonia for 90 days. However, there were no mortalities in rats, guinea pigs, rabbits, monkeys, or dogs exposed continuously to ~57.43 ppm Ammonia for 114 days.[53,63]

Chronic Toxicity Studies

Dermal

Chronic dermal toxicity data on Ammonia were not found in the published literature, nor were these data submitted.

Oral

Enlarged adrenal glands were observed in rabbits that received 124 mg ammonium/kg/day as (w/w/t as Ammonium Hydroxide) by gavage in water for 17 months.[76]

Ammonium Sulfate (included as a potentially similar ammonium salt)

The chronic oral toxicity of ammonium sulfate was evaluated using groups of 10 Fischer 344/DuCrj rats (males and females). Ammonium sulfate was administered in the diet daily at concentrations of 0%, 0.1%, 0.6%, and 3% for 52 weeks. None of the animals died, and there were no macroscopic findings. There was a significant increase in kidney and/or liver weights in males and females of the 3% dietary group, but there were no effects on survival rate, body weights, or hematological, serum biochemical, or histopathological parameters at any concentration. Several non-neoplastic lesions, such as bile duct proliferation in the liver and focal myocarditis in the heart were observed in the control and 3% dietary group, but the difference in results was not statistically significant when the 2 groups were compared.[4] Neoplastic lesions reported in this study are included in Table 8.

Inhalation

Human

Risk Assessment

Chronic occupational exposure (about 14 years) to low levels of airborne Ammonia (12.5 ppm) had no significant effect on pulmonary function or odor sensitivity in a group of workers at a soda ash factory, compared to a control group from the same factory that was not exposed to Ammonia.[77] The ATSDR derived a chronic inhalation minimal risk level (MRL) of 0.1 ppm for Ammonia from this study. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. Derivation of the MRL is described below.

An MRL of 0.1 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to Ammonia. The MRL is based on a NOAEL of 9.2 ppm for sense of smell, prevalence of respiratory symptoms (cough, bronchitis, wheeze, dyspnea, and others), eye and throat irritation, and lung function parameters (forced vital capacity [FVC], forced expiratory volume at end of 1 second of forced expiration [FEV1], FEV1/FVC, forced expiratory flow at 50% of FVC [FEF50], and FEF at 75% of FVC [FEF75]) in humans exposed for an average of 12.2 years in a soda ash plant; no LOAEL was determined.[77] The cohort consisted of 52 workers and 35 controls. The subjects were assessed on two workdays: on the first workday of their workweek and on the last workday of their workweek. Spirometry was performed at the beginning and end of each work shift, so that each worker had four tests done. To determine the exposure levels, exposed and control workers were sampled over one work shift; the average sample collection period was 8.4 hours. All of the participants in the study were males.

Analysis of the results showed no significant differences in the prevalence of reported symptoms, but the exposed workers reported that exposure in the plant aggravated some of their reported symptoms (cough, wheeze, nasal complaints, eye irritation, and throat discomfort). There were no significant differences in baseline lung functions between exposed and control subjects. Analysis of each worker separately showed no significant relationship between the level of Ammonia exposure and changes in lung function. Also, when the workers were divided into groups of individuals that were exposed to low (<6.25 ppm), medium (6.25–12.5 ppm), and high (>12.5 ppm) Ammonia levels, no significant association was found between reporting of symptoms, decline in baseline function, or increasing decline in function over the work shift and exposure to Ammonia. Furthermore, no association was evident between increasing years of exposure and decreasing lung function. However, the power of the indices of both level and length of exposure is low because only eight workers were in areas with relatively high Ammonia exposure. The MRL was calculated by adjusting the mean time-weighted average (TWA) exposure concentration of 9.2 ppm for continuous exposure (8/24 hours x 5/7 days) and dividing by an uncertainty factor of 10 to protect all of the sensitive individuals. A modifying factor of 3 was added for the lack of reproductive and developmental studies.[77]

Based on occupational epidemiology studies, the EPA calculated a chronic inhalation reference concentration (RfC) of 0.5 mg/m^3.[3] The critical effects in these studies were decreased lung function and respiratory symptoms.[78,77,79,80] The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental/reproductive toxicity studies are summarized in Table 7.

Ammonia and Diammonium Phosphate (included as a potentially similar ammonium salt)

A relationship between the duration of exposure and the incidence of exencephaly (concentration-related increase) was observed in an in vitro study in which mouse embryos were cultured with Ammonia (38 to 300 µmol/l) for up to 93 h. In a developmental toxicity study involving pregnant rats exposed to Ammonia in the diet (4293 mg/kg/day; w/w/t as the ammonium ion) from gestation day 1 through day 21 of lactation, body weights of offspring were reduced by 25% (males) and 16% (females). Neither reproductive nor developmental toxicity was reported in a study in which female pigs were exposed (inhalation exposure) to ~7 ppm or ~35 ppm Ammonia from 6 weeks prior to breeding until day 30 of gestation. In a reproductive and developmental toxicity study on diammonium phosphate involving rats, an NOAEL of 1500 mg/kg/day and an LOAEL of >1500 mg/kg/day were reported.[2,4,45,53,81,82,83]

GENOTOXICITY STUDIES

In Vitro

Ammonia was non-genotoxic when tested at concentrations up to 25,000 ppm (with and without metabolic activation) in the following bacterial strains: *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, TA1538, and *Escherichia coli* strain WP2 uvr A.[4,53,45]

Ammonia was non-genotoxic to E. coli strain Sd-4-73 in an in vitro assay without metabolic activation.[45]

In Vivo

Femoral bone marrow cells were examined for polychromatic erythrocytes, and there was no evidence of genotoxicity at the doses administered. Blood samples from 22 workers who had been exposed to Ammonia in a fertilizer factory were compared with samples obtained from 42 unexposed controls. Results (compared to controls) were as follows: increased frequency of chromosomal aberrations, sister chromatid exchanges, and mitotic index, with increasing duration of exposure. However, regarding these results, it has been noted that there are a number of limitations in this study, including gaps in the analysis, small study size, and possible confounding factors such as smoking and exposure to other chemicals.[2,4,19,45,53,84]

Ammonia and Ammonium Chloride (included as a potentially similar ammonium salt)

An increased frequency of micronuclei (compared to controls) was observed in Swiss albino mice that received single intraperitoneal doses of Ammonia (12, 25, or 50 mg/kg). In the micronucleus test, groups of 10 (5 males, 5 females) ddY mice received single intraperitoneal (i.p.) doses of 62.5, 125, 250 and 500 mg/kg ammonium chloride or i.p. doses of 31.3, 62.5, 125, and 250 mg/kg ammonium chloride (4 injections within 24 h).[4]

CARCINOGENICITY STUDIES

Carcinogenicity and tumor promotion studies are summarized in Table 8.

Ammonia and Ammonium Sulfate (included as a potentially similar ammonium salt)

There was no evidence of carcinogenicity in mice dosed orally with Ammonia (dissolved in water; 42 mg /kg/day; w/w/t as the ammonium ion) for 4 weeks. Following the oral dosing of mice (Swiss and C3H) with Ammonia193 mg/kg/day for 2 years, there was no evidence of carcinogenicity and no effect on the spontaneous development of adenocarcinoma of the breast (associated with C3H mouse strain). The life-time oral administration of Ammonia (in drinking water) to Swiss and C3H mice was not associated with any carcinogenic effects. Ammonium sulfate was classified as non-carcinogenic in rats in a study involving dietary concentrations up to 3% daily for 104 weeks. Neoplastic lesions were observed in this study, but were deemed not treatment-related because of the spontaneous occurrence of these lesions in the rat strain (F344/DuCrj) that was tested. Neoplastic lesions were also observed in F344/DuCrj rats after ammonium sulfate was fed in the diet at concentrations up to 3% for 52 weeks.[4,45,53,85,86,87,88,89,90]

Tumor Promotion

A statistically significant increase in the incidence of gastric cancer (70%) was observed in rats dosed orally with the initiator *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) and 0.01% Ammonia, when compared to dosing with MNNG alone.[88] In another study, the size, depth, and metastasis of MNNG-initiated tumors was enhanced in rats dosed orally with Ammonia (~42 mg/kg/day).[89]

OTHER RELEVANT STUDIES

Neurotoxicity

Ammonia is most toxic in the brain, and chronic hyperammonemia may lead to brain damage, especially in children.[8] It has been reported that hyperammonemia is associated with neuronal cell loss and cerebral atrophy that lead to mental retardation and cerebral palsy in pediatric patients.[91] These toxic effects are specific to the developing brain, as neuronal damage is not observed in the brain of adult patients with hyperammonemia due to liver failure.

According to another source, many neurologic disorders are related to congenital or acquired hyperammonemia. Evidence obtained with the use of experimental hyperammonemia models suggests that acute neurotoxic effects of Ammonia are mediated by overactivation of ionotropic glutamate (GLU) receptors, mainly the *N*-methyl-D-aspartate (NMDA) receptors, and, to a lesser degree, the kainic acid [KA]/α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA] receptors.[92] Results from other studies suggest that glutamine is also a mediator of Ammonia neurotoxicity.[93,94]

Toxic levels of Ammonia and alterations in pH, electrolyte disturbances, and membrane potential depolarization are thought to lead to neurological dysfunction, primarily by causing cellular swelling accompanied by brain edema and metabolic dysfunction.[24,95] Studies have suggested that Ammonia is likely to be particularly toxic to astrocytes, as they are the only cells that possess the enzyme glutamine synthetase, responsible for detoxifying Ammonia in the brain through condensation with glutamate.[96,97]

In in vitro studies, it has been demonstrated that acute intoxication with large doses of Ammonia leads to excessive activation of NMDA receptors.[98,99,100,101] Furthermore, excessive activation of NMDA receptors leads to neuronal degeneration and death and is responsible for most of the neuronal damage that is found in brain ischemia.[98]

Cytotoxicity

Lymphocytes separated from peripheral bovine (Holstein-Friesian cows) blood were incubated for 2 h in control medium and test medium with various concentrations of Ammonia (w/v as Ammonium Hydroxide; 0.01 mg/dl, 0.1 mg/dl, 1 mg/dl, and 10 mg/dl).[102] Viability of the lymphocytes, measured by trypan blue exclusion test, was significantly reduced after 2 h of incubation. At a concentration of 0.01 mg/ml, lymphocyte viability was significantly reduced after 24 h and 48 h of incubation. In another experiment, in which lymphocytes were preincubated with Ammonia (w/v as Ammonium Hydroxide; 10 mg/dl) and then washed and resuspended in the fresh medium with Ammonia, the number of viable cells was reduced to 51% ± 8 at 24 h, 40% ± 7 at 48 h, and to 39% ± 6 at 72 h of incubation.

Effect on Mitosis

The ability of Ammonia to affect the mitogenic response of bovine lymphocytes to phytohemagglutinin (PHA) or concanavalin A (Con A) was examined.[102] Lymphocytes from 10 Holstein-Friesian cows were incubated with various concentrations of PHA and Ammonia. Lymphocytes from 6 cows were incubated with Con A and Ammonia. Mitogenic reactivity was measured by the incorporation of methyl-^{3}H-thymidine into the DNA of lymphocytes. Ammonia at concentrations of 0.01 mg/dl (w/V as Ammonium Hydroxide) significantly ($P < 0.01$) suppressed PHA (optimal dose = 0.5 ug/ml) stimulation of lymphocytes from only 1 animal. Other concentrations of Ammonia, at 0.1 mg/dl, 1 mg/dl, and 10 mg/dl (w/V as Ammonium Hydroxide), significantly ($P < 0.01$) reduced the response to PHA of lymphocytes from 5 cows, 9 cows, and from all animals, respectively. These concentrations significantly reduced Con A (optimal dose = 0.5 µg/ml) stimulation of lymphocytes from 1 animal, 5 animals, and all animals, respectively. A significant suppression ($P < 0.01$) of blastogenesis of lymphocytes from 1 cow by 0.01 mg/dl, 6 by 0.1 mg/dl, 14 by 1.0 mg/dl, and from 16 cows by 10.0 mg/dl was observed. The mitogenic response of lymphocytes was reduced when lymphocytes were preincubated with Ammonia for a duration as short as 1 h.

Permeation of Blood Brain Barrier

There is evidence that Ammonia can cross blood-brain barrier (BBB), preferentially by active transport through ion transporters rather than diffusion.[24,103]

Generation of Free Radicals

Elevated concentrations of Ammonia have been shown to generate free radicals in rats and rat cell cultures,[104,105] leading to excessive production of nitric oxide (NO) by stimulating the citrulline-NO cycle.[106]

Immunological Effects

Guinea pigs exposed to 90 ppm Ammonia for 3 weeks developed a significant decrease in the cell-mediated immune response to challenge with a derivative of tuberculin.[107] Furthermore, the response of blood and bronchial lymphocytes to mitogens (phytohemagglutinin, concanavalin A, purified protein derivative of tuberculin) was markedly reduced.

A delayed-type hypersensitivity test was used to evaluate cell-mediated immunity in groups of 8 Hartley guinea pigs.[107] The animals were vaccinated with *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) and exposed to Ammonia (< 15 ppm, 50 ppm, or 90 ppm) for 3 weeks. Exposure to Ammonia was followed by intradermal challenge with a purified protein derivative. Dermal lesion size was reduced in animals that were exposed to Ammonia at a concentration of 90 ppm (Mean diameter of dermal lesion = 8.7 mm, statistically significantly different from control [$p < 0.05$]). Results were not statistically significant in the 2 other exposure groups. Also, blood and bronchial lymphocytes were harvested from guinea pigs exposed to Ammonia, and the cells were then stimulated with the mitogens phytohemagglutinin or concanavalin A. Reduced T cell proliferation was observed. However, bactericidal activity in alveolar macrophages isolated from Ammonia-exposed guinea pigs was not affected. In an *in vitro* experiment in which lymphocytes and macrophages were isolated from unexposed guinea pigs and then treated with Ammonia, reduced proliferation and bactericidal capacity were observed only at concentrations that reduced viability. These results were indicative of nonspecific effects of Ammonia-induced immunosuppression. The authors noted that the data in this study indicate that T cells may be the target of Ammonia exposure, in that specific macrophage effects were not observed.

Neurological Effects

Acute exposure to low levels of Ammonia (100 ppm) has been shown to depress free-access wheel running behavior in rodents.[108]

No overt symptoms of neurological disorders were reported in guinea pigs or monkeys that were exposed to up to 1,105 ppm Ammonia for 6 weeks (Coon et al. 1970).[63]

DERMAL IRRITATION AND SENSITZATION STUDIES

Dermal irritation studies are summarized in Table 9.

Irritation

An undiluted Ammonia solution (as 30% Ammonium Hydroxide) was classified as a corrosive material after topical application to the stratum corneum surface in reconstructed human skin cultures in vitro. At histologic examination of the cultures, epidermal necrosis was observed. The minimum concentration of Ammonia that caused an inflammatory reaction when applied (single application) to the skin of rats and mice (6 per species) was > 25% (rats) and 25% (mice). In a skin irritation study in which groups of 4 rats, guinea pigs, and mice were injected intradermally with Ammonia (0.01 ml), the minimum concentration that caused a positive reaction was 0.05% in rats, mice, and guinea pigs.[109] Ammonia (20% as Ammonium Hydroxide) was corrosive to the skin of rabbits. In another study involving rabbits, 12% aqueous Ammonia was corrosive to the skin, whereas 10% was not. In clinical testing, the application of a saturated aqueous solution of Ammonia to the skin of 16 subjects resulted in blister formation and skin irritation. In a study involving 110 subjects, Ammonia (1:1 aqueous solution) was applied to the skin and minimal blistering time (MBT) served as an indicator of cutaneous irritability. The inflammatory reaction observed was considered slight, and MBT ranged from 3 to 57 minutes. Results from another study in which 50% Ammonia solution was applied to the skin indicated that the time required to produce a full blister was greatly prolonged in the aged, when compared to young adults.[4,19,45,110,109,111,112,113]

Sensitization

Skin sensitization data on Ammonia were not found in the published literature, nor were these data submitted.

OCULAR IRRITATION STUDIES

Ocular irritation studies are summarized in Table 10.

Ammonia (w as Ammonium Hydroxide) at 1 mg was classified as an ocular irritant in rabbits. At a concentration of 28.5%, Ammonia induced corneal opacity in rabbits. In a study involving groups of 6 rabbits, Ammonia caused conjunctivitis at concentrations of 1% to 10%, but not 0.3%; the 10% concentration also caused corneal opacities within 1 h of instillation. Conjunctivitis and corneal damage were also observed in a study involving 3 rabbits, whereby 3% Ammonia, 100 µl was instilled into the eyes. Ammonia was classified as a severe ocular irritant in the in vitro ^{51}Cr-release assay involving human corneal endothelial cell cultures.[114]

In a study involving rats, there was no evidence of ocular irritation following exposure to Ammonia at vapor concentrations ranging from 15 to 1157 ppm. It has been reported that Ammonia can penetrate the eye rapidly and that ocular irritation or damage can occur at concentrations as low as 20 ppm.[2,17,22,36, 45,114,115,116,117]

MUCOUS MEMBRANE IRRITATION STUDIES

The stomachs of male Sprague-Dawley rats were exposed (mounted in ex vivo gastric chamber) to 2 ml of Ammonia (15-60 mmol/l, in saline) for 15 minutes (for microscopic study) or for 60 minutes (for macroscopic study), and exposure was followed by examination for mucosal lesions. Microscopic damage to the gastric mucosa was observed.[118]

CLINICAL STUDIES

Case Reports

A 68-yr-old male patient, employed for 18 years, was exposed frequently to anhydrous Ammonia leaks from a microfilm processor camera while on the job. He was diagnosed with interstitial lung disease and severe restrictive lung disease due to Ammonia inhalation. Marked diffuse interstitial fibrosis throughout the lung was observed.[119]

The excessive formation of Ammonia within the brains of Alzheimer's disease patients and its release into the periphery has been demonstrated.[120,121] Furthermore, a higher expression of AMP-deaminase in the brains of Alzheimer's disease patients has been observed, and this finding indicates the existence of a pathologically elevated source of Ammonia within the brain of Alzheimer's disease patients.[120,122]

A male custodian had used Ammonia (28% Ammonium Hydroxide solution) to clean office floors daily for 19 years.[123] He experienced regular episodes of upper airway irritation, coughing, and eye irritation when mixing the chemical in water. An evaluation of the patient revealed a negative rheumatoid factor and positive antinuclear antibody at a 1:320 dilution. The gallium lung scan was normal, but pulmonary function testing indicated a moderate restrictive defect and a formal exercise study indicated ventilator restriction upon attainment of maximum oxygen consumption. The results of a transbronchial lung biopsy with fiberoptic bronchoscopy revealed interstitial fibrosis with chronic inflammation. Granulomata were not present and cultures for tuberculosis and fungal infection were negative. A decrease in the diameter of the hypopharynx, secondary to hypertrophy of the soft tissues in the hypopharynx, was also observed. The opacification of the optic lens capsule, bronchiectasis, and fibrous obliteration of the small airways observed were described as chronic lesions that follow acute exposure to Ammonia.

Other Clinical Reports

Clinical reports relating to inhalation exposure are summarized in Table 11.

In various clinical reports, individuals were exposed to Ammonia at concentrations ranging from 25 ppm to 700 ppm. The periods of exposure ranged from 5 minutes to 6 weeks (5 days per week [2-6 h/day]). Nose, throat, and eye irritation were observed.[46,72,124,125,126,127,128]

EPIDEMIOLOGICAL STUDIES

Non-Cancer Endpoints

A retrospective study was performed to assess the association between petrochemical exposure and spontaneous abortion. Study participants included 2853 non-smoking women who had been pregnant at least once, 96 of whom had been exposed to Ammonia (actual exposure levels unknown). Exposure during the pre-conception period and the first trimester of pregnancy was calculated based on information on perceived Ammonia exposure. Exposure during the first, second, and third trimesters was recorded separately for each pregnancy. Data analyses did not indicate any effect on spontaneous abortion (Odds ratio: 1.2; 95% confidence interval (CI): 0.5-2.60.[4]

SUMMARY

The safety of Ammonia and Ammonium Hydroxide in cosmetics is reviewed in this safety assessment. According to the Dictionary, both ingredients function as pH adjusters in cosmetic products. Additionally, Ammonia functions as an external analgesic and fragrance ingredient and Ammonium Hydroxide functions as a denaturant in cosmetic products. Functioning as an external analgesic is not a cosmetic use and, therefore, the Panel did not evaluate safety in relation to that use in cosmetics. Additionally, the function of fragrance may be excluded from the purview of the Panel, and is not assessed herein.

According to 2017 VCRP data, Ammonia is being used in 599 cosmetic products (mostly rinse-off products) and Ammonium Hydroxide is being used in 1354 cosmetic products (mostly rinse-off products). The results of a concentration of use survey provided by the Council in 2017 indicate that the highest maximum cosmetic use concentration of Ammonia is 4.6 % (in rinse off products [hair dyes and colors]) and the highest maximum cosmetic use concentration of Ammonium Hydroxide is 12.5% (in rinse off products [hair dyes and colors]). Regarding use concentrations in leave-on products, the highest maximum cosmetic use concentrations are 0.73% (Ammonia - in tonics, dressings, and other hair grooming aids) and 1.5% (Ammonium Hydroxide - in face and neck products [not spray]).

These two ingredients are indistinguishable from each other in aqueous formulation. Since the only cosmetic function of Ammonia applicable to this safety assessment is pH adjustor (which by default means aqueous formulations only) and Ammonium Hydroxide does not exist outside of water, regardless of which ingredient is added the final formulations will contain an equilibrium of molecular Ammonia and the ions of Ammonium Hydroxide in water. Thus, whether toxicity data is reported for Ammonia or Ammonium Hydroxide, it is applicable to both (as the test articles would have had this same equilibrium).

An acute oral LD_{50} of 350 mg/kg has been reported in a study involving rats dosed orally with Ammonia dissolved in water. Severe hemorrhagic lesions have been observed in rats dosed orally with 1% or 3% Ammonia (% as Ammonium Hydroxide).

It has been noted that acute exposure data have demonstrated that injury to respiratory tissues is primarily due to Ammonia's alkaline (i.e., caustic) properties from the formation of hydroxide ion when it comes in contact with water and is solubilized. In acute inhalation toxicity studies, Ammonia was tested at concentrations ranging from 3.5 ppm (cats and rabbits, 1-h exposure) to 54,289 ppm (rats, 10-minute exposure). Exposure to the highest concentration resulted in hemorrhagic lungs, and increased respiratory fluid output was noted at the lowest concentration. In 10-minute exposure studies involving mice, LC_{50s} of $\leq$10,150 ppm have been reported. In mice exposed to Ammonia (100-800 ppm) for 30 minutes, an RD_{50} of 303 ppm was reported. Within the range of concentrations tested (3440 ppm to 12,940 ppm) in 1-h exposure studies involving mice, the following effects have been observed: hepatic lesions, congestion, and necrosis; eye irritation; dyspnea; pneumonitis and atelectasis; histopathological changes in the lung (alveolar disruption and loss of septal continuity), and, in some cases, coma and death.

Exposure durations ranged from 10 minutes (14,170-55,289 ppm) to 1-4 h (3,028-5,053 ppm) in acute inhalation toxicity studies involving rats. For the 10-minute exposure, LC_{50} values were ~ 22,885 ppm (males) and ~31,430 ppm (females) (at highest exposure concentration) and ~14,141 ppm (males) and ~19,769 ppm (females) (at lowest exposure concentration). For the 1-h and 4-h exposures, the LC_{50s} were ~17,633 ppm and ~7068 ppm, respectively, and corneal opacity and signs of typical upper respiratory tract irritation were observed.

In short-term oral toxicity studies involving rats, doses of ~ 42 mg/kg/day for 8 weeks resulted in mucosal atrophy in the stomach antrum, and doses up to 1500 mg/kg/day for 35 days resulted in treatment-related changes in body weight, hematological findings, clinical biochemistry findings, and non-neoplastic histopathological findings.

Ammonia was evaluated at concentrations ranging from 0.6 ppm, to 1,306 ppm in short-term inhalation toxicity studies. The results of these studies indicate histopathological changes of respiratory tissues in several animal species (lung inflammation in guinea pigs and rats; focal or interstitial pneumonitis in monkeys, dogs, rabbits, and guinea pigs; pulmonary congestion in mice; thickening of nasal epithelium in rats and pigs; nasal inflammation or lesions in rats and mice) across different dosing regimens. In general, responses in respiratory tissues increased with increasing Ammonia exposure concentration.

Fatty changes of liver plate cells were seen in rats following continuous exposure to Ammonia (642 ppm) for 90 days. Mild congestion/degenerative changes in internal organs were reported for guinea pigs exposed to ~ 170 ppm Ammonia for 18 weeks. Damaged tracheal mucosae were observed in rats exposed repeatedly to Ammonia (100 ppm) for 12 weeks. Mild leucocytosis was noted in rats after exposure to 143 ppm, but not 43 ppm. Ammonia repeatedly for 3 months. A low incidence of mortalities was observed in mice and guinea pigs exposed continuously to 671 ppm Ammonia (reported as Ammonium Hydroxide) for 90 days. However, there were no mortalities in rats, guinea pigs, rabbits, monkeys, or dogs exposed continuously to ~57.43 ppm for 114 days.

Enlarged adrenal glands were observed in rabbits that received 124 mg /kg/day Ammonia (w/w/t as Ammonium Hydroxide) by gavage in water for 17 months.

In a developmental toxicity study involving pregnant rats exposed to Ammonia in the diet (4293 mg/kg/day; w/w/t as the ammonium ion) from gestation day 1 through day 21 of lactation, body weights of male and female offspring were reduced. Neither reproductive nor developmental toxicity were reported in a study in which female pigs were exposed (inhalation exposure) to ~7 ppm or ~35 ppm Ammonia from 6 weeks prior to breeding until day 30 of gestation. In a reproductive and developmental toxicity study on diammonium phosphate involving rats, a NOAEL of 1500 mg/kg/day and an LOAEL of >1500 mg/kg/day were reported.

In the Ames test with and without metabolic activation, Ammonia was non-genotoxic in Salmonella typhimurium strains and in Escherichia coli strain WP2 uvr A. Without metabolic activation, it was nongenotoxic to E. coli strain Sd-4-73. An increased frequency of micronuclei (compared to controls) was observed in Swiss albino mice that received single intraperitoneal doses. Ammonium chloride was non-genotoxic in ddY mice the micronucleus test.

Increased frequencies of chromosomal aberrations, sister chromatid exchanges, and mitotic index, with increasing duration of exposure were reported for workers who had been exposed to Ammonia in a fertilizer factory. However, it was noted that some of the limitations associated with this study include small study size and confounding factors such as smoking and exposure to other chemicals.

Ammonia (whether reported as Ammonia or Ammonium Hydroxide) was not carcinogenic in Swiss and C3H mice dosed orally. A statistically significant increase in the incidence of gastric cancer (70%) was observed in rats dosed orally with MNNG and 0.01% Ammonia, when compared to dosing with MNNG alone. In another study, the size, depth, and metastasis of MNNG-initiated tumors were enhanced in rats dosed orally with Ammonia (~42 mg/kg/day).

It has been reported that hyperammonemia (a metabolic disturbance characterised by an excess of Ammonia in the blood) is associated with neuronal cell loss and cerebral atrophy that lead to mental retardation and cerebral palsy in pediatric patients.

At a concentration of 0.01 mg/ml Ammonia, lymphocyte (from cows) viability was significantly reduced after 24 h and 48 h of incubation. In another study, the mitogenic response of lymphocytes was reduced after preincubation with Ammonia.

Guinea pigs exposed to 90 ppm Ammonia for 3 weeks developed a significant decrease in the cell-mediated immune response to challenge with a derivative of tuberculin.

No overt symptoms of neurological disorders were reported in guinea pigs or monkeys that were exposed to up to 1,105 ppm Ammonia for 6 weeks.

In rabbits, Ammonia (1 mg of Ammonium Hydroxide) was classified as an ocular irritant and 28.5% Ammonia (reported as Ammonium Hydroxide) induced corneal opacity. Additionally, Ammonia caused conjunctivitis in rabbits at concentrations of 1% to 10% (reported as Ammonium Hydroxide), but not 0.3%.

The minimum concentration of Ammonia that caused an inflammatory reaction when applied (single application) to the skin of rats and mice (6 per species) was > 25% (rats) and 25% (mice). In a skin irritation study in which groups of 4

rats, guinea pigs, and mice were injected intradermally with Ammonia (0.01 ml), the minimum concentration that caused a positive reaction was 0.05% in rats, mice, and guinea pigs.[109] Ammonia (reported as Ammonium Hydroxide; 20% and 12%) was corrosive to the skin of rabbits, whereas the 10% concentration was not.

The application of a saturated aqueous solution of Ammonia (reported as Ammonium Hydroxide) to the skin of 16 subjects resulted in blister formation and skin irritation. In a study involving 110 subjects, Ammonia (reported as Ammonium Hydroxide; 1:1 aqueous solution) was applied to the skin and the inflammatory reaction observed was considered slight.

Microscopic damage to the gastric mucosa was observed in the stomachs of male rats exposed (ex vivo) to Ammonia (up to 60 mmol/l of Ammonium Hydroxide) for 15 minutes.

In various clinical reports, ocular, nasal, and throat irritation were observed in human subjects exposed to Ammonia in the 25 ppm to 700 ppm concentration range.

A retrospective study was performed to assess the association between petrochemical exposure and spontaneous abortion. Study participants included 2853 non-smoking women who had been pregnant at least once, 96 of whom had been exposed to unknown Ammonia concentrations. Data analyses did not indicate any effect on spontaneous abortion.

Request for Additional Data

- Dermal absorption data
- Sensitization data

Table 1. Definition, Idealized Structures, and Functions of the Ingredients in this Safety Assessment. [1; CIR Staff]

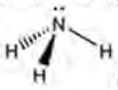
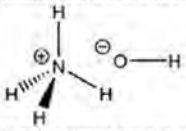
Ingredient CAS No.	Definition & Idealized Structures	Function
Ammonia	Ammonia is an inorganic gas that conforms to the formula:  (See also Ammonium Hydroxide)	External Analgesics; Fragrance Ingredients; pH Adjusters
Ammonium Hydroxide	Ammonium Hydroxide is an inorganic base that conforms to the formula:  [In reality however, the solid, anhydrous salt does not exist. Instead, Ammonium Hydroxide is only present as an aqueous ion pair, the result of hydrolysis (not dissociation of a solid salt), in equilibrium with dissolved ammonia]	Denaturants; pH Adjusters

Table 2. Physical and Chemical Properties of Ammonia and Ammonium Hydroxide

Property	Value	Reference
Ammonia		2
physical form and/or color	Gas at room temperature; colorless	2
molecular weight (Daltons (Da))	17.03	2
water solubility (% w/w at 20°C)	33.1	2
Other solubility (%w/w at 25°C)	10 (absolute ethanol); 16 (methanol); soluble in chloroform and ether	2
density (g/L)	0.7710 (gas);	2
density (g/L at -33.5°C and 1 atm)	0.6818 liquid); 0.7 (liquid)	2,9
vapor density (air = 1)	0.5967	2
specific gravity (g/L at 25°C)	0.747	2
melting point (°C)	-77.7	2,9
boiling point (°C)	-33.35	2,9
autoignition temperature (°C)	650	2
vapor pressure (atm at 20°C)	8.5	2
log K_{ow} (estimated)	0.23	2
Ammonium Hydroxide		
density (g/L at 20°C)	0.89801(28% aqueous)	2
Formula weight (Da)	35.05	9
log K_{ow} (estimated)	-4.37	10

Table 3. Frequency and Concentration of Use According to Duration and Type of Exposure.[14,15]

	Ammonia		Ammonium Hydroxide		
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	
Totals/Conc. Range	599	0.00002-4.6	1354	0.00028-12.5	
Duration of Use					
Leave-On	7	0.00002-0.73	163	0.003-1.5	
Rinse off	592	0.00015-4.6	1191	0.00028-12.5	
Diluted for (bath) Use	NR	NR	NR	NR	
Exposure Type					
Eye Area	1	NR	42	0.022-0.58	
Incidental Ingestion	NR	NR	NR	NR	
Incidental Inhalation- Sprays	3***	0.73*	6*	0.29-1.3*	
Incidental Inhalation- Powders	3***	0.00002-0.14**	NR	0.45-1.5**	
Dermal Contact	6	0.00002-0.14	159	0.0012-1.7	
Deodorant (underarm)	NR	NR	NR	NR	
Hair - Non-Coloring	10	0.00006-1.4	72	0.00028-3.6	
Hair-Coloring	582	2.8-4.6	1104	2.5-12.5	
Nail	1	0.00008-0.00075	3	0.003-1.2	
Mucous Membrane	NR	NR	1	NR	
Baby Products	NR	NR	NR	NR	

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for Bath Product Uses.

*It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.

**It is possible that these products may be powders, but it is not specified whether the reported uses are powders.

***Not specified whether a powder or spray, so this information is captured for both categories of incidental inhalation.

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 4. Acute Oral Toxicity Studies

Ingredient	Animals	Protocol	Results
Ammonia (0.3%)	Rats	Administered by gavage (dose = 33.3 mg/kg)	Gastric mucosal lesions produced within 5 minutes.[42]
Ammonia (dissolved in water)	Male Wistar rats (groups of 10)	Administered by gavage according to Organization for Economic Co-operation and Development (OECD) Guideline 401. Dosing followed by 14-day observation period	LD_{50} (calculated) = 350 mg/kg.[4,43,45]
Ammonium Hydroxide (1% or 3%)	Rats	Administered by gavage	Severe hemorrhagic lesions produced.[44]

Table 5. Acute Inhalation Toxicity

Ingredient	Animals/Protocol	Results
Ammonia (21,400 ppm)	Mice. 30-minute exposure	Signs and symptoms included eye irritation (blinking and scratching), dyspnea, frothing, convulsions, excitation/escape behavior, coma, and death. Histopathology of the lungs of mice that died showed alveolar disruption and loss of septal continuity.[22,47]
Ammonia (8,770-12,940 ppm)	Mice (groups of 20). 10-minute exposure	LC_{50} =10,150 ppm.[46,48,53]
Ammonia (8,723-12,870 ppm)	Mice. 10-minute exposure	At 8,723 ppm, 25% of the animals died. At 12,870 ppm, and 80% of the animals died. LC_{50} = 10,096 ppm.[22,48]
Ammonia (3,600-5,720 ppm)	Mice. 1-h exposure	Nasal and eye irritation, followed by labored breathing, in all groups. Gross examination of surviving mice showed mild congestion of the liver at the intermediate (4550 ppm) and high (5720 ppm) concentrations. LC_{50} = 4837 ppm (95% CI = 4409–5305 ppm).[22,46,53]
Ammonia (1,190-4,860 ppm)	ICR male mice (groups of 12). 1-h exposure	In animals that survived 14-day observation period, pathologic lesions included mild-to-moderate pneumonitis (dose-related severity), focal atelectasis in the lungs (4,860 ppm), and degenerative hepatic lesions (dose-related severity, 3,440–4,860 ppm). LC_{50} = 4,230 ppm.[46,53]
Ammonia (4,840 ppm)	Mice. 1-h exposure	Signs and symptoms included eye irritation (blinking and scratching), dyspnea, frothing, convulsions, excitation/escape behavior, coma, and death. Histopathology of the lungs of mice that died showed alveolar disruption and loss of septal continuity.[22,53]
Ammonia (3,440 ppm)	Mice. 1-h exposure	Liver necrosis.[49]
Ammonia (92 mg/m^3 [~132 ppm] to 1243 mg/m^3 [~1785 ppm])	SPF mice of the OF1-ICO strain. Nose-only exposure for 45 minutes	Mice appeared more susceptible to ammonia in presence of dry air (RD_{50} (exposure concentration producing a 50% decrease in respiratory rate) = 582 [407 ppm] and 732 mg/m^3 [547 ppm] in dry and wet air, respectively).[22,58]
Ammonia (100-800 ppm)	Male Swiss-Webster mice. 30-minute exposure	RD_{50} = 303 ppm (95% confidence limits = 188–490 ppm).[22,52,53]
Ammonia (9,870 mg/m^3 [14,170 ppm] to 37,820 mg/m^3 [54,289 ppm])	SPF-bred Wistar rats (5 males, 5 females/group). 10-minute exposure to 54, 289 ppm and 60-minute exposure to 14,170 ppm	LC_{50} (higher concentration) = 15,940 mg/m^3 (~22,885 ppm) (males) and 31,430 mg/m^3 (~45,124 ppm) (females). LC_{50} (lower concentration) = 9,850 mg/m^3 (~14,141 ppm) (males) and 13,770 mg/m^3 (~19,769 ppm) (females). Hemorrhagic lungs in animals that died.[4,54]
Ammonia (9,000-35,000 ppm)	Male Sprague-Dawley rats: 4 groups of 6 (9,000 to 26,000 ppm), 1 group of 8 (30,000 ppm), and 1 group of 4 (35,000 ppm). Exposure for 20 minutes in head-out exposure system	Lung edema increased in all groups. Dose-dependent increases in ocular irritation, lacrimation, and labored breathing. LC_{50} (determined by probit analysis) = 23,672 ppm.[55]

Table 5. Acute Inhalation Toxicity

Ingredient	Animals/Protocol	Results
Ammonia (9,000 to 23,000 ppm)	Groups of 6 male Sprague-Dawley rats. Exposure for 20 minutes in head-only exposure system for 20 minutes	Peak inspiratory and expiratory flow decreased after exposure to 20,000 and 23,000 ppm. Weight loss, and increased total blood cell counts (white blood cells, neutrophils, and platelets) after exposure to 20,000 ppm. Morphological changes at histopathologic examination of lungs and trachea: alveolar, bronchial, and tracheal edema; epithelial necrosis, and exudate at 20,000 ppm.[56]
Ammonia (3028-14,044 ppm)	Male and female SPF-bred Wistar rats (Hsd Cpb:WU strain; 5 males, 5 females). Nose-only exposure to 9,222-14,044 ppm for 1 h and 3,028-5,053 ppm for 4 h	Signs typical of upper respiratory tract irritation. No gross abnormalities in any organ or nasal passages were found at necropsy of surviving rats (2 weeks post-exposure). Rats that died had corneal opacity, collapsed lungs, nasal discharge, reddened larynx, and tracheal epithelial desquamation. LC_{50} (1-h exposure) = = 12,303 mg/m^3 [~17,633 ppm]). LC_{50} (4-h exposure = 4,923 mg/m^3 [~7068 ppm]).[57] -
Ammonia (6210-9840 ppm)	Groups of 10 male CFE rats. 1-h exposure	Signs of eye and nasal irritation observed immediately, followed by labored breathing and gasping. Surviving animals exposed to the low concentration weighed less than controls on day 14, and gross examination showed mottling of the liver and fatty changes at the two highest concentrations. LC_{50} = 7338 ppm (95% CI = 6822–7893 ppm).[22,50-53]
Ammonia (431, 1436, and 4307 ppm)	Rats. Inhalation exposure	Decrease in static muscular tension and other sublethal effects.[53]
Ammonia (1436, 4307, and 6814 ppm)	White rats. Inhalation exposure	Dyspnea, irritation of respiratory tract and eyes, cyanosis of extremities, and increased excitability.[53]
Ammonia (92 mg/m^3 [~132 ppm] to 1243 mg/m^3 [~1785 ppm])	Groups of 4 male specific pathogen free (SPF) Wistar rats of the Hsd Cpb:WU (SPF) strain. Nose-only exposure for 45 minutes	RD_{50} = 972 and 905 mg/m^3 (corresponding to ~1396 and ~1299 ppm, respectively) in rats in dry and wet air, respectively.[22,58]
Ammonia (500 ppm)	Rats. Inhalation exposure	Reduced body weight.[59]
Ammonia (144 ppm)	Rats. Inhalation exposure for 5, 10, 15, 30, or 60 minutes	No effects.[53]
Ammonia (5,200-12,800 ppm)	Rabbits. 1-h exposure	Average survival: 18 h (gassed after cannulation), 33 h (gassed before cannulation). 2- to 3-fold increase in production of respiratory tract fluid. No change in water content of lungs. Increased blood hemoglobin. Increased plasma lipids.[22]
Ammonia (10,360 ppm, average)	Rabbits. 1-h exposure	Congestion of respiratory tract tissues.[22]
Ammonia (50 ppm and 100 ppm)	16 New Zealand White rabbits. Inhalation Exposure for 2.5 h to 3 h	Significant decrease in rate of respiration.[53]
Ammonia (3.5 ppm and 8.7 ppm)	54 rabbits. Exposure for 1 h	Increased respiratory tract fluid output by 2- to 3-fold. No appreciable effect on water content of respiratory tract tissues. Transient decrease in blood hemoglobin. Lipemia also observed.[53]

Table 5. Acute Inhalation Toxicity

Ingredient	Animals/Protocol	Results
Ammonia (5,200-12,800 ppm)	Cats. 1-h exposure	Average survival: 18 h (gassed after cannulation), 33 h (gassed before cannulation). 2- to 3-fold increase in production of respiratory tract fluid. No change in water content of lungs. Increased blood hemoglobin. Increased plasma lipids.[46,61]
Ammonia (10,360 ppm, average)	Cats. 1-h exposure	Congestion of respiratory tract tissues.[46,60] –
Ammonia (1,000 ppm)	20 cats. 10-minute exposure	Biphasic course of respiratory pathology Effects at 24 h post-exposure included severe dyspnea, anorexia, and dehydration; rhonchi and coarse rales evident upon auscultation. Gross pathology revealed varying degrees of congestion, hemorrhage, edema, interstitial emphysema, and collapse of the lungs at all time points. Pulmonary resistance increased throughout the study.[53,61]
Ammonia (3.5 ppm and 8.7 ppm)	18 cats. Exposure for 1 h	Increased respiratory tract fluid output by 2- to 3-fold. No appreciable effect on water content of respiratory tract tissues. Transient decrease in blood hemoglobin.[50]

Table 6. Short-Term and Subchronic Toxicity Studies

Ingredient	Animals	Protocol	Results
Short-term Oral Studies			
Ammonia (0.01% in drinking water)	Rats	~ 42 mg/kg/day for 8 weeks	Mucosal atrophy in stomach antrum and enlargement of proliferative zone in antral and body mucosa. [42]
diammonium phosphate (17.9% NH_4 and 46.86% P_2O_5 equivalent)	Groups of Crj: CD(SD) rats (5 males, 5 female/group)	Administered by gavage daily (doses of 0, 250, 750, and 1500 mg/kg/day, 7 days/week) for 35 days	Clinical signs were not observed, and none of the animals died. However, there were treatment-related changes in body weight, hematological findings, clinical biochemistry findings, and non-neoplastic histopathological findings. Histological examination of stomachs revealed some submucosal inflammation at all doses, but this change was not dose-dependent and was not statistically significant at the low dose. LOAEL for general toxicity = 750 mg/kg/day.[4,53,65]
Short-term Inhalation Studies			
Ammonia (~1,306 ppm)	Rats	5 days/week (8 h/day)	Exposure tolerated for 42 days. [63]
Ammonia (~223 ppm or ~1105 ppm)	Sprague-Dawley and Long-Evans rats (males and females, groups of 15); Male New Zealand albino rabbits (groups of 3); Princeton-derived guinea pigs (males and females, groups of 15); Male squirrel monkeys (Saimiri sciureus, groups of 3); Beagle dogs (groups of 2)	Exposure 5 days per week (8 h/day) for 6 weeks	Lung effects: Gross necropsies normal. Focal pneumonitis in 1 of 3 monkeys at 223 ppm. Nonspecific lung inflammation in guinea pigs and rats, but not in other species at 1105 ppm. Upper respiratory tract effects: mild to moderate dyspnea in rabbits and dogs exposed to 1105 ppm during week 1 only; no indication of irritation after week 1. Nasal turbinates not examined for gross or histopathologic changes[3,45,63]
Ammonia (1,086 ppm)	Rats, squirrel monkeys, and guinea pigs	Inhalation exposure 5 days per week (8 h/day) for 6 weeks	No fatty changes of liver plate cells. No pathological changes in kidney.[63]
Ammonia (653 ppm)	Rats	Continuous inhalation exposure for 25 days	Nearly 64% lethality.[63]
Ammonia (~653 ppm)	Sprague-Dawley or Long-Evans rats (males and females, 15 to 51/group)	Inhalation exposure for 65 days	Lung effects: Focal or diffuse interstitial pneumonitis in all animals. Upper respiratory tract effects: Dyspnea and nasal irritation/discharge.[3,63]
Ammonia (650 ppm; Ct [product of concentration and exposure time (ppm-h)] =1,014,000)	51 rats	Continuously for 65 days	32 of 51 rats dead by day 25 (390,000 ppm-h); 50 of 51 rats dead by day 65 (1,014,000 ppm-h).[46,63]
Ammonia (500 ppm)	27 male rats	Continuous inhalation exposure for up to 8 weeks	After 3 weeks, nasal irritation and inflammation of upper respiratory tract, but no effects observed in bronchioles and alveoli. No lesions observed at 8 weeks.[53,59]

Table 6. Short-Term and Subchronic Toxicity Studies

Ingredient	Animals	Protocol	Results
Ammonia (250 ppm)	F344 rats (6/sex/group)	Exposure in inhalation chamber for 35 days	Increased thickness of nasal epithelium (3 to 4 times) and nasal lesions at 150 ppm.[3,64]
Ammonia (221 ppm; Ct [ppm-h] = 53,040)	Rats, guinea pigs, rabbits, squirrel monkeys, and beagle dogs	5 days per week (8 h per day) for 6 weeks	No effect.[46,63]
Ammonia (10 or 150 ppm)	Sherman rats (5/sex/group)	Inhalation exposure from bedding for 75 days	Increased thickness of nasal epithelium (3 to 4 times) and nasal lesions at 150 ppm.[3,53,64]
Ammonia (50 or 90 ppm)	Male Wistar rats (8-14 per group)	Inhalation exposure continuously for 50 days	None of the animals died and there were no treatment-related effects.[53,70]
Ammonia (12% solution)	50 maleWhite albino mice	Vapor exposure 6 days per week (15 minutes/day) for 4, 5, 6, 7, or 8 weeks	Nasal mucosa adversely affected. Histological changes progressed from weeks 4–8 from crowding of cells forming crypts and irregular arrangements to epithelial hyperplasia, patches of squamous metaplasia, loss of cilia, and dysplasia of the nasal epithelium. One animal that had loss of polarity of the epithelium, hyperchromatism, and mitotic figures with an intact basement membrane also had a carcinoma *in situ* in one nostril. At week 8, one mouse had an invasive adenocarcinoma of the nasal mucosa. Histochemical results were also abnormal.[3,80]
Ammonia (78 ppm, 271 ppm, and 711 ppm)	Groups of 10 male Swiss mice	Exposure for 4, 9,or 14 days (6 h/day)	No clinical signs of toxicity were noted for mice exposed to ammonia. Rhinitis and pathologic lesions with metaplasia and necrosis were seen only in the respiratory epithelium of the nasal cavity of mice inhaling 711 ppm, the severity of the lesions increased with duration of exposure, ranging from moderate on day 4, severe on day 9, to very severe on day 14. No lesions were seen in the controls or in mice inhaling the 78 ppm. No effects were seen at 271 ppm, even after 9 days of exposure.[22,65]
Ammonia (303 ppm)	Groups of 16 to 24 male Swiss Webster mice	Exposure for 5 days (6 h/day)	Histopathological findings, which were confined to the respiratory epithelium of the nasal cavity, included minimal exfoliation, erosion, ulceration, and necrosis; moderate inflammatory changes; and slight squamous metaplasia.[22,66]
Ammonia (20 ppm)	Swiss albino mice (males and females, groups of 4)	Exposure for 7, 14, 21, 28, or 42 days	Lung congestion, edema, and hemorrhage observed after 42 days.[3,67]
Ammonia (170 ppm; Ct [ppm-h] =30,600 to 91,800)	Guinea pigs	5 days per week (6 h per day) for 6 weeks	No histopathologic changes.[46,74]

Table 6. Short-Term and Subchronic Toxicity Studies

Ingredient	Animals	Protocol	Results
Ammonia (50 ppm)	Guinea pigs (males and females, groups of 6)	Exposure for 42 days	Lung congestion, edema, and hemorrhage.[3,67]
Ammonia (20 ppm)	Guinea pigs (males and females, groups of 2)	Exposure for 7, 14, 21, 28, or 42 days	Lung congestion, edema, and hemorrhage after 42 days.[3,67]
Ammonia (100 ppm [average range = 20 to 203 ppm; Ct [ppm-h] =100,800) alone and with corn starch dust	Yorkshire-Landrace pigs (groups of 6)	Continuously for 6 weeks	Tracheal damage (thickened tracheal epithelium [50 to 100% increase] and goblet cells reduced) at end of week 2 in animals exposed to 100 ppm (33,600 ppm-h) without dust. Changes more prominent by week 6. Conjunctival irritation more severe in pigs exposed to ammonia and corn starch dust, persisting for 2 weeks.[3, 44,129]
Ammonia (10 ppm and 50 to 150 ppm; Ct [ppm-h] = 42,000 to 126,000)	Duroc Pigs (groups of 36)	Continuously for 5 weeks	Excessive nasal, lacrimal and mouth secretions at 50, 100, and 150 ppm; more pronounced at 100 and 150 ppm, gradually diminishing over 1-2 weeks. No histopathologic changes in nasal turbinates or lung.[4,6,71]
Ammonia (12, 61, 103, or 145 ppm)	Duroc pigs (males and females, groups of 9)	Exposure for 5 weeks	Excessive nasal, lacrimal, and mouth secretions, and increased frequency of cough at 103 and 145 ppm.[3,71]
Ammonia (5 ppm [range = 0 to 7 ppm] to 100 ppm [range = 90 to 112 ppm])	Belgian Landrace pigs (groups of 7)	Nasal lavage technique. 6-day exposure in chamber	No-observed-effect value for Ammonia-induced somatic growth inhibition < 25 ppm. Nasal irritation down to 25 ppm. Conjunctival irritation observed in 4 pigs exposed to 100 ppm. Lethargy in groups exposed to 25, 50 and 100 ppm for 2 to 3 days after placement in chamber.[68]
Ammonia (0.6, 10, 18.8, or 37 ppm)	Pigs (different breeds, groups of 24)	Inhalable dust exposure for 5 weeks	No increase in incidence of respiratory diseases.[3, 69]
Ammonia (~1.8, ~3.9, ~7.3, or ~14.2 ppm)	Pigs (different breeds, groups of 24)	Inhalable dust exposure for 5 weeks	No increase in incidence of respiratory diseases.[3, 69]
		Subchronic Inhalation Studies	
Ammonia (642 ppm)	Rats	Continuous exposure for 90 days	Fatty changes of liver plate cells.[63]
Ammonia (43 ppm or 143 ppm)	White rats	Inhalation exposure for 3 months (25- or 60-minute exposures every 48 h)	Mild leukocytosis after exposure to 143 ppm. No adverse effects after exposure to 43 ppm.[53]
Ammonia (100 ppm)	Rats	Inhalation exposure 5 days per week (5 h/day) for 12 weeks	Damaged tracheal mucosae.

Table 6. Short-Term and Subchronic Toxicity Studies

Ingredient	Animals	Protocol	Results
Ammonia (~170 ppm)	12 male guinea pigs (additional 6 were controls)	Inhalation exposure 5 days per week (6 h/day) for 18 weeks	No significant findings after 6 and 12 weeks of exposure. Results at 18 weeks were: relatively mild congestion of the liver, spleen, and kidneys; degenerative changes in adrenal glands; hemosiderosis in spleen (indicative of hepatotoxicity); and cloudy swelling in epithelium of proximal kidney tubules, with albumin precipitation in lumen
Ammonium Hydroxide (671 ppm)	515 rats and 15 guinea pigs	Inhalation exposure continuously for 90 days	13 rats and 4 guinea pigs died.[6,43]
Ammonium Hydroxide (~57.43 ppm)	Sprague-Dawley rats (males and females), Long-Evans rats (males and females), Princeton-derived guinea pigs (males and females), male New Zealand albino rabbits, male squirrel monkeys, and purebred male beagle dogs	Inhalation exposure continuously for 114 days	No mortalities or signs of toxicity. Necropsy observations were normal and there were no treatment-related histopathological findings.

Table 7. Developmental and Reproductive Toxicity Studies

Ingredient	Animals/Embryos	Protocol	Results
		In Vitro Study	
Ammonium ion (38 to 300 µmol/l)	Mouse embryos (conceived in vivo)	Embryos cultured in modified mouse mbal fluid medium (mMTF) or mMTF supplemented with 300 µmol/L ammonium ion for 48, 69, or 93 h before being transferred to pseudo-pregnant mouse dams	Examination on gestational day 15 showed apparent relationship between the duration of exposure and the incidence of exencephaly. Increased incidence of exencephaly with increased ammonium concentration (38–300 µmol/L) and decreased percentage of implantation sites with increased ammonium concentration.[82]
		Oral Studies	
ammonium ion	Pregnant rats	Feeding with ammonium ion in the diet (4293 mg ammonium/kg/day) from gestation day 1 through day 21 of lactation	Body weights of offspring reduced by 25% (males) and 16% (females).[2,83]
diammonium phosphate (17.9% NH_4 and 46.86% P_2O_5 equivalent)	Groups of Crj: CD(SD) rats (5 males, 10 females [reproductive subgroup])	Administered by gavage daily (doses of 0, 250, 750, and 1500 mg/kg/day) for, at most, 28 days (males) and 53 days (females).	No treatment-related deaths and no signs of overt clinical toxicity. Body weight gain was reduced during the first week of gestation (82% of control) in females dosed with 1500 mg/kg/day, but returned to control levels for remainder of study. Mating performance and fertility were unaffected by treatment, and parental treatment had no apparent effect on the offspring to day 4 of age. NOAEL for reproductive and developmental toxicity = 1500 mg/kg/day; LOAEL = > 1500 mg/kg/day.[4,45]
diammonium phosphate	Groups of 10 (5 males, 5 females) Crj: CD(SD) rats	Administered by gavage daily for, at most, 28 days (males) and 53 days (females). Doses of 0, 250, 750, and 1500 mg/kg/day.	Mating performance and fertility unaffected by dosing. Also, dosing had no apparent effect on offspring up to 4 days of age. NOAEL (for reproductive and developmental toxicity) = 1500 mg/kg/day; LOAEL = 1500 mg/kg/day.[4,55]
		Inhalation Study	
Ammonia (7 ppm or 35 ppm)	Female pigs	Exposure for 6 weeks (7 ppm or 35 ppm). Exposure to ~7 ppm or ~ 35 ppm from 6 weeks prior to breeding until day 30 of gestation	No statistically significant differences in ovarian or uterine weights after 6 weeks of exposure. After exposure from 6 weeks prior to breeding until day 30 of gestation, no statistically significant differences in age at puberty, number of live fetuses, fetal length, or fetus-to-corpus luteum ratio compared to pigs exposed to only about 7 ppm . No unexposed controls were included in this study.[81]

Table 8. Carcinogenicity and Tumor Promotion Studies

Ingredient	Animals	Protocol	Results
		Oral Studies	
Ammonia (dissolved in water)	Mice	Dose of 42 mg ammonium/kg/day by gavage for 4 weeks.	No evidence of carcinogenic effect.[93]
Ammonium Hydroxide	Swiss and C3H mice	Exposure of mice to 193 mg ammonium/kg/day, as Ammonium Hydroxide (in drinking water), for 2 years	No carcinogenic effects, and did not affect spontaneous development of breast cancer (adenocarcinoma), which is common to C3H female mice.[45, 63, 88]
Ammonium (combined with pyrocarbonate)	16 mice	Gavage	Lung tumors in 9 of 16 mice. It was noted that the Ammonia and pyrocarbonate may have reacted in vivo to form the carcinogen, urethane.[93]
Ammonium ion (and diethyl pyrocarbonate)	Pregnant mice	Exposure (by gavage) during pregnancy and lactation	No lung tumors.[87]
Ammonium Sulfate	Groups of 10 F344/DuCrj rats (male and female)	Dietary concentrations of 0%, 1.5%, 3% daily for 104 weeks	Survival rates of control, 1.5%, and 3% groups were 88%, 78%, and 76%, respectively, for males, and 76%, 80%, and 80%, respectively, for females. Neoplastic lesions (not treatment-related; occur spontaneously in rats of this strain): C-cell adenomas/adenocarcinomas in the thyroids, fibroadenomas/adenomas/adeno-carcinomas in mammary glands, adenomas/adenocarcinomas in pituitary glands, interstitial cell tumors in testes, and endometrial stromal polyps in uteri. The only macroscopic finding at necropsy was massive, nodular or focal lesions suggesting neoplastic change. Ammonium Sulfate classified as non-carcinogenic.[4]
Ammonium Sulfate	Groups of 10 F344/DuCrj rats (male and female)	Dietary concentrations of 0%, 0.1%, 0.6%, and 3% for 52 weeks	Neoplastic lesions reported included malignant pheochromocytoma of the adrenal gland in males of the 3% dietary group, 2 adenomas in the anterior pituitary of females of the 3% dietary group, and uterine endometrial stromal polyp in a female control rat.[4]

Inhalation Study			
Ammonia (12% solution)	10 male mice	Vapor exposure 6 days per week (15 minutes/day) for 4, 5, 6, 7, or 8 weeks	Histological changes progressed from (weeks 4 to 8) from crowding of cells forming crypts and irregular arrangements to epithelial hyperplasia, patches of squamous metaplasia, loss of cilia, and dysplasia of the nasal epithelium. One mouse had a carcinoma *in situ* in 1 nostril. At week 8, 1 mouse with invasive adenocarcinoma of the nasal mucosa. Authors noted that prolonged exposure to Ammonia may interfere with normal protective reflexes of the respiratory nasal mucosa, resulting in the accumulation of particulate matter initiating or promoting a neoplastic process.[90]
Tumor Promotion			
Ammonia (dissolved in water)	Rats	Rats pretreated with the initiator *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG) in drinking water for 4 weeks, prior to receiving 0.01% Ammonia solution in drinking water for 24 weeks	Statistically significantly greater incidence of gastric cancer (70% of rats) and number of rumors per rumor-bearing rat (2.1) than rats that received only MNNG and tap water (31% and 1.3 tumors/rat).[33,88]
Ammonia	Rats	Rats pretreated with MNNG prior to dosing with Ammonia (~ 42 mg/kg/day)	The size, depth, and metastasis of the MNNG-initiated tumors enhanced in rats dosed with Ammonia.[89]

Table 9. Dermal Irritation Studies

Ingredient	Animals/Subjects/Cells	Protocol	Results
Skin Irritation Studies			
In Vitro Studies			
Undiluted Ammonium Hydroxide (30% active material in neat substance)	Reconstructed human skin cultures	Test substance applied topically to stratum corneum surface of cultures. Skin culture damage or cytotoxicity measured as decreased 3-[4,5-dimethylthiazol-2- yl] 2,5-diphenyltetrazolium bromide (MTT) vital dye metabolism. In time-course experiments, the time (in minutes) of test material exposure eliciting a 50% reduction of MTT metabolism (i.e., t50 value) was calculated.	Histologic examination of the cultures indicated gradations of epidermal necrosis quantitated using a specially designed grading scale, which correlated well with the corrosivity of treatment chemicals and cytotoxicity measurements. Ammonium Hydroxide (30% active in neat substance) was classified as corrosive (t50 = 0.90 minutes).[110]
Animal Studies			
Ammonia	Wistar rats (3 males, 3 females) and ddY mice (3 males, 3 females)	Test solutions (1 ml/kg or 1 g/kg) applied once, unoccluded, to shaved skin of the back. Area of application was 3 x 4 cm for rats and 1 x 2 cm for mice. Distilled water control. Test sites observed for inflammatory reactions for 1 week after application.	Minimum concentration of Ammonia that caused a positive reaction was >25% (minimum amount = >250 mg/kg) in rats and 25% (minimum amount = 250 mg/kg) in mice.[109]
Ammonia	Wistar rats (4), Hartley guinea pigs (4), and ddY mice (4)	Injected intradermally with test solutions (0.01 ml) at 4 spots on shaved dorsal skin. Saline served as the control. The test sites were evaluated for skin irritation for up to 1 week after application.	The minimum concentration that resulted in a positive reaction was 0.05% in rats (minimum amount = 25 µg/kg), mice (minimum amount = 250 µg/kg), and guinea pigs (minimum amount = 12.5 µg/kg).[109]
Ammonium Hydroxide (10% and 20%)	Groups of 3 New Zealand Albino rabbits	Each concentration (0.5 ml) applied to the skin (2 replicates at each dose)	Results positive for skin corrosion at 20% concentration. Negative results at 10% concentratyion.[99,45]
Ammonium Hydroxide (10% and 12% aqueous)	Female Albino New Zealand White rabbits	Each solution (0.1 ml) applied, under an occlusive patch ("1 x 1"), to the skin for 4 h. There were 3 rabbits per dose, with 2 replicates per rabbit at each concentration.	The 12% solution was corrosive to the skin, but the 10% solution was not.[4]
Human Studies			
Ammonium Hydroxide (saturated aqueous solution)	16 subjects (10 men, 6 women)	Applied (via a chamber) to middle of ventral aspect of forearm	Formation of a well-defined, sub-epidermal blister (positive reaction) observed within a few minutes of chamber application; skin irritation observed in all subjects.[111]

Table 9. Dermal Irritation Studies

Ingredient	Animals/Subjects/Cells	Protocol	Results
Ammonium Hydroxide (1:1aqueous solution)	110 subjects	Test substance (0.5 ml) placed in 8 mm well drilled in acrylic plastic block (3 x 3 x 1 cm) that was strapped to the skin. Block (used to measure minimal blistering time [MBT, indicator of cutaneous irritability, defined as total exposure in well that results in a single bulla, occupying the total area of contact]).	MBT ranged from 3 to 57 minutes. Inflammatory reaction considered slight; healing was rapid and without scarring. Intensity of the dermatitis provoked by a 24-h exposure to sodium lauryl sulfate was strongly correlated with the MBT.[112]
Ammonium Hydroxide solution (50% solution)	Young adults and older adults	Blistering response measured	Mild discomfort during procedure. The initial response, characterized by the appearance of tiny follicular vesicles, occurred more quickly in older adults. The time required to produce a full blister was greatly prolonged in the aged.[113]

Table 10. Ocular Irritation Studies

Ingredient	Animals/Cells	Test Protocol	Results
In Vitro			
Ammonium Hydroxide	Human corneal endothelial cell cultures	^{51}Cr-release assay. Performed by loading the cells with isotope, incubating the cells with Ammonium Hydroxide, and measuring the isotope that was recovered in the medium.	Severe ocular irritant (ED_{50} = 3.9×10^{-4} M).[114]
Animal			
Ammonia	Not available	Not available	Ammonia can penetrate the eye rapidly. Ocular irritation or damage can occur at concentrations beginning at 20 ppm.[19]
Ammonia (15, 32, 310, or 1157 ppm vapor concentrations)	Rats	Exposure for 24 h	No clinical signs or evidence of irritation to the eyes or mucous membranes.[22,36]
Ammonium Hydroxide	Rabbits	Instillation of test substance (1 mg) followed by ocular rinsing	Ocular irritant.[45]
Ammonium Hydroxide (28.5%)	Rabbits	Brief exposures (2 seconds)	Corneal opacity.[2,115]
Ammonium Hydroxide (0.3%, 1%, 2.5%, and 10%)	New Zealand albino rabbits (groups of 6)	Draize test. Test substance (0.1 ml) instilled into the eye. In 1 group, eyes rinsed after instillation	Conjunctivitis (at 1% to 10%, but not at 0.3%). Ammonium Hydroxide (10%) produced pannus in 5/6 unwashed rabbit eyes and 2.5% produced pannus in 1/6 unwashed and 6/6 washed eyes. Ammonium Hydroxide at 1% produced pannus in 3/6 washed eyes. Keratoconus was produced by 10% Ammonium Hydroxide in 4/6 unwashed eyes and 2/6 washed eyes and 2.5% produced keratoconus in 2/6 unwashed eyes. Ammonium Hydroxide (10%) caused corneal opacities within 1 h of instillation.[116]
Ammonium Hydroxide (prepared with 3% Ammonia)	3 New Zealand White Albino Rabbits	Draize test. Test substance (100 µl) instilled into eye	Conjunctivitis (score = 3 at 96 h; mean maximum Draize score = 3), chemosis (score = 3 at 96 h; mean maximum score = 4), iritis (score = 1; mean maximum Draize score = 2), corneal opacity (score = 4; mean maximum Draize score = 4), and mean surface of corneal damage (70% corneal damage; mean maximum Draize value = 100%). Risk of serious damage to the eyes.[117]

Table 11. Other Clinical Reports

Ingredient	Number of Subjects	Protocol	Results
		Inhalation Exposure	
Ammonia (700 ppm)	Number of subjects not available	Not available	Eye irritation.[124]
Ammonia (500 ppm)	Number of subjects not available	30-minute exposure	Variable lacrimation.[124]
Ammonia (500 ppm)	Number of subjects not available	30-minute exposure	Increased blood pressure and pulse rate.[124]
Ammonia (500 ppm)	Number of subjects not available	30-minute exposure	Nasal and throat irritation, increased minute volume, and cyclic pattern of hyperpnea.[124]
Ammonia (500 ppm)	7 men	30-minute exposure	Increase in ventilation minute volume of 50-250%, accompanied by cyclic increase in respiratory rate. Irritation of the nose and throat. No significant change in nitrogen or urea in blood and urine. No significant change in serum nonprotein nitrogen.[125]
Ammonia (500 ppm)	7 subjects	30-minute exposure via face mask	Ventilation minute volume increased 50 to 250% over pre-exposure values. Respiratory minute volumes fell below pre-exposure levels at termination of exposure.[46,125]
Ammonia (101 to 335 ppm)	Number of subjects not available	20-minute exposure	Decrease in exercise ventilation minute volume at 151-335 ppm, related either to a decrease in respiratory rate (at 151 ppm) or tidal volume (at 205 and 335 ppm), no significant effects at 101 ppm.[46,126]
Ammonia (50 to 140 ppm)	16 subjects	2-h exposure. Testing repeated after a 1-week interval.	110 ppm tolerable for all subjects. 140 ppm intolerable at 1 h (4 subjects) and at 2 h (4 subjects). No significant increase in vital capacity, forced expiratory volume at end of 1 second of forced expiration (FEV_1), or forced inspiratory volume inhaled at end of 1st second of forced inspiration (FIV_1). Lowest-observed-adverse-effect level (LOAEL) of 50 ppm for mild irritation to the eyes (6 subjects), nose (20 subjects), and throat (9 subjects). LOAEL divided by uncertainty factor of 30 (10 to protect sensitive individuals and 3 for the use of a minimal LOAEL)[72]
Ammonia (135 ppm)	6 subjects	5-minute exposure	Chest irritation in 1 of 6 subjects.[124]
Ammonia (135 ppm)	Number of subjects not available	5-minute exposure	Nose and throat irritation.[124]
Ammonia (135 ppm)	Number of subjects not available	5-minute exposure	Eye irritation with lacrimation.[124]

Table 11. Other Clinical Reports

Ingredient	Number of Subjects	Protocol	Results
Ammonia (25, 50, and 100 ppm)	6 subjects	Exposure: 5 days per week (2 to 6 h per day) for 6 weeks	Mild to moderate irritation of the eyes, nose and throat: 16/54 (30%) of observations on 6 subjects in week 2; 12/90 (13%) in week 3; 2/60 (3%) in week 4; 0/78 in week 5; and 5/78 (6%) in week 6. No apparent effects on pulse, respiration rate, blood pressure, FVC, or FEV_1.[127]
Ammonia (25-100 ppm)	Not available	Exposure to varying concentrations for varying periods (2-6 h) 5 days/week for 6 weeks	Decreasing signs of irritation of the mucous membranes of the eyes, nose and throat over the 6-week observation period were reported, and there was no evidence of adverse health effects.[96,127]
Ammonia (72 ppm)	Number of subjects not available	5-minute exposure	Eye irritation with lacrimation.[124]
Ammonia (50 ppm)	Number of subjects not available	5-minute exposure	Eye irritation with lacrimation.[124]
Ammonia (50 ppm)	Number of subjects not available	120-minute exposure	Eye irritation.[124]
Ammonia (50 ppm)	Number of subjects not available	120-minute exposure	Nose and throat irritation. Urge to cough.[124]
Ammonia (30 and 50 ppm)	6 subjects	10-minute exposure	Barely perceptible irritant effects (nose and eye) in 2 of 6 subjects (30 ppm). Faint to moderate irritation (nose and eye) in 5 of 6 subjects (50 ppm).[51]
Ammonia (30 ppm and 50 ppm)	6 subjects	10-minute exposure	Moderate irritation of nose and eyes at 50 ppm (4 of 6 subjects), but not at 30 ppm.[51]
Ammonia (32 ppm)	Number of subjects not available	5-minute exposure	Eye irritation with lacrimation.[124]
Ammonia (> 30 ppm)	Not available	Not available	Immediate irritation of the nose and throat.[51,128,72]
Ammonia	Not available	Not available	Tolerance appears to develop with repeated exposure.[128,72]

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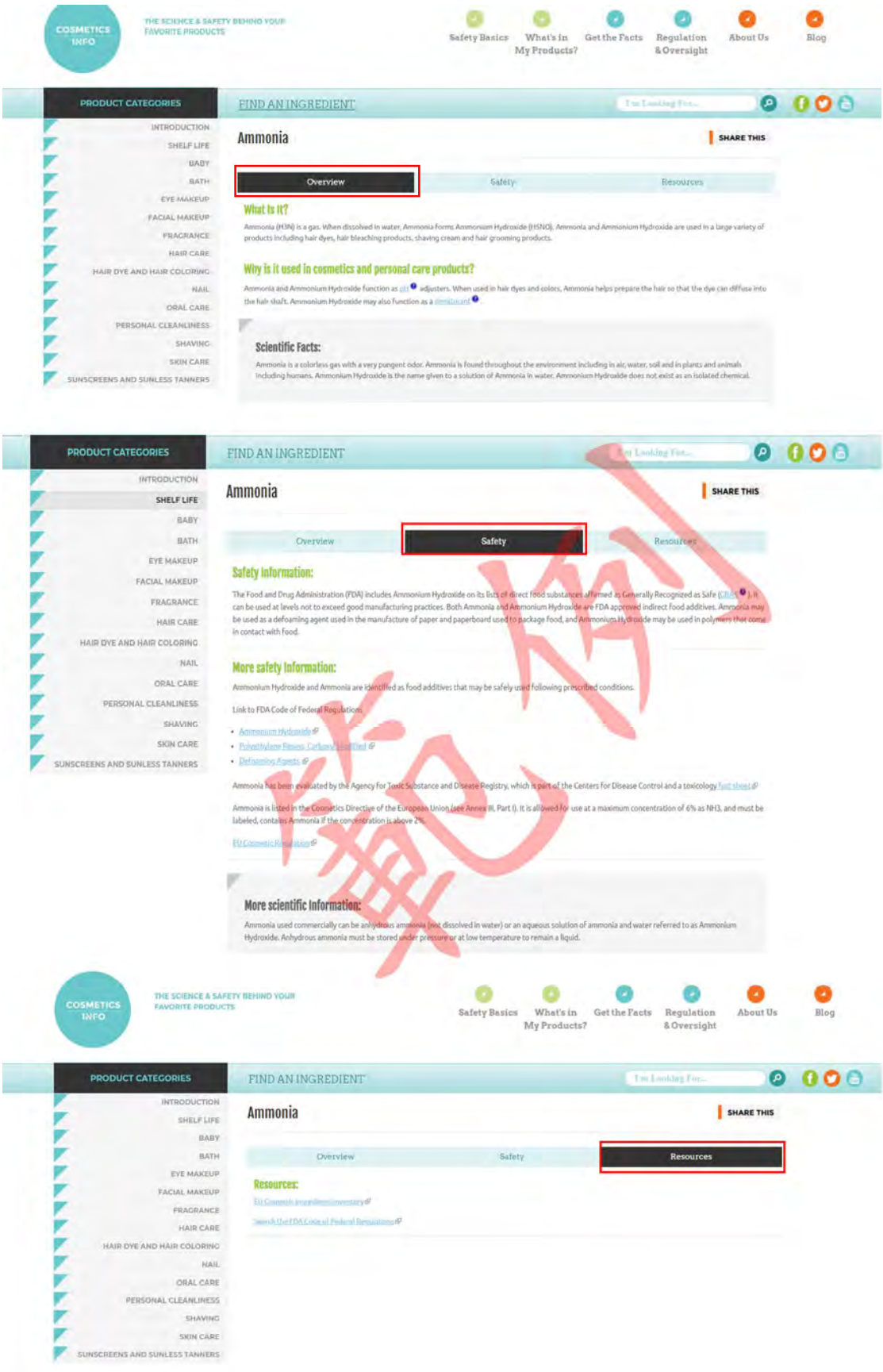


化粧品產品資訊檔案(範例)

<肌膚調理凝膠>

＜PIF <u>無特定之格式</u>，本範例<u>僅提供參考用</u>＞

中華民國 111 年 7 月

目　　錄

頁 次

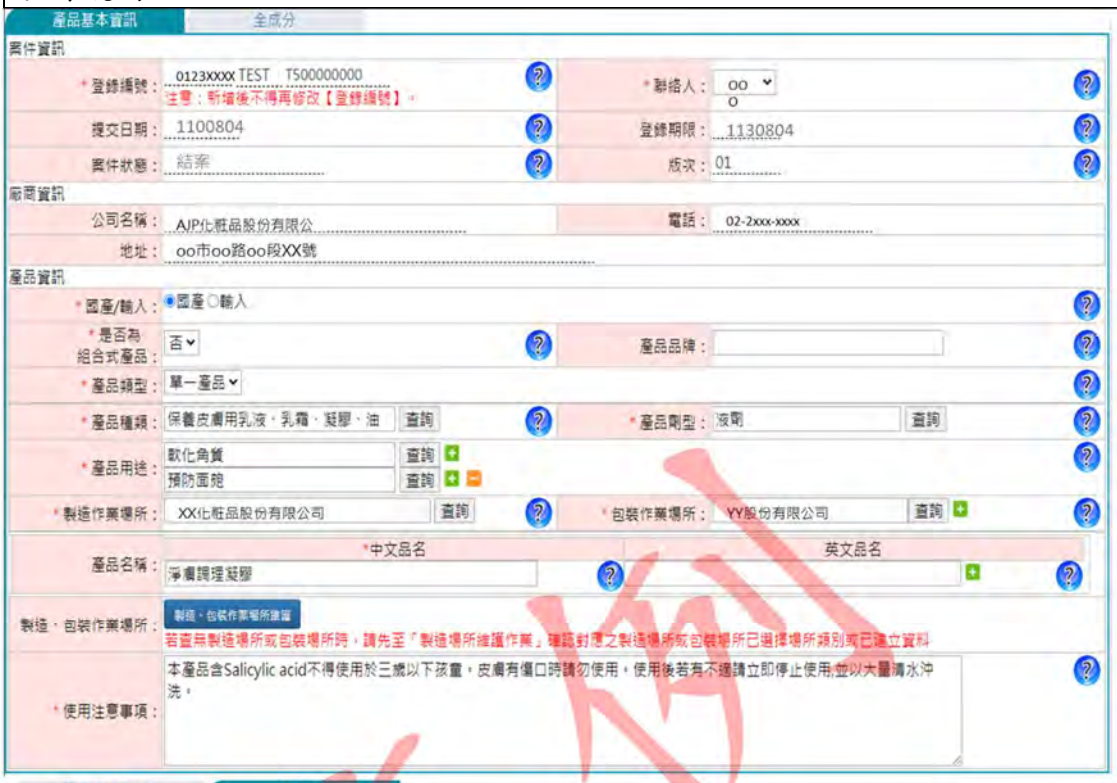
I. 產品敘述

(1) 產品基本資料

項目	內容描述
產品名稱	肌膚調理凝膠
產品類別	化粧水/油/面霜乳液類
產品劑型	液劑
用途	軟化角質、面皰預防。
製造作業場所資訊	製造廠：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	充填廠名稱：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：oo 市 oo 路 oo 段 XX 號 公司負責人：李○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：0123XXXXTESTT500000000


產品基本資訊 全成分

案件資訊

*登錄編號：0123XXXX TEST T500000000 注意：新增後不得再修改【登錄編號】。

*聯絡人：oo o

提交日期：1100804

登錄期限：1130804

案件狀態：結案

版次：01

廠商資訊

公司名稱：AJP化粧品股份有限公

電話：02-2xxx-xxxx

地址：oo市oo路oo段XX號

產品資訊

*國產/輸入：●國產 ○輸入

*是否為組合式產品：否

產品品牌：

*產品類型：單一產品

*產品種類：保養皮膚用乳液、乳霜、凝膠、油 查詢

*產品劑型：液劑 查詢

*產品用途：軟化角質 查詢；預防面皰 查詢

*製造作業場所：XX化粧品股份有限公司 查詢

*包裝作業場所：YY股份有限公司 查詢

產品名稱：*中文品名 淨膚調理凝膠；英文品名

製造、包裝作業場所：製造、包裝作業場所維護

若查無製造場所或包裝場所時，請先至「製造場所維護作業」確認對應之製造場所或包裝場所已選擇場所類別或已建立資料

*使用注意事項：本產品含Salicylic acid不得使用於三歲以下孩童，皮膚有傷口時請勿使用，使用後若有不適請立即停止使用並以大量清水沖洗。


產品基本資訊 全成分

如需多筆案件資料匯入請至[產品基本資訊]頁籤，使用多筆匯入功能。 全成分匯入

一頁40筆, 共11筆 第1到11筆

產品型號：肌膚調理凝膠

成分資訊 *-單位：%(W/W)

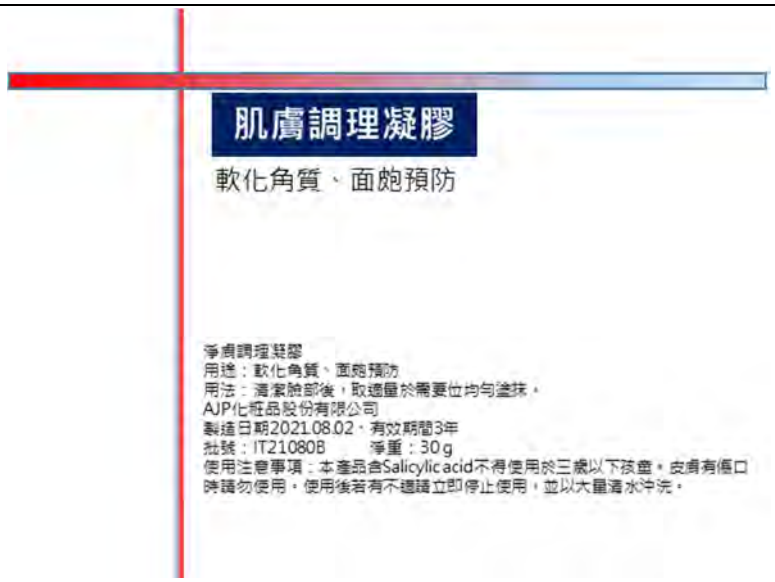
序號	*成分名稱	*含量	限量成分用途 *公告限量成分才需填寫	提醒事項
1	AQUA 查詢	適量		
2	Alcohol 查詢	適量		
3	Propylene Glycol 查詢	適量		
4	Hamamelis Virginiana (Witch Hazel) Leaf Extract 查詢	適量		
5	Glycyrrhiza Uralensis (Licorice) Root Extract 查詢	適量		
6	Sodium Acrylates Copolymer 查詢	適量		
7	Lecithin 查詢	適量		
8	Salicylic acid 查詢	標誌量 1.5000000000000	軟化角質、面皰預防	用途：軟化角質、面皰預防,限
9	Triethanolamine 查詢	適量		
10	METHYLPARABEN 查詢	標誌量 0.4000000000000	防腐劑(以acid計,混合使用)	用途：防腐劑(以acid計,混合使
11	Tocopherol 查詢	適量		

(3) 全成分名稱及其各別含量

INCI Name	Cas No.	w/w%	功能
Aqua	7732-18-5	74.4	溶劑
Alcohol	64-17-5	10.0	溶劑
Propylene Glycol	57-55-6	5.0	助溶劑
Hamamelis Virginiana (Witch Hazel) Leaf Extract	84696-19-5	3.0	皮膚調理劑
Glycyrrhiza Uralensis (Licorice) Root Extract	94349-91-4	2.5	皮膚調理劑
Sodium Acrylates Copolymer (and) Lecithin	-	2.0	增稠劑
Salicylic acid	69-72-7	1.5	軟化角質、面皰預防
Triethanolamine	102-71-6	1.0	pH 調節劑
Methylparaben	99-76-3	0.4	防腐劑
Tocopherol	10191-41-0	0.2	抗氧化劑
Total		100.0	

(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)	
外盒	

標籤/仿單	 肌膚調理凝膠 用途：軟化角質、面皰預防 用法：清潔臉部後，取適量於需要部位均勻塗抹。 全成分：Aqua、Alcohol、Propylene Glycol、Hamamelis Virginiana (Witch Hazel) Leaf Extract、Glycyrrhiza Uralensis (Licorice) Root Extract、Sodium Acrylates Copolymer (and) Lecithin、Salicylic acid(1.5% w/w)、Triethanolamine、Methyl Paraben、Tocopherol。 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/地址/電話： 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：2021.08.02 有效期間：3 年 批號：IT21080B 淨重：30 g 使用注意事項：本產品含 Salicylic acid 不得使用於三歲以下孩童。皮膚有傷口時請勿使用。使用後若有不適請立即停止使用，請以大量清水沖洗，並至皮膚科醫生診斷治療。如曾有對阿斯匹靈過敏的藥物史，則不建議使用本產品。

(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：

製造廠（場所）地址：

核定劑型及作業項目：

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)

符合化粧品優良製造準則聲明書(**範例**)

符合化粧品優良製造準則聲明書

Declaration of Conformity

本業者／本人(製造或輸入)之化粧品符合中華民國之化粧品優良製造準則，產品資料如下：

I hereby declare that the products described below manufactured in conformity with Cosmetic Good Manufacturing Practice

一、製造廠名稱：

Manufacturer's Name

二、製造廠地址：

Manufacturer's Address

三、製造劑型：

Product forms

四、作業項目：

The process of operations

以上聲明書所保證之內容，如有造假不實或違背相關法規等情事，本業者／本人願自行負擔法律上一切責任。

Where violations of this declaration occur, I agree to take the legal responsibilities.

立聲明書人：　(Signature)

Applicant

負責人/代表人：　(Signature)

Person in charge

統一編號或身分證字號：

Company Tax ID No. / ID Number

地址：

Address:

申請廠商蓋公司章

負責人或代表人章

中華民國　年　月　日

Date　year　month　day

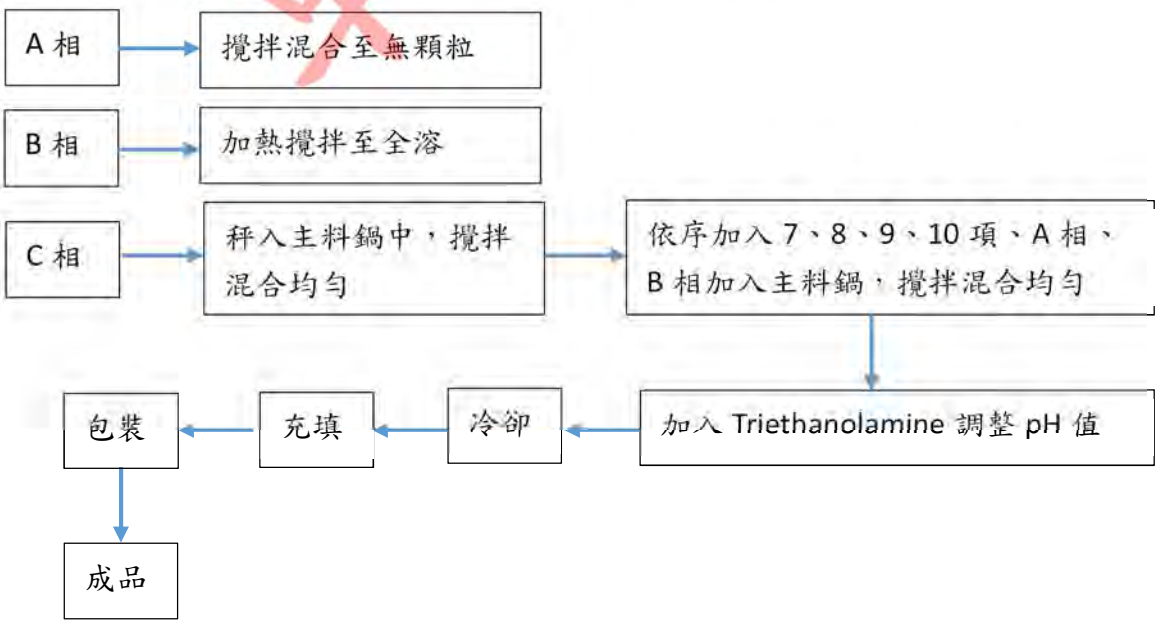
(6) 製造方法、流程

相	項	INCI Name	Cas No.	w/w%
A	1	Alcohol	64-17-5	10.0
	2	Salicylic acid	69-72-7	1.5
B	3	Aqua	7732-18-5	20.0
	4	Methylparaben	99-76-3	0.4
C	5	Aqua	7732-18-5	54.4
	6	Sodium Acrylates Copolymer (and) Lecithin		2.0
	7	Propylene Glycol	57-55-6	5.0
	8	Hamamelis Virginiana (Witch Hazel) Leaf Extract	84696-19-5	3.0
	9	Glycyrrhiza Uralensis (Licorice) Root Extract	94349-91-4	2.5
	10	Tocopherol	10191-41-0	0.2
	11	Triethanolamine	102-71-6	1.0

製程簡述：

1. A 相: 第 1、2 項秤入小杯中，攪拌混合至無顆粒備用。
2. B 相: 預留部分水與第 4 項，加熱攪拌至全溶備用。
3. C 相: 將第 5、6 項秤入主料鍋中，攪拌混合均勻。
4. 依序將 7、8、9、10 項、步驟 1(A 相)及步驟 2(B 相)加入主料鍋，攪拌混合均勻。
5. 緩緩加入第 11 項攪拌均勻，調整至符合規格 pH 值即可。

製程流程圖：



(7) 使用方法、部位、用量、頻率及族群

使用方法、部位及用量：清潔臉部後，取適量針對需要部位均勻塗抹。

請於洗臉、肌膚保養後使用。取適量於指尖後，塗抹於需要之部位。

請避免使用於全臉(可能因肌膚狀態導致出現乾燥問題) 。

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

產品截至 2021 年 10 月有一件不良反應案例，相關資訊如下

產品名稱	肌膚調理凝膠	產品批號	IT2109XXX
通知日期	2021/10/07	通知來源	消費者客訴
不良反應類型	皮膚刺激	發生頻率	單次
不良反應描述	消費者第一次使用本產品，於臉部塗抹本產品後開始有刺激情形，症況持續半小時未趨緩，消費者以清水去除產品後刺激感症狀消除。		
產品使用期間	2021/10/01~ 2021/10/07	有無併用其他產品	無
停用後情形	症狀消除	就醫狀況	未就醫
不良反應結果	非嚴重不良事件		
後續處理			
本公司接獲消費者客訴後已請消費者先暫停使用此產品，並告知消費者如有後續不良反應請至醫療院所進行後續診斷治療。本案處理相關資料經提供安全資料簽署人員審閱，經評估本案應為個案偶發情形，不影響本產品之安全性。請消費者如就醫後有後續醫師診斷證明等資料，亦請提供後再由安全資料簽署人員協助評估產品安全性。			

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

成品 CoA			
檢測項目	規格	實際檢驗結果	檢驗方法
外觀	不流動膠體	不流動膠體	目視
顏色	白色不透明	白色不透明	目視
氣味	無特殊氣味	無特殊氣味	嗅覺
pH	4.5±0.2	4.3	使用已校正之 pH meter 依 pH meter 檢測方法測定
黏度	15,000 ~20,000 mPa·s	19,050 mPa·s	使用已校正之黏度計依黏度計檢測方法測定
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； 綠膿桿菌 陰性； 金黃色葡萄球菌 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 公布建議檢驗方法-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	6.0~8.5	7.48	使用已校正之線上(on line) pH meter 測定
導電度	<20 µS/cm	16.4 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：Alcohol

Product Name	ethanol/ethanol absolute
CAS NO	64-17-5
EINECS No.:	200-578-6
Chemical formula:	C_2H_6O
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, H_2O, 20℃)
Boiling point:	78.4℃
Vapor pressure:	5.8 kpa,20℃
Explosive limit:	3.1-27.7%(V)

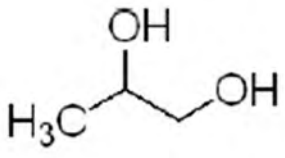
Characteristics	Specifications	Results
Specific Gravity @ 60°F (15.56°C)	NMT 0.7962	0.7959
Proof	NLT 199.0	199.12
Ethyl Alcohol, % volume	NLT 99.5	99.3
Appearance	Bright and clear, free from suspended matter	Pass
Order	Characteristic ethanol	Pass
Water, wt. %	0.7 max	0.6
Color, Pt-Co	0.0	Pass
Chloride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

INCI name：Propylene Glycol

Product Specification

Product Name:
Propylene Glycol – meets USP testing specifications

Product Number:	**P4347**
CAS Number:	57-55-6
Formula:	C3H8O2
Formula Weight:	76.09 g/mol



TEST	Specification
Identity	Pass
Specific Gravity	1.035 - 1.037
Acidity	≤ 0.20 ml
Water (by Karl Fischer)	≤ 0.2 %
Residue on Ignition	≤ 3.5 mg
Chloride Content	≤ 0.007 %
Sulfate	≤ 0.006 %
Heavy Metal	≤ 5 ppm
Residual Solvents Testing	Meets Requirements
Assay	≥ 99.5 %

INCI name：Hamamelis Virginiana (Witch Hazel) Leaf Extract

CERTIFICATE OF ANALYSIS

Product Name	**WITCH HAZEL HYDROSOL**
Botanical Name	Hamamelis virginiana

PROPERTIES	SPECIFICATIONS	RESULTS
Appearance	Clear colorless to slightly cloudy liquid	CONFORMS
Odour	Delicate, fresh, herbaceous, slightly woody aroma	CONFORMS
Specific Gravity (g/mL)	0.980 - 1.020 @ 25°C	CONFORMS
Refractive Index	1.300 - 1.350 @ 20°C	CONFORMS
pH	4.50 - 7.00	CONFORMS
Solubility	Soluble in water and alcohol; Insoluble in fixed oils	CONFORMS

HEAVY METAL TESTS	SPECIFICATIONS	RESULTS
Lead (Pb)	na	NOT DETECTED
Cadmium (Cd)	na	NOT DETECTED
Copper (Cu)	na	NOT DETECTED
Arsenic (As)	na	NOT DETECTED
Mercury (Hg)	na	NOT DETECTED

INCI name：Glycyrrhiza Uralensis (Licorice) Root Extract

COMMON NAME	Licorice Root CO2
LATIN NAME	*Glycyrrhiza uralensis*
COUNTRY OF ORIGIN	China, Manufactured in the EU
CULTIVATION METHOD	Conventional
TYPE	CO2 Total Extract / Carrier Oil
EXTRACTION METHOD	Super Critical Extraction
PLANT PART	Root
USE	Body / Skin Care

	SPECIFICATIONS (Range)	
SPECIFIC GRAVITY @20°C	<1 g/cm^3	*na*
REFRACTIVE INDEX @20°C	*na*	*na*
OPTICAL ROTATION @20°C	*na*	*na*

PHYSICAL APPEARANCE	Viscous/gel-like liquid	*Conforms*
COLOR	Brown to reddish	*Conforms*
ODOR	Light, sweet, woody	*Conforms*
SOLUBILITY	Soluble in fixed oils	
SPECIAL USE INSTRUCTIONS	Dilute before use. May require gentle heating to liquefy.	

PRIMARY CONSTITUENTS	Licoricidin, Licorisoflavan. This product contains 50% MCT Oil (from RSPO certified sustainable palm).

COMPONENTS	RANGE %	%		COMPONENTS	RANGE %	%
LICORICIDIN	*na*	7.3		SUM OF IDENTIFIED ISOFLAVANS	>=8.5	9.3
LICORISOFLAVAN A	*na*	2		CONTENT OF ALCOHOL (ETHANOL)	2-4	2.2
** EU Allergen*						

INCI name：Sodium Acrylates Copolymer (and) Lecithin

NameL	Lecigel™
Segment	Personal care
INCI name	Lecithin Sodium Acrylates Copolymer
IUPAC name	N/A
CAS numbers	N/A
Chemical group	Complex lipids
Chemical properties	N/A
Physical properties	N/A
Appearance Powder Colors	Off-white

CHARACTERISTICS		LECIGEL™
INCI Name		Sodium Acrylates Copolymer (and) Lecithin
Typical texture		Aqueous gels (without oily components), gel-creams, emulsions.
Richness		Silky and light feel
Appearance		Beige powder
Dosage %		01-2%
% of oily phase emulsified		10% of oil per % of Lecigel™, max 20% oil (2% Lecigel™)
pH		Optimum: 5-8, possible: 4-8 if % increased
Viscosity		Achieved at T0
process	Hot process	Yes
	Cold process	Yes
	Introduction via oil phase	Yes
	Introduction in aqueous phase	Yes
	Introduction at the end of process	Yes
	Emulsification step: Aqueous phase introduced into oily phase	Yes
	Emulsification step: Oily phase introduced into aqueous phase	Yes
Compatibilities	Oily phase	Compatible with all kind of oily phase. Affinity with medium polarity emollients.
	Sun protection	Good with chemical sunfilters. Limited compatibility with Titanium Dioxide and Zinc Oxide vs incompatibility with acrylates.
	Pigments	Yes
	Pearls	Yes
	Electrolytes	Low
	Alcohols	Up to 50% (2% Lecigel™)
	Glycerols esters	Yes
	Organic acids	Yes
	Preservatives	No incompatibility known
	Surfactants	Yes
Comments		Introduction of destabilizing agents is recommended after gel development. Non-shear sensitive

INCI name：Salicylic acid

Certificate of Analysis

Product Name : **Salicylic acid**
Acidum salicylicum

According to: **Ph. Eur.7.0**

CAS Number: **69-72-7**

Test	Units	Specifications	Results
Physicochemical Characteristics			
Appearance		white or almost white, crystalline powder or white or colourless, acicular crystals.	**complies (A)**
Solubility		slightly soluble in water, sparingly soluble in methylene chloride.	**complies (A)**
Identification A	°	158 - 161	**159 (A)**
Identification B		complies	**complies (A)**
Sol. In 95/96% Ethanol		complies	**complies (B)**
Colouration of ethanolic sol.	Hazen	< 10,0	**< 10 (B)**
Sulfates	%	≤ 0,0200	**0,0160 (B)**
Assay	%	99,5 – 100,5	**100,5 (B)**
Heavy metals (Pb)	%	≤ 0,0020	**< 0,0010 (B)**
Chlorides	%	≤ 0,0100	**< 0,0050 (B)**
Ash sulphated	%	≤ 0,1000	**0,0260 (B)**
4-hydroxybenzoic acid	%	≤ 0,10	**0,0360 (B)**
4-hydroxyisophthalic acid	%	≤ 0,0500	**0,0240 (B)**
Phenol	%	≤ 0,0100	**< 0,0060 (B)**
Total impurities	%	≤ 0,20	**< 0,11 (B)**
No other related subst.> 0,05%	%	complies	**complies (B)**
Loss on drying	%	≤ 0,50	**0,08 (B)**

INCI name：Triethanolamine

Triethanolamine

Product Information

Product Name	:	Triethanolamine
Molecular Formula	:	$C_6H_{15}NO_3$
Molecular Weight	:	149.19
CAS No.	:	102-71-6
EC No.	:	203-049-8
HS Code	:	2922 13 10
Shelf Life	:	3 years

Technical Specification

Appearance	:	Clear colourless to pale yellow hygroscopic viscous liquid, turning brown on exposure to light
Solubility	:	1 mL miscible in 1 mL of water
FTIR (Liquid film)	:	Matches with the standard pattern
Refractive index (n 20/D)	:	1.4800 - 1.4900
Density (d 20/4)	:	1.120 - 1.130 g/mL
Chloride (Cl)	:	<= 0.0001%
Diethanolamine	:	<= 0.8%
Ethanolamine	:	<= 0.1%
Iron (Fe)	:	<= 0.0001%
Lead (Pb)	:	<= 0.0001%
Sulphate (SO_4)	:	<= 0.001%
Sulphated ash	:	<= 0.005%
Water (K.F.)	:	<= 0.2%
Assay (GC/HCl Titration)	:	99.00 - 102.00%

Risk and Safety Information

WGK	:	1
RTECS	:	KL9275000
Flash Point(°F)	:	354.2 °F
Flash Point(°C)	:	179 °C
Storage Temperature(°C)	:	Store below 30°C

Transport Information

Marine Pollutant	:	No
ADR/RID	:	Not Dangerous Goods
IMDG	:	Not Dangerous Goods
IATA	:	Not Dangerous Goods

INCI name：Methyl Paraben

methylparaben

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Common Name	methylparaben		
CAS Number	99-76-3	**Molecular Weight**	152.147
Density	1.2±0.1 g/cm3	**Boiling Point**	265.5±13.0 °C at 760 mmHg
Molecular Formula	$C_8H_8O_3$	**Melting Point**	125-128 °C(lit.)
MSDS	Chinese USA	**Flash Point**	116.4±12.6 °C

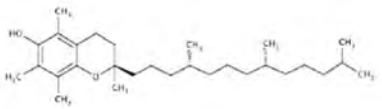
Chemical & Physical Properties

Density	1.2±0.1 g/cm3
Boiling Point	265.5±13.0 °C at 760 mmHg
Melting Point	125-128 °C(lit.)
Molecular Formula	$C_8H_8O_3$
Molecular Weight	152.147
Flash Point	116.4±12.6 °C
Exact Mass	152.047348
PSA	46.53000
LogP	1.87
Vapour Pressure	0.0±0.6 mmHg at 25°C
Index of Refraction	1.547
Stability	Stable. Incompatible with strong oxidizing agents, strong bases.
Freezing Point	131℃

INCI name：Tocopherol

Product Specification

Product Name	DL-alpha-Tocopherol
CAS Number	10191-41-0
EINECS	233-466-0



Molecular Weight	430.72
Molecular Formula	C29H50O2
Storage Temp.	+4°C

Property	Specification
Physical Description	Pale yellow to brown, clear viscous liquid
Identification	According to EP, USP
Specific Optical Rotation	-0.01 - +0.01 °
Sulphated Ash	≤ 0.1%
Acidity	≤ 1.0ml
Heavy Metals (as Pb)	≤ 10ppm
Lead (Pb)	≤ 2ppm
Arsenic (As)	≤ 1ppm
Cadmium (Cd)	≤ 1ppm
Mercury (Hg)	≤ 0.1ppm
Zinc (Zn)	≤ 10ppm
Related Substances	Impurity A: ≤ 1.0%
	Impurity B: ≤ 1.5%
	Impurity C & D: ≤ 1.0%
	Any Other Impurity: ≤ 0.25%
	Total Impurities: ≤ 2.5%
Assay	96.0 - 102.0 % (USP)
Assay	96.0 - 102.0 % (EP)
Pharmacopoeia Specification(s)	EP, USP

(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之各個成分毒理資料，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：Alcohol

- 毒物動力學：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、水及乙醇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%的乙醇中不到 1 小時會產生大約 100 mg 的乙醇吸收，這相當於 1.5 ml 含有 10% (v/v)乙醇的酒。Pendlington 等人(2001)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 個樣品中有 22 個可測到乙醇的存在，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。作者得出的結論是，使用含酒精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 8300mg/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/生化變化較小。雌性大鼠的生化變化較小，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的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）時未影響生育力或發育。[1]
- 人體數據：乙醇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害。[1] 乙醇的大部分全身毒性與長期濫用酒精有關。儘管乙醇已變性使其不適合食用，但仍有刻意或意外食入含有變性酒精產品之情況發生。乙醇在一些測試系統中具有遺傳毒性，並且已經提出乙醇的遺傳毒性作用是通過其代謝物乙醛所導致的。簡要總結長期攝入酒精的影響，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乙醇全身暴露，因此美國化粧品成分審查(Cosmetic Ingredient Review, 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.

2. INCI name：Propylene Glycol

- 經皮吸收：使用 84%丙二醇(Propylene Glycol, PG)中含有 10%油酸(Oleic acid)和 6%二甲基異山梨醇(Dimethyl isosorbide)的助溶劑，測[^{14}C]丙二醇通過切除的雌性無毛小鼠皮膚的皮膚滲透率。在 24 小時內，丙二醇的累積滲透率為使用量的 57.1%。使用熱發射衰減-傅立葉變換紅外光譜法 (Thermal emission decay–Fourier transform infrared, TED-FTIR)測定皮膚最外層中丙二醇的皮膚吸收。使用浸泡

丙二醇的棉絮塗在一位受試者的指尖上 30 分鐘，並擦拭該部位乾燥 1 分鐘，測出的角質層表層厚度為 0.71 mm。在 3 小時內每 25 分鐘進行一次測量，每次測量時間為 15 分鐘，發現殘留在角質層表面丙二醇濃度隨時間降低。在第 12 和第 32 分鐘，丙二醇的最大濃度出現在<1 mm 的深度，而在第 107 和第 157 分鐘，丙二醇的最大濃度出現在 3~4 mm 的深度。在 6 mm 深度處，丙二醇的最大濃度為 0.2%。作者認為丙二醇分子僅擴散到角質層中，深度約為 6~7mm 且不會到達真皮層。[1]

- 急性毒性：對於丙二醇進行一項急性研究，其中雌性 ICR 小鼠腹膜內腹腔注射(Intraperitoneal injection, ip)劑量分別為 2600、5200 或 10400 mg/kg PG。除注射高劑量小鼠外，所有小鼠在注射後均存活 6 天（此試驗未載明高劑量小鼠死亡的數量）。在 2600 和 5200 mg/kg PG 組中未觀察到毒性跡象，例如：嗜睡和毛皮捲皺。[1] 丙二醇最低的口服 LD_{50} 值範圍在 18~ 23.9 g（5 個不同物種）之間，報告顯示皮膚 LD_{50} 為 20.8 g。[3]
- 皮膚刺激性/致敏性：以雄性無毛 SKH1 hr/hr 小鼠評估 100%丙二醇的皮膚刺激潛力。將丙二醇滴入 3 隻小鼠背側的聚氯乙烯杯中（體積 0.3 cm^3）。測試物質與皮膚保持接觸 24 小時，在 24 小時結束時，犧牲小鼠並用顯微鏡檢查暴露之皮膚樣品。丙二醇的刺激性很小，總分為 7 分（最高分為 77 分）。使用皮內注射 0.02 ml 未稀釋的丙二醇進行臨床安全性評估，會在幾分鐘內產生風疹塊(wheal-and-flare)反應，而相同體積的表皮注射不會產生任何反應。人類受試者在施用各種濃度的丙二醇後，研究人員認為志願受試者有時會出現主觀或感官刺激，將皮膚對丙二醇的反應可分為 4 類：(1)刺激性接觸性皮膚炎；(2)過敏性接觸性皮膚炎；(3)非免疫性接觸性蕁麻疹；(4)主觀或感官刺激。[1]
- 重複劑量毒性：大鼠重複食用添加丙二醇之飲用水或飼料，水中含量為 10%（估計約為 10 g/kg bw/day）或飼料中為 5%（劑量為 2.5 g/kg bw/day）長達 2 年。兩者以貓為實驗動物，至少進行 90 天的實驗顯示，可觀察到亨氏小體(Heinz bodies)增加及較高劑量下（飲食中 6-12%或 3.7~10.1 g/cat/day）之其他血液學影響（紅血球數量和存活率降低），報告評估 NOAEL = 80 mg/kg bw/day；LOAEL = 443 mg/kg bw/day。[3]
- 致癌性：在大鼠飲食中添加 100% PG 2.5 g/kg bw/day 持續 2 年，或

給予雌性大鼠（總劑量未說明）14 個月或小鼠劑量估計約為 2 g/kg bw/week 終生試驗，這些數據支持丙二醇無致癌性。[3]

- 光敏感性：在 2 年臨床安全性評估試驗期間，針對患有光過敏性接觸性皮膚炎的 30 名男性和 52 名女性，使用標準系列防曬霜以及一些額外的化學物質（包括丙二醇,未說明劑量）進行了光斑貼測試(Photopatch test)。將過敏原一式兩份塗抹在背面並用不透明膠帶覆蓋。24 小時後，取下膠帶，評估測試部位，一組測試部位用 320~400 nm 光譜 5 J/cm^2 的 UVA 劑量照射（使用 Daavlin UVA 儀），得到 10.4 mW/cm^2 的輻射照度。照射後未覆蓋的測試部位分別在 24 和 72 小時後進行評估。雖然其他測試試劑具些微陽性反應，但丙二醇不會產生光過敏或接觸過敏反應。[1]
- 人體數據：丙二醇是食品中天然存在的化學物質，通過化學合成進行生產。它通常用作食品製備中的加工助劑、溶劑、載體和增稠劑。美國食品和藥物管理局(FDA)、香料和萃取物製造商協會(The Flavor and Extract Manufacturers Association of the United States, FEMA)以及糧農組織/世衛組織聯合食品添加劑專家委員會(The Joint FAO/WHO Expert Committee on Food Additives, JEFCA) 認為丙二醇普遍被認為是安全的(Generally Recognized As Safe, GRAS) 並被批准為食品添加劑，適用於所有食品類別，最高為 2%（FAO/WHO Expert Committee, 1974 年）。[2]
- 其他安全資料：2012 年 CIR 專家小組審查了用於化粧品和個人護理產品的丙二醇的現有文獻和安全數據。他們得出結論當配方為對皮膚無刺激性時，它可安全地用於化粧品中。美國食品和藥物管理局將丙二醇列入其公認安全(Generally Recognized As Safe, GRAS)物質清單， 2003 年，國家毒理學計劃人類生殖風險評估中心專家小組審查丙二醇的生殖和發育影響潛力並得出結論是“對人類生殖或發育毒性的擔憂可以忽略不計”。[4]
- 參考資料：

1. Safety Assessment of Propylene Glycol, Tripropylene Glycol, and PPGs as Used in Cosmetics. International Journal of Toxicology Vol.31(Supplement 2) 245S-260S, CIR, 2012.
2. Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in Sprague-Dawley rats and Beagle dogs. Toxicology Vol. 287, Issues 1-3, Pages 76-90, 5 September, 2011.

3. SIDS Initial Assessment Report For SIAM 11, Propylene glycol. OECD SIDS, 2001.
4. Cosmetics Info 網站：
https://cosmeticsinfo.org/ingredient/propylene-glycol

3. INCI name：Hamamelis Virginiana (Witch Hazel) Leaf Extract

- 經皮吸收：金縷梅(Hamamelis virginiana (witch hazel))萃取與衍生成分因其成分為複雜的混合物，因此不易得到毒理代謝動力學數據。然而，一家製造商報告顯示，以治療量塗抹金縷梅萃取物於皮膚上，由於其成分具有收斂性，因此無法滲透到皮膚的深層；也不會被吸收到血液循環中。[1]
- 急性毒性：單劑量口服 10 至 20 g 金縷梅製劑對小鼠和大鼠沒有毒性作用(未提供進一步的細節)。紐西蘭白兔(n = 2/sex)施用含有金縷梅乙醇(Hamamelis virginiana (witch hazel) ethanol extract)萃取物(0、20、100 或 300 mg/kg)的栓劑。該萃取物的特徵是至少具有 10%的單寧(Tannins)和沒食子酸(Gallic acid)。栓劑由硬脂(Hard fat)、白蜂蠟(White beeswax)和膠態無水二氧化矽(colloidal anhydrous silica)所組成。栓劑被熔化並用刻度移液管給予單劑量。施用後觀察兔子 7 小時，然後持續每天觀察 2 週，在施用後第 2、7 和 14 天進行肛門直腸區域的局部檢查，並在觀察期的最後一天採集血液樣本。實驗結果顯示沒有兔子死亡，測試組之間的體重沒有差異，肝腎功能無變化。所有兔子的血清尿素含量均呈非劑量依賴性增加，且沒有觀察到血液學影響，推估 NOAEL >300 mg/kg bw。[1]
- 重複劑量毒性：Sprague Dawley 大鼠(n = 5/sex)施用含有金縷梅乙醇萃取物(0、20、100 或 300 mg/kg/day)的栓劑，持續 28 天。栓劑被熔化並用刻度移液管給藥，施用後觀察大鼠 1 小時，之後每天觀察並秤重，每週評估飼料和水的消耗量，並在觀察期的最後一天通過心臟穿刺採集血液樣本。犧牲大鼠並進行屍體解剖檢查，包括消化道檢查。從安慰劑組和高劑量組的兩隻大鼠/sex 中分離出肝臟、腎臟和直腸活檢組織；這些樣品以甲醛固定並在光學顯微鏡下檢查。實驗結果顯示沒有大鼠死亡，也沒有觀察到臨床症狀，測試組之間的體重增加沒有差異，觀察到的器官（肝、腎、脾、下頜下唾液腺、

心臟、睾丸和肺）在安慰劑組和試驗組中相似，肝和腎功能沒有變化，血清脂質和蛋白質譜沒有變化，且沒有觀察到血液學影響，推估 NOAEL > 300 mg/kg bw/day.。大鼠口服金縷梅劑量 100 mg/kg/day 三個月，報告顯示沒有異常現象。[1]

- 皮膚刺激性：兩種分別含有 5%和 10%金縷梅樹皮/葉子/樹枝萃取物的混合物產品以 EpiDerm™ 檢測結果為陰性。在對金縷梅萃取物（5%在環戊矽氧烷 Cyclopentasiloxane 中）EpiDerm™ 分析中，預測刺激潛力為陰性。以含有 8.5%金縷梅水 25µl 臉部產品進行人類反覆刺激斑貼試驗(Human Repeat-Insult Patch Test, HRIPT)。使用 Finn chambers 將測試物質施用於受試者 (n = 11) 的肩胛骨區域 48 小時，在移除後 24 小時觀察測試部位，發現測試物質是無刺激性的。對含有 6.02%金縷梅水的仿曬劑進行了為期 4 週的使用研究，在測試期前和後檢查女性受試者(n = 19)的紅斑、水腫和乾燥以及非皮膚炎性和皮膚炎性病變。在測試的最後兩天，一名受試者在施用後 5 分鐘產生“刺痛”，但皮膚檢查沒有刺激現象。[1]
- 皮膚致敏性：分別以高達 0.45%金縷梅葉萃取物和 25.80%金縷梅水溶液在人類反覆刺激斑貼試驗中，沒有刺激性或致敏性發生。
- 生殖毒性：沒有發現已發表的發育或生殖毒性研究，也未有相關發表的數據。[1]
- 遺傳毒性：對含有 6%金縷梅葉萃取物，以高達 3100 µg/plate 金縷梅葉萃取物的產品，進行 Ames 測試，分析結果為陰性。金縷梅水溶液（未指定濃度）在沙門氏菌哺乳動物微粒體試驗中，無論是否有代謝激活性，但皆沒有遺傳毒性。[1]
- 致癌性：將含金縷梅葉水萃取物（10mg 在生理食鹽水中）0.5ml 每週一次皮下注射到 NIH 黑色大鼠(n = 15/sex)的腹部，持續長達 78 週，並以生理食鹽水作為對照。萃取物是將採集的野生葉子磨成粉末，用熱水提取，然後凍乾。該劑量基於初步研究，已確定不會產生任何全身毒性或局部壞死以及結痂（此劑量確實引起了一些腫脹，並在 1 至 2 週內消失）的植物濃度。注射進行了 78 週或直到檢測到腫瘤。當檢測到的腫瘤長到足夠大時，犧牲大鼠並進行屍體解剖檢驗。接受萃取物試驗的大鼠再繼續觀察 12 週，然後將它們犧牲並進行屍檢。檢查了腫瘤組織和器官（包括區域淋巴結、肺、肝、脾和腎），對照組未檢出腫瘤，試驗組中的三隻雄鼠在第 72 至 73 週發現腫瘤，在雌性大鼠中未觀察到腫瘤。兩隻雄鼠（第 24 和 57

週）和一隻雌鼠（第 59 週）死於肺部感染，試驗組患有腫瘤大鼠的數量並未顯著多於對照組。[1]

- 光毒性：對含有 6%金縷梅葉萃取物的產品混合物進行體外光毒性試驗，測試物質（高達 17000 µg/ml；1020 µg/ml 金縷梅葉萃取物）施用於 BALB/c 3T3 細胞，分別暴露或未暴露於 5 J/cm^2 的 UVA 劑量。不論在使用或不使用 UVA 照射測試的任何劑量濃度下均未觀察到細胞毒性。[1]
- 人體案例報導：一名 31 歲的非特定性女性開始使用一種含有“金縷梅蒸餾液”的新型眼部凝膠之後，1 週內眼睛周圍出現水腫。 同時，她接受 1%氫化可體松-17-丁酸酯治療下肢皮膚炎。她停止使用眼用凝膠，而是開始使用替代療法（未說明）。在接下來的幾天裡，水腫擴散到面部和頸部的其他部位，然後表現為濕疹。她接受皮質類固醇的全身治療，並被告知不要使用任何化粧品或其他治療方法。之後皮膚炎消退，沒有復發。對她進行眼霜及其成分的人類反覆刺激斑貼試驗，在第 3 天的數據顯示對眼霜(+)和金縷梅蒸餾物具有濃度依賴性的陽性結果(1%, -; 5%, +?; 10%, +; 50%, ++；100% , ++)，暴露於越高濃度金縷梅蒸餾物，發生皮膚炎風險越高。[1]
- 其他安全性資料：美國食品和藥物管理局允許在成藥(Over-the-Counter, OTC)皮膚保護劑和肛門直腸藥物產品中使用金縷梅萃取物（來自樹皮、樹葉和樹枝）作為收斂劑。化粧品成分審查已評估金縷梅的安全性。[2]
- 參考資料：

1. Safety Assessment of Hamamelis virginiana (Witch Hazel)-Derived Ingredients as Used in Cosmetics, CIR, 2018.
2. Cosmetics Info 網站：https://cosmeticsinfo.org/ingredient/hamamelis-virginiana-witch-hazel-leaf-water

4. INCI name：Glycyrrhiza Uralensis (Licorice) Root Extract

- 毒物動力學：禁食一晚之大鼠（未指定品系；n = 5），口服來自栽培來源(756 mg/10 ml/kg）或來自中國野生來源(452 mg/10 ml/kg)的甘草根萃取物，每種製劑經測定含有 45 mg/kg 甘草次酸(Glycyrrhetic Acid)。在 0、1、2、4、6、9 和 12 小時從尾靜脈收集

血液樣品，然後通過 HPLC 分析甘草次酸。兩種來源的血液樣品中檢測到的甘草次酸量相似，高峰值濃度在 9 小時（栽培來源為 1.90 ±0.40 μg/ml，野生來源為 1.51±0.91 μ g/ml）。在 24 小時未檢測到甘草次酸 (Yamamoto et al. 2003)。雄性 Wistar 大鼠禁食過夜後口服甘草萃取物（烘烤和未烘烤；含有 45 mg/kg 甘草甜素 glycyrrhizin）。定期從尾靜脈收集血樣 (0.3 ml)，持續 24 小時，測定血漿甘草次酸 24 小時平均濃度與時間曲線下面積 (AUC_{0-24} 小時)。在血漿中檢測到甘草次酸（但不是甘草甜素），並在口服兩種萃取物後 9 小時達到高峰值。口服烘烤過的和未烘烤過的甘草萃取物的大鼠血漿中甘草次酸沒有差異。烘焙和未烘焙甘草的 $AUCs_{0-24}$ 小時相似（分別為 14.2± 9.0 μg/ml 和 12.5±4.9 μg/ml），最大濃分別度為 1.48±0.86 μg/ml、1.47±0.63 μg/ml (Majima et al. 2004)。[1]

- 急性毒性：在小鼠口服甘草萃取物的 LD_{50} 值為>7.5 g/kg，大鼠口服 LD_{50} 值範圍在 14.2~18.0 g/kg 之間。腹腔注射 2 g/kg 的 18α-甘草次酸對成年雌性 Sprague-Dawley 大鼠是致命的，該劑量導致心臟功能逐漸受損，大鼠的組織病理學顯示腦、小腦和肺水腫伴腎瘀血， 且發現到乳凸肌和心肌細胞腫脹的局部性變化。據研究顯示，靜脈注射 70 mg/kg 甘草甜素的小鼠會出現驚厥和輕微溶血的急性毒性作用，在較低劑量的甘草甜素下沒有觀察到毒性作用(Isbrucker & Burdock 2006)。[3]
- 重複劑量毒性：Kobuke et al. (1985)研究消耗甘草酸二鈉(Disodium glycyrrhizin)對雄性和雌性 B6C3F1 小鼠的慢性影響。一項初步亞慢性研究顯示，雄性小鼠的最大耐受劑量為 0.15%（~375 mg/kg），雌性小鼠的最大耐受劑量為 0.3%（~750 mg/kg）。甘草甜素分別以 0、0.04、0.08、0.15 或 0.3%的濃度在飲用水中餵食 96 週，給予雄性小鼠每日的劑量濃度大約為 0、71、166 或 229 mg/kg，給予雌性小鼠劑量濃度大約為 0、117、217 或 407 mg/kg。甘草甜素(Glycyrrhizin)施用對平均體重、累積死亡率和平均死亡時間、腫瘤發生率或腫瘤類型及分佈沒有顯著影響，結論是長期每天給這些小鼠服用甘草甜素並沒有任何慢性毒性或致癌性的證據。[3]
- 生殖毒性：BALB/c 小鼠口服野生或栽種之烏拉爾甘草根萃取物(50、100 或 200 mg/kg)減少小鼠的耳腫脹。Sprague-Dawley 大鼠(n = 15；6 週齡)口服烏拉爾甘草根萃取物(500、1000 或 2000mg/kg bw/day)，持續 9 週，對照組給予水，監測體重和攝食量。在試驗期結束時，

採集血液樣本，然後犧牲大鼠並進行屍體剖檢。試驗期間無臨床症狀，體重和飼料消耗量沒有差異，器官重量包括生殖系統沒有差異，高劑量組前列腺重量略有下降，但不顯著。高劑量組睾丸精子數量略有減少，但不顯著。對日常產生的精子數量沒有影響，附睾精子計數沒有劑量依賴性變化，對精子的運動性或形態沒有影響。血清睾固酮在 9 週內下降（高劑量組為 28.6%），但不顯著，組織病理學檢查無明顯發現，研究結論是大鼠的 NOAEL > 2000 mg/kg bw/day (Shinet al. 2008)。[1]

- 基因/遺傳毒性：沒有可用的基因毒性研究報告。[3]
- 光毒性：CTFA (2001a)提供關於溶解在 Earle 緩衝溶液(Earle's buffered salt solution, EBSS)中的甘草萃取物數據。該萃取物用 3T3 中性紅(Neutral Red, NR)吸收光毒性試驗進行測試，濃度最高爲 1,000 mg/L。甘草萃取物在 3T3 中性紅吸收光毒性試驗中未引起細胞毒性作用(NR_{50} > 1000 mg/L)，但在使用 5 J/cm^2 UVA 的體外試驗中觀察到光細胞毒性作用(NR_{50} = 13.2 mg/L)。使用 EpiDermTM 光毒性測試和 6 J/cm^2 UVA 測試甘草萃取物的光毒性，在該體外測試中沒有引起細胞毒性和光細胞毒性作用。在對白化天竺鼠進行的高達 2.5%的甘草萃取物的光敏試驗中，無論有或沒有 UVA 照射的情況下，暴露於任何甘草萃取物都沒有出現陽性反應。[1]
- 其他安全性資料：根據 CIR 專家小組得出的結論是，在使用含有甘草衍生成分的化粧品和個人護理產品時，接觸甘草成分會比吃甘草糖少得多。此外，在甘草中發現的化合物的皮膚滲透性很低，這也會限制甘草成分對皮膚暴露量。因此，CIR 專家小組得出結論，Glycyrrhiza Glabra (Licorice) Rhizome /Root, Glycyrrhiza Glabra (Licorice) Leaf Extract , Glycyrrhiza Glabra (Licorice) Root, Glycyrrhiza Glabra (Licorice) Root Extract, Glycyrrhiza Glabra (Licorice) Root Juice, Glycyrrhiza Glabra (Licorice) Root Powder, Glycyrrhiza Glabra (Licorice) Root Water, Glycyrrhiza Inflata Root Extract 和 Glycyrrhiza Uralensis (Licorice) Root Extract 一般公認安全(Generally Recognized as Safe, GRAS)，可安全用作化粧品成分。[2]
- 參考資料：

1. Safety Assessment of Glycyrrhiza Glabra (Licorice) Rhizome/root, Glycyrrhiza Glabra (Licorice) Leaf Extract, Glycyrrhiza Glabra (Licorice) Root, Glycyrrhiza Glabra (Licorice) Root Extract,

Glycyrrhiza Glabra (Licorice) Root Juice, Glycyrrhiza Glabra (Licorice) Root Powder, Glycyrrhiza Glabra (Licorice) Root Water, Glycyrrhiza Inflata Root Extract, and Glycyrrhiza Uralensis (Licorice) Root Extract. Final Report of the Cosmetic Ingredient Review Expert Panel, CIR, 2008.

2. Cosmetics Info 網站：https://cosmeticsinfo.org/ingredient/glycyrrhiza-uralensis-licorice-root-extract
3. Assessment report on Glycyrrhiza glabra L. and/or Glycyrrhiza inflata Bat. and/or Glycyrrhiza uralensis Fisch., radix. Committee on Herbal Medicinal Products, European Medicines Agency, 2013.

5. INCI name：Sodium Acrylates Copolymer

◆ 毒物動力學：通過管飼法向 5 隻雄性大鼠施用 55~75mg 的丙烯酸酯共聚物(Acrylates Copolymer)，作爲甲基丙烯酸甲酯 Methyl methacrylate 和丙烯酸乙酯(Ethylacrylate)的完全聚合共聚物；以標有 ^{14}C 的乾燥薄膜形式提供，具體活性爲 0.17 μCi/mg)。在管飼前 5 天和後 7 天收集尿液和糞便，然後犧牲動物，收集組織樣本並評估放射性。另外 9 隻雄性對照大鼠也被給予單次口服劑量的測試製品，在管飼後 1、3 或 14 天犧牲 3 隻動物，並收集組織樣本。在施用標記物質後的 5 天內，放射性的平均總恢復超過 90%施用劑量。在管飼 48 小時後，糞便中可測得超過 97%的放射性。尿液中幾乎沒有放射性(0.0092%)，血液和組織中的放射性濃度在試驗動物和對照動物之間沒有顯著差異。研究結論是，只有不到 0.02%的管飼試驗品被胃腸道吸收，任何被吸收的物質都會迅速排出體外。三組 4 隻雄性和 4 隻雌性 Sprague-Dawley 大鼠通過管飼給藥 13 天丙烯酸酯共聚物(作為丙烯酸甲酯 Methyl acrylate、甲基丙烯酸甲酯 Methyl methacrylate 和甲基丙烯酸 Methacrylic acid 的完全聚合共聚物；劑量未說明)，然後給予單劑量放射性標記的測試材料(每隻動物 10 μCi；在甲基丙烯酸部分的游離羧基處進行 ^{14}C 標記)。一組動物在最後一次給藥後 24 小時被犧牲，另一組在 72 小時被犧牲，最後一組保留 10 天，收集尿液和糞便。大部分劑量在給藥後 72 小時內

94%隨糞便排出，在尿液中回收到很少或沒有放射性 (< 0.1%)，組織和組織內容物佔總回收率的< 0.01%，並且屍體中的放射性濃度低於偵測極限。[1]

- 急性毒性：丙烯酸酯共聚物報告了以下 LD_{50} 值：> 16 g/kg（兔皮膚），> 16 ml/kg（皮膚）、> 9 g/kg（皮膚）、9 g/kg（大鼠皮膚）、> 5.2 mg/L（大鼠）。乙烯/丙烯酸共聚物對大鼠經皮和口服給藥後具有口服 LD_{50} >5 g/kg "低急性毒性"。乙烯/丙烯酸銨鹽(Ethylene/Acrylic acid Copolymer)對大鼠的口服 LD_{50} 為 41.5 ml/kg。在一項急性吸入研究中，暴露於乙烯/丙烯酸聚合物銨鹽水性乳液的 6 隻大鼠中，沒有死亡發生。醋酸乙烯酯/馬來酸酯/丙烯酸酯共聚物溶液(Acetate/Maleate/Acrylate Copolymer solution)的兔子經皮 LD_{50} 和大鼠經口 LD_{50} >5 g/kg。對於大鼠，聚丙烯酸(Polyacrylic acid)和聚丙烯酸鈉(Sodium Polyacrylate)的口服 LD_{50} 值分別為 2.5 和> 40 g/kg；雄性大鼠分別為 0.34 和 2.59 ml/kg。[1]
- 重複劑量毒性：使用含有約 22.7%丙烯酸酯共聚物（作為甲基丙烯酸甲酯和丙烯酸乙酯的完全聚合共聚物）明膠膠囊進行試驗，給予 4 隻雄性和 4 隻雌性比格犬 26 週。使用的劑量濃度為 50、125 和 250 mg dry copolymer/kg bw/day，相當於 200、500 和 1000 mg test material/kg bw/day。4 隻雄性和 4 隻雌性比格犬對照組被給予空膠囊。對照組和高劑量組均包括另外 3 隻雄性和 3 隻雌性比格犬，這些比格犬在給藥終止後恢復 3 週。與對照組相比，高劑量動物的體重增加較少，並且差異在第 12 週時具有統計學意義，低劑量組和中劑量組的雄性比格犬體重略低於對照組，這些組別的雌性比格犬體重沒有觀察到變化。接受試驗的雌性比格犬心臟和右側甲狀腺的相對重量增加，但認為這些變化與試驗無關，因為在顯微鏡下沒有觀察到差異。其他觀察結果被認為沒有毒理學意義，NOAEL 被確定為 250 mg dry copolymer/kg bw/day。[1]
- 皮膚刺激性/致敏性：在使用兔子進行的皮膚刺激研究中，丙烯酸酯共聚物無至輕度刺激性。但在另一項貼膚研究中，在 72 小時時觀察到一隻動物出現非常輕微到界限分明的紅斑和嚴重的紅斑。在 47 名受試者以 25%丙烯酸酯共聚物的稀釋水溶液進行損傷皮膚重覆斑貼試驗(Repeated Insult Patch Test, RIPT)中發現不是刺激物或致敏劑。在臨床測試中，30%固體丙烯酸酯共聚物為非刺激物或致敏劑，並且 100%固體丙烯酸酯共聚物溶於 15%氨水溶液或 25%丙酮

溶液也不是致敏劑。未稀釋的聚丙烯酸鈉在 50 名受試者中未產生刺激性或致敏性。[1]

- 致癌性：在已發表的研究文獻未發現對丙烯酸酯共聚物致癌性。[1]
- 生殖毒性:在大鼠口服分子量 4500 或 90000 Da 聚丙烯酸鈉(Sodium Polyacrylate)研究中未觀察到生殖毒性效應。兩項口服研究，其中將丙烯酸酯共聚物(作為甲基丙烯酸甲酯和丙烯酸乙酯的完全聚合共聚物）分散體以 1:10 的比例噴灑到粉狀日糧上，然後將粉狀日糧與基礎日糧混合進行測試。在第一項研究中，每組 20 隻交配的 Wistar 雌性大鼠在妊娠第 6 天至第 15 天被餵食 0、500 或 2000 mg dry copolymer/kg bw/day，並在妊娠第 19 天犧牲妊娠大鼠。在第二項研究中，10 隻交配的紐西蘭雌性白兔在妊娠第 6 至 18 天接受相同劑量的試驗，並在妊娠第 29 天犧牲。在大鼠或兔子中沒有母體毒性跡象，並且沒有觀察到任何一個物種的生殖或發育影響。在大鼠和兔子中，母體和胎兒的 NOAEL 均為 2000 mg dry copolymer/kg bw/day。[1]
- 人體數據：在檢查工作場所暴露影響時，暴露於各種丙烯酸聚合物粉塵（以及其他材料）的員工沒有過多的 X 光胸部異常，包含瀰漫性肺纖維化的異常。此外，肺功能測試 (pulmonary function testing, PFT) 也沒有過多的異常。[1]
- 其他安全性資料：消費者安全科學委員會(Scientific Committee on Consumer Safety, SCCS)就苯乙烯/丙烯酸酯共聚物(Styrene/Acrylates copolymer)和苯乙烯/丙烯酸鈉共聚物(Sodium styrene/Acrylates copolymer)奈米材料用於免沖洗化粧品時最大濃度的安全性發表意見，考慮到合理可預見的暴露條件限制為 0.06%。[2]
- 參考資料：

1. Amended Safety Assessment of Acrylates Copolymers as Used in Cosmetics, CIR, 2019.
2. SCCS OPINION on Styrene/Acrylates copolymer (nano) and Sodium styrene/Acrylates copolymer (nano), 2018.

6. INCI name：Lecithin

- 毒物動力學：在 8 名人類受試者中，口服 500 mg 磷脂酰絲胺酸(Phosphatidylserine)，作為大豆卵磷脂磷脂酰絲胺酸膠囊(Soy

Lecithin Phosphatidylserine Capsules)導致血漿磷脂酰絲胺酸峰值為佔血漿總磷脂濃度 3.95%，而背景磷脂酰絲胺酸值為總血漿磷脂的 1.8%~2.2%。[1]

- 急性毒性：小鼠對來自牛大腦皮層磷脂質(Phospholipids From Bovine Cerebral Cortex, BC-PS)的急性口服毒性很低：$LD5_0$> 5000 mg/kg bw。對大鼠每天管飼劑量高達 1000 mg/kg bw BC-PS 26 週或對狗每天管飼劑量高達 1000 mg/kg bw BC-PS 長達 1 年均無不良影響。[2]
- 重複劑量毒性：一組 48 隻雄性和 48 隻雌性 SPF Wistar 大鼠被餵食 4%大豆卵磷脂(Soya Lecithin)2 年，而對照組僅餵食飼料。在給藥前測定飼料消耗和體重，間隔長達一週，並在第 102 週研究終止。雄性和雌性大鼠的平均卵磷脂攝入量分別為 1470 和 2280 mg/kg bw/day。試驗組和對照組之間在死亡率、飼料消耗或體重方面沒有觀察到統計學上的顯著差異，但與對照組相比，試驗組的飼料消耗和體重有時更大。試驗組動物與對照動物的血液學數值相似，器官重量以及大體和微觀變化也是如此。在雄鼠中，副甲狀腺增生的增加，歸因於磷酸鹽攝入量的增加。試驗組和對照組的腫瘤形成發生率相似，心肌纖維化的發生率略有增加與副甲狀腺增生有關。[1]
- 皮膚刺激性/眼睛刺激性/致敏性：65%卵磷脂溶液和含有 2.25%或 3.0% (65%卵磷脂)產品對未沖洗的兔子眼睛無刺激性或極低刺激性。含有 0.83%卵磷脂粉末(以 25%進行測試)的肥皂具有中等刺激性，而在 Draize 測試中，含卵磷脂的脂質體實際上無刺激性。在臨床刺激性研究中，含有 0.3%或 3%卵磷脂(65%卵磷脂溶液)、含有 0.83%卵磷脂粉末的肥皂(以 0.5%測試)和卵磷脂脂質體的化粧品配方通常無刺激性，幾乎察覺不到的紅斑是觀察到最嚴重的反應。氫化卵磷脂(Hydrogenated Lecithin)不是刺激物，且含有氫化卵磷脂的 15%凡士林不是致敏劑。此外，含有 3%卵磷脂(65%卵磷脂溶液)仿曬油、含有 0.1%卵磷脂(65%卵磷脂溶液)的睫毛膏和含有 0.3%卵磷脂(65%卵磷脂溶液)粉底均不致敏。[1] 卵磷脂對皮膚和眼睛沒有刺激性。[2]
- 生殖毒性：一項兔子生殖毒性研究顯示，在每天 450 mg/kg bw/day 的磷脂酰絲胺酸的灌食劑量下，沒有胎兒異常，但胎兒體重略降低，NOAEL 為 150 mg/kg bw/day。[2]
- 致癌性：25 隻雌性水牛鼠(Buffalo rats)單次注射 0.2 mL 4-硝基喹啉 1-氧化物(4-nitroquinoline 1-oxide)的 0.25% 混合物(在 10%卵磷脂水

溶液中)，直至劑量達到 10 mg，每週重複注射。15 隻大鼠接受相同總劑量的卵磷脂水混合物給藥 20 次，水牛鼠在 264 至 329 天後被犧牲。注射 4-硝基喹啉 1-氧化物/卵磷脂且在開始給藥 264 天後存活的 25 隻動物中有 19 隻發現患有肺腫瘤，另有 11 例肉瘤和 2 例子宮內膜肉瘤。在注射卵磷脂水溶液的 13/15 存活大鼠中，沒有發現任何腫瘤。[1]

- 遺傳毒性/致突變性：使用不同磷脂進行的致突變性研究（細菌回復突變試驗、人淋巴細胞體外染色體畸變試驗、小鼠淋巴瘤細胞基因突變試驗、HELA S3 細胞 UDS 體外試驗和體內口腔微核試驗）沒有顯示遺傳毒性的證據(Heywood et al., 1987)。[2]
- 光毒性：含有 0.3%卵磷脂（65%卵磷脂溶液）的粉底在人類受試者中不是光敏劑。在移除第 1 個、第 4 個、第 7 個和第 10 個誘導貼片和激發貼片後，受試者在 12 英寸處暴露於紫外線光源（360 nm 峰值輸出）下 1 分鐘。光照後 48 小時測定光敏感反應，顯示卵磷脂和氫化卵磷脂（Hydrogenated Lecithin, 在凡士林中的含量均為 15%）在人類受試者中沒有光毒性或光敏感性。[1]
- 人體案例報導：一名有哮喘和花生過敏史的 3 歲男孩因上呼吸道感染後出現哮喘而接受治療。在使用異丙托溴銨吸入器(ipratropium bromide inhaler)2 次吸入中的第二次後，他在 1 小時內出現呼吸窘迫和全身性蕁麻疹。所有症狀在停藥後 48 小時內消退。大豆卵磷脂是定量吸入器中的一種賦形劑，強烈懷疑會導致不良反應。[1]
- 其他安全性資料：美國食品和藥物管理局將卵磷脂列入其普遍認為安全(Generally Recognized as Safe, GRAS)的物質清單，卵磷脂和氫化卵磷脂的安全性已經過 CIR 專家小組的評估，用於沖洗產品是安全的。CIR 專家小組將卵磷脂和氫化卵磷脂在免洗產品中的使用限制為≤15%的濃度。CIR 專家小組指出，含卵磷脂的脂質體可能會增強其他成分通過皮膚的滲透，並且在配製含有 CIR 專家小組基於缺乏皮膚吸收數據或皮膚吸收問題無法確認安全性的成分之產品時應小心。CIR 專家小組認為，含有卵磷脂和氫化卵磷脂的化粧品和個人護理產品在硝酸鹽(Nitrate)或其他亞硝化劑(other nitrosating agents)的存在下可能會產生亞硝胺(Nitrosoamines)。[3]
- 參考資料：

1. Safety Assessment of Lecithin and Other Phosphoglycerides as Used in Cosmetics. International Journal of Toxicology Vol. 39

(Supplement 2) 5S-25S, CIR, 2020.
2. Safety and efficacy of lecithins for all animal species. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), EFSA Journal 14(8), 4561, 2016.
3. Cosmetics Info 網站：
https://cosmeticsinfo.org/ingredient/lecithin

7. INCI name：Salicylic acid

- 毒物動力學：來自口服給藥人體研究的數據中顯示，肝微粒體酶代謝系統將水楊酸鹽與甘氨酸(Glycine)結合，形成葡萄糖苷酸(Glucuronides)，或將它們氧化成羥基苯甲酸(Hydroxybenzoic acids)。人類口服後，水楊酸在胃中以未結合的形式存在，在胃腸道吸收良好，並迅速分佈在整個細胞外液和大多數組織中。在肝臟和腎臟中發現高濃度（未說明），血漿中 50%~80%的水楊酸與白蛋白和其他蛋白質結合。[1]
- 經皮吸收：體外皮膚滲透數據顯示，水楊酸可通過豬、小鼠和大鼠皮膚經皮吸收。水楊酸的體外經皮吸收使用 Franz 擴散裝置和厚度 500±50 µm 豬皮進行評估。測試液由磷酸鹽緩衝溶液、蒸餾水、牛血清蛋白和慶大黴素(Gentamicin sulfate)組成。將含有水楊酸 (~3% w/v) 的乙醇-水 (1:1) 溶液應用於整個皮膚表面 24 小時。通過 8 次連續膠帶剝離去除處理過的角質層，然後將真皮與表皮分離。使用高效液相色譜分析每種不同活性成分，發現完整皮膚水楊酸（表皮、真皮和測試液）的皮膚吸收率為 34.48%±2.56 (n = 6)，總回收率為 99.28%±4.31。兔子（水楊酸 Salicylic acid、水楊酸鈉 Sodium salicylate 和水楊酸三乙醇胺 TEA Salicylate）、天竺鼠（水楊酸）、大鼠（水楊酸甲酯 Methyl salicylate、水楊酸和水楊酸三乙醇胺）、狗（水楊酸三乙醇胺）、豬（水楊酸三乙醇胺）和猴子（水楊酸）的體內經皮吸收數據，顯示以下經皮吸收模式：滲透率與施用濃度成正比，吸收取決於載體（例如，乙醇>水），與正常皮膚相比，受損皮膚的吸收更大，大約 10%的水楊酸鹽可留在皮膚中。[1] 鑑於不同研究報告的皮膚滲透值的高度可變性，消費者安全科學委員會(Scientific Committee on Consumer Safety, SCCS)評估水楊酸的皮膚吸收率為 60%。[2]

- 急性毒性：當大鼠皮膚接觸水楊酸丁辛酯(Butyloctyl salicylate)、水楊酸甲酯(Methyl salicylate)、水楊酸和水楊酸十三烷基酯(Tridecyl salicylate)時，研究顯示急性經皮 LD_{50s} >2 g/kg。[1] 大鼠口服水楊酸的 LD_{50} 為 400~3700 mg/kg。大鼠口服含有高達 2%水楊酸製劑的 LD_{50} 為 10~20 g/kg，相當於純物質的 200~400 mg/kg bw。在人類中，水楊酸鈉(Sodium salicylate)或阿司匹靈的口服致死劑量在成人中估計為 20~ 30g，但在一個案例中攝入更高的量（為 130 g 阿司匹靈）並沒有導致致命後果(Goodman & Gilman，2006)。3 歲以下的兒童對水楊酸鹽的敏感性高於成人。[2]
- 重複劑量毒性：在最高劑量為 120 mg/kg bw/day 的水楊酸製劑下，在兔子身上進行的亞慢性皮膚毒性研究未發現全身毒性，皮膚刺激是主要的觀察結果。在大鼠中進行的慢性口服毒性研究，在 200 天內以 200 mg/kg bw/day 的濃度服用乙醯水楊酸(Acetylsalicylic acid)，與該劑量濃度的對照組相比，沒有顯著的毒性作用。在人類中，當在 12~24 小時內以單劑量或分劑量口服給予 10 g 或更多水楊酸鹽(Salicylates)時，顯現毒性作用。在人類中，通過皮膚途徑引起的嚴重水楊酸中毒通常與皮膚的疾病狀態有關，這種疾病因身體大面積多次使用而加劇。將水楊酸應用於大面積區域，尤其是兒童，可能會因高劑量的皮膚吸收而產生毒性風險(Galea & Goel, 1989; Chiaretti et al., 1997)。[2]
- 皮膚刺激性：將大約 0.5g 水楊酸測試物質塗抹在 1 隻雄性及 2 隻雌性紐西蘭白兔 6.25cm^2的面積上並用 0.5 ml 純淨水潤濕，半封閉地施加到測試部位 4 小時。在貼片去除後 1、24、48 和 72 小時以及暴露後 7、10 和 14 天檢查皮膚。在試驗期間沒有觀察到死亡和全身毒性的臨床跡象，在任何動物的施用部位均未引起任何皮膚反應，研究結論是水楊酸不會刺激兔子皮膚。[2]
- 眼睛刺激性：使用類似於 Draize Test（崔氏試驗/兔子點眼試驗）的方法評估水楊酸的主要眼部刺激潛力。在這項研究中，水楊酸會引起嚴重的眼睛刺激，角膜、虹膜和結膜的平均評分在 24 小時、48 小時和 72 小時分別為 51.5、40.3 和 38.7。此外，在 Draize Test 眼睛刺激試驗文獻中顯示水楊酸引起的嚴重刺激在施用後 21 天內並沒有恢復，角膜和結膜的 Draize 評分分別為 54.1 和 10.3。[2]
- 皮膚致敏性：用含有高達 2%水楊酸的製劑進行的人體反覆刺激皮膚斑貼試驗結果證實，局部使用不會引起皮膚過敏。水楊酸不是已

知的致敏劑。[2]

- 生殖毒性：消費者安全科學委員會(SCCS)認為水楊酸不具生殖毒性。[2]
- 遺傳毒性：在化粧品和非食品科學委員會(SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS, SCCNFP)進行的風險評估中，計算水楊酸 MoS 時參考的 NOAEL 為 75 mg/kg bw/day，該值源自對水楊酸鈉、乙醯水楊酸、水楊酸甲酯或水楊酸的幾項大鼠口服致畸性研究。根據測試程序，乙醯水楊酸或水楊酸在懷孕期間的不同時間點（例如：妊娠第 8 至 14 天、妊娠第 9 和第 11 天，或妊娠第 7 至 17 天），給予大鼠每日口服劑量 75~500 mg/kg。結果顯示高達 75 mg/kg bw/day 的水楊酸既沒有致畸性也沒有胚胎毒性，超過該劑量觀察到胎兒畸形（骨骼畸形、唇裂）、再吸收和產期死亡。此外，考慮到有關人體經皮吸收局部使用水楊酸之所有可用的體外和體內數據，選擇 50%皮膚吸收值，這也是消費者安全科學委員會(SCCS)提出的默認吸收值。[1、2]
- 致突變性：在 OECD 476 研究中，結果顯示水楊酸不會誘導突變。在 OECD 473 等研究中，水楊酸也不會導致染色體畸變。[2]
- 致癌性：根據遺傳毒性陰性結果和現有致癌性的一些證據，消費者安全科學委員會(SCCS)認為水楊酸不太可能是致癌物。[2]
- 光毒性：儘管消費者安全科學委員會(SCCS)職權範圍內化粧品的風險評估是基於成分的評估而不是化粧品配方的評估，但 SCCS 已經審查使用商業化配方（可能是化粧品）的光毒性研究的測試結果。SCCS 認為，根據研究顯示（人類和小鼠），水楊酸不具有光刺激性、光敏感性或光致癌性。[2]
- 其他安全性資料：根據 CIR 專家小組的評估，水楊酸及其鹽類和酯類（包括水楊酸三乙醇胺 TEA-salicylate）的安全性已由 CIR 專家小組多次評估。然而，根據 CIR 標準程序，使用水楊酸三乙醇胺作為防曬成分並未納入審查範圍（CIR 不審查非處方藥中的活性成分）。2003 年，CIR 專家小組評估了科學數據並得出結論，水楊酸三乙醇胺和其他水楊酸鹽在避免皮膚刺激時配製使用是安全的，配製時可避免增加皮膚對陽光的敏感性，或者，當預計會增加光敏感性時，可增加使用說明需做日常防曬。2019 年，CIR 專家小組進行重新評估，根據所有可用科學數據，CIR 專家小組得出結論，當配製為無刺激性時，水楊酸和 17 種水楊酸鹽成分（包括水楊酸三乙醇胺 TEA-salicylate/水楊酸三甲苯 Trolamine salicylate）在目前化粧品使用濃

度中是安全的。[3]

◆ 參考資料：

1. Amended Safety Assessment of Salicylic Acid and Salicylates as Used in Cosmetics, CIR, 2019.
2. SCCS OPINION on salicylic acid (CAS 69-72-7) Submission I, 2019.
3. Cosmetics Info 網站：https://www.cosmeticsinfo.org/ingredients/salicylic-acid/

8. INCI name：Triethanolamine

◆ 經皮吸收：在體外使用人皮膚樣本進行三乙醇胺(Triethanolamine)水包油 (o/w) 乳液皮膚吸收研究，使用 1%三乙醇胺和 5%硬脂酸(Stearic acid)以及使用 5%三乙醇胺和 10.5%硬脂酸製備乳液，這些乳液的 pH 值分別為 8.0 和 8.2。因為含有三乙醇胺市售乳液的 pH 值為 7.0，因此還配製 pH 值為 7.0 的乳液，作為測試樣品以 3 mg/cm^2 的濃度施用於皮膚 24 小時，暴露皮膚的面積為 0.64cm^2。及使用 pH 值為 8 的乳液在 24 小時測量滲透和吸收，使用 pH 值為 7.0 的乳液在 24 和 72 小時測量滲透和吸收。24 小時皮膚樣品以膠帶剝離，而 72 小時樣品沒有。使用 pH 值為 8 的乳液，1%和 5%三乙醇胺乳液之間的滲透率沒有統計學上的顯著差異。使用 pH 值為 7 且三乙醇胺濃度為 1%的乳液，在比較 24 小時和 72 小時數值時，觀察到的滲透率沒有統計學上的顯著差異。使用 5%乳液、pH 7 的三乙醇胺總回收率存在統計學顯著差異，24 小時的回收率低於 72 小時的回收率。在小鼠體內[^{14}C]丙酮中的三乙醇胺被迅速吸收，並且吸收隨著劑量的增加而增加。大多數放射性物質通過尿液排出，72 小時內排出 48%~56%，主要以未改變的三乙醇胺形式排出。與小鼠相比，三乙醇胺在大鼠中被吸收得更慢且更不廣泛。在大鼠中，19% ~28% 的劑量在 72 小時內被吸收，13%~24%的劑量在尿液中回收，主要是未改變的三乙醇胺。在對大鼠進行的口服給藥研究中，三乙醇胺在胃腸道中迅速吸收，大部分以未改變的三乙醇胺形式排出體外。[1]

◆ 急性毒性：使用 6 隻兔子為一組測試三乙醇胺的皮膚急性毒性。在 24 小時封閉貼片下，將 91.8%和 88.1%未稀釋三乙醇胺施用於 3 隻兔子完整和磨損的皮膚，實際三乙醇胺暴露量為 2 g/kg，沒有動物

死亡，但在 24 小時內發現了輕度紅斑和水腫。使用天竺鼠和大鼠測試三乙醇胺的口服急性毒性。在天竺鼠中，未稀釋的三乙醇胺 LD_{50} 為 8 g/kg，而阿拉伯樹膠溶液中三乙醇胺的 LD_{50} 為 1.4 ~7.0 g/kg。大鼠未稀釋三乙醇胺的口服 LD_{50} 範圍為 4.19 ~ 11.26 g/kg。[1]

- 重複劑量毒性：正如最初 CIR 專家小組對三乙醇胺安全性評估所述，在 10 隻天竺鼠每天(5 天/週)施用三乙醇胺 8 g/kg，進行封閉貼片(closed-patch)連續暴露試驗中之毒性顯示，所有天竺鼠在第 17 次試驗時死亡，且觀察到腎上腺、肺、肝和腎損害。在一項為期 13 週的研究中，將含有 0.1% ~0.15%或 1.5%三乙醇胺的染髮劑配方以 1 mg/kg 的劑量塗抹在 12 隻兔子的背部，持續 1 小時，每週兩次。一半動物的試驗部位皮膚損傷，沒有觀察到全身毒性，也沒有組織形態學毒性證據。在一項為期 6 個月的研究中，對大鼠尾部施用三乙醇胺 1 小時/天(5 天/週)，6.5%的三乙醇胺溶液未觀察到毒性作用。然而，使用 13%的三乙醇胺溶液，肝臟和中樞神經系統功能發生變化。將大鼠的飲用水添加 1.4 mg/L 三乙醇胺，經皮給藥 13%三乙醇胺沒有增加毒性作用。在為期 2 週的研究中，將未稀釋的三乙醇胺（純度未說明）經皮施用於 B6C3F1 小鼠和 F344 大鼠，每週 5 天。小鼠的三乙醇胺施用劑量濃度為 0.21、0.43、0.84、1.69 和 3.37 g/kg，大鼠的三乙醇胺施用劑量濃度為 0.14、0.28、0.56、1.13 和 2.25 g/kg，施用部位慢性壞死性皮膚炎在大鼠中發生的頻率和嚴重程度高於小鼠，兩種物種均未檢測到腎臟或肝臟病變。[1] 根據 OECD 411 進行鼠真皮亞慢性毒性試驗推估 NOAEL：250 mg/kg bw/day。[3]
- 生殖/發育毒性：在妊娠第 1、4、7、10、13、16 和 19 天，將含有 0.1%~0.15%或 1.5%三乙醇胺的染髮劑局部施用於 20 隻妊娠大鼠的剃光皮膚，在懷孕第 20 天時，沒有觀察到對發育影響。將 0.5 g/kg 丙酮（純度未說明）的三乙醇胺經皮塗在雄性和雌性 F344 大鼠背部的皮膚上，在交配前 10 週，每天施用 1.8 mL/kg，並通過妊娠和哺乳，未觀察到對交配或生育力或後代生長或存活的影響。瑞士 CD-1 小鼠每天服用 2 g/kg 三乙醇胺，體積為 3.6 mL/kg，沒有觀察到不利的影響。[1]
- 皮膚刺激性：在 250 至 2000 mg/kg bw 的三乙醇胺丙酮溶液或淨重 4000 mg/kg bw 三乙醇胺，在最高劑量組觀察到皮膚刺激，腎臟和肝臟重量隨著劑量增加而增加。在大鼠中，將 125~1000 mg/kg bw 的三乙醇胺丙酮溶液或 2000 mg/kg bw 的三乙醇胺施用於大鼠 13

週，在施用部位觀察到刺激性反應。[1]

- 致敏性：三乙醇胺對動物和人類都可能是一種皮膚刺激物，但尚未證明它是一種致敏劑。[1]
- 致突變性/基因毒性：在代謝激活的 Ames 試驗、基因轉化試驗、基因重組鑑定法(rec-assay)、代謝激活的姐妹染色單體交換試驗、染色體畸變試驗和細胞轉化試驗中，三乙醇胺的基因毒性皆為陰性。[1]
- 致癌性：在為期 2 年的皮膚致癌性研究中，雄性和雌性小鼠的三乙醇胺劑量濃度分別高達 1000 和 2000 mg/kg bw/day，雄性和雌性大鼠的三乙醇胺劑量濃度分別高達 125 和 250 mg/ bw/day。得出的結論是，基於肝血管肉瘤的發生，產生三乙醇胺可能導致雄性小鼠致癌的證據，基於雌性小鼠肝細胞腺瘤發病率增加，提供致癌活性的一些證據，基於雄性大鼠腎小管細胞腺瘤的發病率邊際增加，提供可能致癌之證據，並沒有對雌性大鼠觀察到致癌性的證據。根據初步數據，推測三乙醇胺可能通過膽鹼耗竭模式導致小鼠肝臟腫瘤。[1]
- 其他安全性資料：根據 CIR 專家小組已多次評估三乙醇胺(Triethanolamine)、二乙醇胺(Diethanolamine)和乙醇胺(Ethanolamine)的安全性。1983 年，CIR 專家小組評估了科學數據並得出結論，三乙醇胺、二乙醇胺和乙醇胺可安全用於不連續、短暫使用，然後從皮膚表面徹底沖洗乾淨之化粧品和個人護理產品，在長期與皮膚接觸的產品中，三乙醇胺和二乙醇胺的濃度不應超過 5%，乙醇胺應僅用於沖洗產品。三乙醇胺和二乙醇胺不應用於含有 N-亞硝化劑(N-nitrosating agent)的產品中，以防止形成可能致癌的亞硝胺(Nitrosamines)。[2]
- 參考資料：

1. Safety Assessment of Triethanolamine and Triethanolamine-Containing Ingredients as Used in Cosmetics. International Journal of Toxicology 32 (Supplement 1) 59S-83S, CIR, 2013.
2. Cosmetics Info 網站：https://cosmeticsinfo.org/ingredient/triethanolamine
3. Triethanolamin EC-Safety Data Sheet, 2019.

9. INCI name：Methylparaben

- 經皮吸收：測試濃度介於 0.1%-2%，Methylparaben 對羥基苯甲酸甲酯、對羥基苯甲酸丙酯和對羥基苯甲酸丁酯在人類屍體皮膚(0.37-0.91 cm/h×10^{-4})和小鼠皮膚(1.17-1.76 cm/h×10^{-4})中的滲透係數估計值相似。[1]
- 急性毒性：大鼠急性口服毒性 LD_{50} 大於 5600 mg/kg，在已發表文獻中沒有新的口服或皮膚急性毒性研究。[1,2] 小鼠皮下注射對羥基苯甲酸甲酯，劑量大於 165 mg/kg 會暫時引起疲勞、失調、和呼吸窘迫，急性致死皮下劑量大於 333 mg/kg，而大鼠皮下注射毒性大於 500 mg/kg bw。[1,2]
- 皮膚刺激性：未稀釋的 Methylparaben 對羥基苯甲酸甲酯以 Draize 測試，九隻兔子將 0.1 mL 的對羥基苯甲酸酯塗在剃毛之皮膚上並覆蓋 24 小時，最終的主要刺激指數為 0.67，顯示對皮膚有輕微刺激性。[1]
- 眼睛刺激性：將 0.1mL 0.20%的對羥基苯甲酸甲酯滴入兔眼，在此測試濃度下，對羥基苯甲酸甲酯誘導輕度短暫性結膜充血。在關於刺激性的調查各種眼科藥物成分，0.1%至 0.2%對羥基苯甲酸甲酯在等滲溶液中滴注到眼睛中不會引起兔子和天竺鼠的眼睛刺激性。[2]
- 皮膚致敏性：對羥基苯甲酸甲酯、對羥基苯甲酸乙酯、對羥基苯甲酸丙酯和對羥基苯甲酸丁酯(0.1％在生理鹽水中)皮下注射至未指定數量的天竺鼠，每週 3 次，共 3 週(10 次注射)。結果顯示對羥基苯甲酸酯未誘導任何過敏反應。含有 0.1%至 0.8%的一種或兩種對羥基苯甲酸酯的產品配方(包括對羥基苯甲酸甲酯，對羥基苯甲酸乙酯，對羥基苯甲酸丙酯和對羥基苯甲酸丁酯)的皮膚配方進行皮膚刺激和致敏測試，沒有證據顯示這些成分的刺激性或致敏性。[2,3]
- 重複給藥毒性：口服慢性毒性每劑量各 24 隻雄性和雌性大鼠餵食含有 0、2 或 8%的對羥基苯甲酸甲酯 96 週，試驗組動物攝入量分別為 1050 mg/kg bw 及 5500 mg/kg bw， NOAEL 為 5500 mg/kg bw/day。[1,2,3]
- 致突變性/遺傳毒性：對羥基苯甲酸甲酯確實在中國倉鼠卵巢細胞試驗中增加了染色體畸變。[1`2]
- 致癌性：當在小鼠或大鼠皮下注射或在大鼠陰道內給藥時，對羥基苯甲酸甲酯無致癌性。[1`2]

- 生殖毒性：非生殖毒性物質。小鼠的飲食添加 0.1%或 1.0%的對羥基苯甲酸甲酯的體內研究報告顯示沒有精子毒性作用。在暴露於 1,000 ppm 或 10,000 ppm 飲食 8 週的大鼠中，對羥基苯甲酸甲酯與異常精子發生率顯著升高有關，4% ~ 5%的精子中大部分為無頭精子，對照組則為 2.3%，荷爾蒙濃度大致並無變化；研究結果顯示未觀察到不良反應的濃度是測試最高濃度 10,000 ppm，對應於對羥基苯甲酸甲酯的 NOAEL 約為 1,140 mg/kg bw/day。[1]
- 毒物代謝動力學：大鼠的肝微粒體對於對羥基苯甲酸酯類的活性最高，其次是小腸和肺微粒體。其中對羥基苯甲酸丁酯被肝微粒體最有效地水解，而對具有較短和較長烷基側鏈的對羥基苯甲酸酯則顯示出較低的水解活性。相反於大鼠小腸微粒體對較長側鏈的對羥基苯甲酸酯表現出相對較高的活性，人肝微粒體對於對羥基苯甲酸酯的水解活性最高，其活性隨側鍊長度的增加而降低。人小腸微粒體的特異性模式與大鼠小腸微粒體相似。[1,2]
- 光毒性：對含有 0.1%~0.8%的對羥基苯甲酸甲酯、對羥基苯甲酸丙酯和/或對羥基苯甲酸丁酯的產品配方進行光致敏性和光毒性測試，沒有發現明顯的光反應性證據。[2]
- 人體數據：對羥基苯甲酸酯施於 50 名受試者背部，其中 5、7、10、12 和 15%對羥基苯甲酸甲酯在丙二醇中。每天施用 5 天後被移除，並對施測部位評分。濃度為 5%的對羥基苯甲酸甲酯不會產生刺激，而較高的濃度會產生一些皮膚刺激。另一 50 位受試者的人類反覆刺激斑貼試驗，結果並無皮膚致敏反應。[3,4]
- 參考資料：

1. Amended Safety Assessment of Parabens as Used in Cosmetics. International Journal of Toxicology, Vol. 39 (Supplement 1) 5S-97S, CIR, 2020.
2. Safety Assessment of parabens as Used in Cosmetics, CIR, 2018.
3. Final Amended Report on the Safety Assessment of Methylparaben, Ethylparaben, Propylparaben, Isopropylparaben, Butylparaben, Isobutylparaben, and Benzylparaben as used in Cosmetic Products. International Journalof Toxicology, Vol. 27 (Supplement 4) 1-82, 2008.

10. INCI name：Tocopherol

- 毒物動力學：對口服生育酚(Tocopherols)和生育三烯酚(Tocotrienols)的分佈進行了大量研究，研究顯示生育酚幾乎分佈於體內所有組織，其分佈和代謝因組織而異。α-生育酚是人體和動物組織中維生素 E 的主要形式，具有最高的口服生物利用度，而 D-α-生育酚（天然維生素 E）的全身利用度大約是合成生育酚(all-*rac*-tocopherol)的兩倍。α-生育酚在運輸到體內系統方面的競爭力超過α-生育三烯酚。口服生育酚和生育三烯酚分佈於皮膚和脂肪組織。在人體評估生育酚補充劑的代謝，兩名男性受試者在 0 小時服用 6 粒富含γ-生育酚的膳食補充劑軟膠囊，並在 10 小時服用 6 粒以上的軟膠囊。每個軟膠囊含有 200 mg β-生育酚、78 mg δ-生育酚、133 mg α-生育酚和 2 mg 生育三烯酚。在 0、12、24 和 48 小時收集糞便和尿液樣本，並在 0 和 12 小時收集血液樣本。在 24 小時後，在人類糞便樣品中發現側鏈降解產物，並且代謝物濃度隨著時間的推移而增加。 在 24 小時時，γ-生育酚衍生的代謝物比δ-和α-衍生的代謝物更顯著。尿液中發現的主要代謝物是羧乙基羥色胺 (Carboxyethyl hydroxychromans) 和羧甲基丁基羥色胺 (Carboxymethylbutyl hydroxychromans)[1]
- 經皮吸收：向雌性無毛 SKH-1 小鼠背部皮膚施用 5 mg/cm^2 α-生育酚 24 小時，導致表皮中α-生育酚增加 62 倍，真皮增加 22 倍。[1]
- 急性毒性：在 GLP 實驗室，根據 OECD 203 虹鱒魚(*Oncorhynchus mykiss*(reported as *Salmo gairdneri*))評估魚的結構異構體 DL-α-生育酚(CAS: 10191-41-0)急性毒性數據，暴露 96 小時後，LC_0/LC_{50} 被確定為> 10 mg/L。在 5 隻雌性和 5 隻雄性紐西蘭白兔研究急性皮膚毒性。給藥前對 3 隻雄性和 2 隻雌性的暴露部位使用 22 號一次性皮下注射針尖穿過角質層的小切口造成皮膚擦傷，這些擦傷其深度不足以干擾真皮或導致出血，其餘 2 隻雄兔和 3 隻雌兔的皮膚完好無損。在第 14 天發現 1 隻動物死亡，一些動物表現出活動性下降、食慾不振、流鼻涕和腹瀉，3 隻動物表現出體重減輕。兔子測試項目的急性經皮 LD_{50} 估計> 5000 mg/kg bw。[2]
- 重複劑量毒性：一項對大鼠混合生育酚磷酸酯(Tocopheryl Phosphate)的亞慢性口服毒性研究報告，雄性和雌性大鼠的 NOAEL 值分別相當於 587 和 643 mg /kg bw/day (Gianello et al., 2007)。美

國食品和營養委員會(Food and Nutrition Board, FNB)得出結論，來自幾項大型人類干預試驗和其他臨床試驗的可用數據（劑量反應關係）不足以確定α-生育酚的 NOAEL。專家組使用動物數據顯示 LOAEL 為 500 mg /kg bw/day，以異常出血為關鍵效應(DRI, 2011; ERNA [online])。[4]

- 皮膚致敏性：DL-α-生育酚在天竺鼠最大化試驗中呈現中度致敏，在局部淋巴結檢測 (Local Lymph Node Assay, LLNA)中被歸類為具有中度致敏潛力。在 1998 年至 2007 年梅奧診所對 1,814 名患者進行了臨床斑貼試驗，11 例患者對凡士林中的生育酚（濃度為 10%或未規定）有陽性反應，1 例對未稀釋的生育酚有反應，陽性反應率為 0.66%。在 2005 年至 2006 年間由北美接觸性皮膚炎協會 (North American Contact Dermatitis Group, NACDG)對 4,454 名患者進行的測試中，未稀釋的 DL-α-生育酚的斑貼試驗陽性反應率為 0.7%。在 NACDG 測試(NACDG patch testing)對至少 1 種與防曬劑來源相關 NACDG 篩查過敏原有過敏反應的患者中（2001-2010 年 NACDG 進行斑貼試驗的所有患者為 0.52%），DL-α-生育酚是最常見的與防曬劑來源相關的非活性成分過敏原，124 名患者中有 6 名(4.8%)對生育酚有反應。[1]
- 遺傳毒性：根據歐洲化學品管理局(The European Chemicals Agency, ECHA)彙整數據中，生育酚在哺乳動物細胞試驗中沒有遺傳毒性。D-γ-生育酚(純度 92.6%)的遺傳毒性潛力在中國倉鼠卵巢 (Chinese Hamster Ovary, CHO) 細胞試驗中進行了評估，暴露於 2.9 和 14.6 mg/mL（分別為 6.8 和 34 mM）D-γ-生育酚 5 小時，結果顯示沒有代謝激活性。[1]
- 光毒性：根據 CIR 專家小組在對 11 名受試者進行的一項研究中，結果顯示在輻射前 24 小時使用 0.2 mL 生育酚乙酸酯(DL-α-tocopheryl acetate)進行封閉斑貼試驗下沒有光毒性產生。[1]
- 致癌性：UVB 照射 10 週後，用 5 mg D-α生育酚局部處理 SKH-1 小鼠 15 週，與僅暴露於載體的小鼠相比，雌性小鼠的腫瘤多發性有增加的趨勢。與對照組相比，在用生育酚處理後觀察到腫瘤負荷增加但未達統計顯著差異，然而，服用生育酚的動物的惡性腫瘤較少。在腫瘤促進研究中觀察到不同的結果，較高劑量生育酚增加了腫瘤的多樣性，並且在 98 天後比在 153 天後增加更多。[1]
- 參考資料：

1. Safety Assessment of Tocopherols and Tocotrienols as Used in Cosmetics. International Journal of Toxicology, Vol. 37 (Supplement 2) 61S-94S, CIR, 2018.
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4. DRI (Dietary Reference Intake for vitamin E). Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes: Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academy Press, 2000. http://ods.od.nih.gov/pdf/factsheets/vitamine.pdf ; see also: http://www.ianrpubs.unl.edu/pages/publicationD.jsp?publicationId=295

(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試驗安定性試驗。

產品名稱	肌膚調理凝膠			
包裝材質	HDPE			
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	不流動膠體	不流動膠體	不流動膠體	不流動膠體
顏色	白色不透明	白色不透明	白色不透明	白色不透明
氣味	無特殊氣味	無特殊氣味	無特殊氣味	無特殊氣味
pH	4.32	4.46	4.38	4.65
黏度	17823 mPa·s	16964 mPa·s	16833 mPa·s	17028 mPa·s
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	肌膚調理凝膠		
產品批號	IT21080B		
產品製造日期	2021.08.02		
包裝材質	HDPE	試驗日期	110.08.09
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 公布建議檢驗方法-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

樣品名稱 (Sample Name)	肌膚調理凝膠				
測試日期(Date Tested): 110.07.01~110.08.05					
試驗參考方法(Method Code): ISO 11930:2019					
測試菌種 (Organism)					
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	8.8×10^5	9.4×10^5	8.2×10^5	9.7×10^4	8.3×10^4
第 7 天	<10	<10	<10	2.4×10^2	1.9×10^3
第 14 天	<10	<10	<10	<10	2.6×10^2
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

肌膚調理凝膠相關功能性測定，依產品宣稱之功能提供相關佐證資料。

(15) 與產品接觸之包裝材質資料

包裝材料	材質	產品淨重
肌膚調理凝膠-瓶身	HDPE	30 g
肌膚調理凝膠-瓶蓋	HDPE	30 g

III. 安全評估資料

(16) 產品安全資料

肌膚調理凝膠每日皮膚暴露量計算

參考 2021 年 3 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 11 版(SCCS/1628/21)，並依用途、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	臉部皮膚
接觸種類	駐留產品
每日使用頻率	2/day
肌膚調理凝膠使用表面積(cm^2)	565
肌膚調理凝膠駐留因子	1

每日皮膚暴露量($E_{product}$)

對於此肌膚調理凝膠，參考 2021 年 3 月發布之 SCCS 化粧品成分測試及其安全性評估指引第 11 版(SCCS/1628/21)表 3A，查表得知每日皮膚暴露量：

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)*
Face cream	1.54	24.14	1.00	**1.54**	**24.14**

在 MoS 計算中使用的每日皮膚暴露量為 24.14 mg/kg bw/day。

備註: 此產品雖屬面部局部使用，但以保守嚴謹之條件進行評估，故以全臉使用方式進行安全評估，並不表示建議消費者依此用量使用。

肌膚調理凝膠各成分 MoS 值計算

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

SED= Eproduct (每日皮膚暴露量)×C/100(配方百分比)×DAp/100(皮膚吸收率)

*M*oS= PODsys/*S*ED

SED (mg /kg bw/day)為全身暴露劑量；Eproduct (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；PODsys 一般常用 NOAEL 估算。

SCCS 化粧品成分測試及其安全性評估指引第 11 版 (SCCS/1628/21) 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 天研究確認明確的每日使用的劑量反應點(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 DAp(%)	NOAEL (mg /kg bw/day)	SED (mg /kg bw/day)	MoS
Aqua	76.4	-	-	-	>100
Alcohol	10.0	100	1200	2.4140	497
Propylene Glycol	5.0	10	40	0.1207	331
Hamamelis Virginiana (Witch Hazel) Leaf Extract	3.0	100	93	0.7242	128
Glycyrrhiza Uralensis (Licorice) Root Extract	2.5	100	692	0.6035	1147
Sodium Acrylates Copolymer	2.0	100	115	0.4828	238
Lecithin	2.0	100	75	0.4828	155
Salicylic acid	1.5	50	37.5	0.1811	207
Triethanolamine	1.0	100	250	0.2414	1036
Methyl Paraben	0.4	100	2750	0.0966	28468
Tocopherol	0.2	100	293.5	0.0483	6077

INCI name	NOAEL 校正說明
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。
Propylene Glycol	以貓為實驗動物，進行90天口服實驗報告評估NOAEL = 80 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，將80*50% =40 mg/kg bw/day。
Hamamelis Virginiana (Witch Hazel) Leaf Extract	Sprague Dawley大鼠施用含有金縷梅乙醇萃取物持續28天，推估 NOAEL>300 mg/kg bw/day，考慮試驗天數(28天)之不確定因子，將 300*28/90 =93 mg/kg bw/day。
Glycyrrhiza Uralensis (Licorice) Root Extract	大鼠(n = 15；6週齡)口服烏拉爾甘草根萃取物持續9週，NOAEL為 >2000 mg/kg bw/day，考慮口服生物可用率50%及試驗天數(9週)之 不確定因子，將2000*50%*9/13=692 mg/kg bw/day。
Sodium Acrylates Copolymer	比格犬口服試驗12週，NOAEL為250 mg/kg bw/day，考慮口服生物 可用率50%及試驗天數(12週)之不確定因子，將250*50%*12/13 =115 mg/kg bw/day。
Lecithin	一項兔子生殖毒性口服研究(未說明天數)顯示NOAEL為150 mg/kg bw/day。考慮口服生物可用率50%之不確定因子，將150*50%=75 mg/kg bw/day。
Salicylic acid	參照SCCS將水楊酸的NOAEL設置為75 mg/kg bw/day作為MoS計算 時參考，該值源自大鼠口服水楊酸的幾項致畸性研究。考慮口服 生物可用率50%之不確定因子，將75*50% =37.5 mg/kg bw/day。
Triethanolamine	根據OECD 411進行鼠真皮亞慢性毒性試驗推估NOAEL：250 mg/kg bw/day，無須校正。
Methyl Paraben	大鼠口服慢性毒性試驗96週得知NOAEL 5500 mg/kg bw/day，考慮 口服生物可用率50%之不確定因子，5500*50% =2750mg/kg bw/day。
Tocopherol	大鼠生育酚磷酸酯(Tocopheryl Phosphate)的亞慢性口服毒性研究 報告， NOAEL值相當於587 mg /kg bw/day，考慮口服生物可用率 50%之不確定因子，587*50% =293.5 mg/kg bw/day。

肌膚調理凝膠安全評估結論

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據以結論，推定肌膚調理凝膠在預期正常合理使用條件下，本產品為可安全使用之產品，不致對人體健康造成傷害。

標籤警語和使用說明

肌膚調理凝膠的包裝材料/標籤上提到了以下警告和使用說明：

使用方式：清潔臉部後，取適量於需要部位均勻塗抹。

使用注意事項：本產品含 Salicylic acid 不得使用於三歲以下孩童。皮膚有傷口時請勿使用。使用後若有不適請立即停止使用，請以大量清水沖洗，並至皮膚科醫生診斷治療。如曾有對阿斯匹靈過敏的藥物史，則不建議使用。內含 Salicylic acid，已依我國特定用途成分名稱及使用限制表應刊載之注意事項進行標示。

此產品曾有消費者反應發生皮膚刺激性之現象，為避免類似之不良反應發生，建議於產品上加註說明：

1. 使用時請避開眼周黏膜處。
2. 如有使用不適之情況發生時，請立即停用及就醫。

安全評估理由

此肌膚調理凝膠的安全性評估基於每種成分的毒理學特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. 本產品所含之 Salicylic acid 含量為 1.5% (限量 0.2~2%)未超過特定用途成分化粧品名稱及使用限制表之規定。
3. 根據本產品「肌膚調理凝膠」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「肌膚調理凝膠」產品配方具有足夠安定性及微生物安全性。
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通過 ISO 11930:2019 Criteria A 之標準。

Table B.1 — Evaluation criteria

Log reduction values ($R_x = \lg N_0 - \lg N_x$) required[a]								
Micro organisms	Bacteria			*C. albicans*			*A. brasiliensis*	
Sampling time	T7	T14	T28	T7	T14	T28	T14	T28
Criteria A	≥ 3	≥ 3 and NI[b]	≥ 3 and NI	≥ 1	≥ 1 and NI	≥ 1 and NI	≥ 0[c]	≥ 1 and NI
Criteria B	Not performed	> 3	≥ 3 and NI	Not performed	> 1	≥ 1 and NI	> 0	≥ 0 and NI

a In this test, an acceptable range of deviation of 0,5 log is accepted (see 5.7).

b NI: no increase in the count from the previous contact time.

c $R_x = 0$ when $\lg N_0 - \lg N_x$ (no increase from the initial count).

5. 評估包裝材料是合適的且安全的與本產品接觸之包材 HDPE (high-density polyethylene，高密度聚乙烯)，硬度大，且可耐各種腐蝕性液體的侵蝕，耐熱度約 90-110℃，因此常被用於製造塑膠袋、軟片盒、廚具、電池外殼、紙容器表面的 PE 淋膜、及食用油容器等。HDPE 一般無毒性，即使在極高濃度下，也僅對動物產生可逆性的肝臟傷害(如肝脂肪增加)；另外 PE 不會增加罹癌的機會，因此在使用上具有相當的安全性。
6. 根據 SCCS 化粧品成分測試及其安全性評估指引第 11 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，雖然此肌膚調理凝膠實際使用時僅塗抹於臉部局部位置，但為了審慎評估其暴露風險，計算安全邊際值(MoS)時之每日皮膚暴露量仍以全臉部使用方式考量及估算。
7. Sodium Acrylates Copolymer (and) Lecithin 是一複合成分，在此配方列表中未列出其各別添加之比例，故皆以添加最高比例 2.0%進行 SED 計算。
8. 此肌膚調理凝膠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. 目前此產品目前出現一個案發生皮膚刺激性反應，但在立即停用後狀況即消失，建議此個案之消費者可就醫，釐清此不良反應發生狀況。未來如有其他不良影響和嚴重不良影響的相關案例資訊會立即更新，並及時提供給安全資料簽署人員，以重新評估此產品之安全性。

（請簽名並加上日期）

安全資料簽署人員簽名及日期

*請檢附安全資料簽署人員之符合之學歷及資格證明文件

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(亦須包含 Fragrance 內含成分)之品質規格或各成分之檢驗報告(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：Salicylic acid

SAFETY DATA SHEET

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name : Salicylic acid

Product Number :
Brand :

1.2 Other means of identification

2-Hydroxybenzoic acid

1.3 Relevant identified uses of the substance or mixture and uses advised against

Identified uses :

1.4 Details of the supplier of the safety data sheet

Company :

Telephone :
Fax :
E-mail address :

1.5 Emergency telephone

Emergency Phone # :

SECTION 2: Hazards identification

2.1 GHS Classification

Acute toxicity, Oral (Category 4), H302
Serious eye damage/eye irritation (Category 1), H318
Reproductive toxicity (Category 2), H361

2.2 GHS Label elements, including precautionary statements

Pictogram

Signal word: Danger

Hazard statement(s)

H302	Harmful if swallowed.
H318	Causes serious eye damage.
H361	Suspected of damaging fertility or the unborn child.

Precautionary statement(s)

Prevention

P201	Obtain special instructions before use.
P202	Do not handle until all safety precautions have been read and understood.
P264	Wash skin thoroughly after handling.
P270	Do not eat, drink or smoke when using this product.
P280	Wear protective gloves/ protective clothing/ eye protection/ face protection.

Response

P301 + P312 + P330	IF SWALLOWED: Call a POISON CENTER/ doctor if you feel unwell. Rinse mouth.
P305 + P351 + P338 + P310	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/ doctor.
P308 + P313	IF exposed or concerned: Get medical advice/ attention.

Storage

P405	Store locked up.

Disposal

P501	Dispose of contents/ container to an approved waste disposal plant.

2.3 Other hazards - none

SECTION 3: Composition/information on ingredients

Substance / Mixture : Substance

3.1 Substances

Synonyms : 2-Hydroxybenzoic acid

Formula : $C_7H_6O_3$

Molecular weight : 138.12 g/mol

CAS-No. : 69-72-7

EC-No. : 200-712-3

Hazardous ingredients

Component	Classification	Concentration
Salicylic acid		
	Acute Tox. 4; 1; Repr. 2; H302, H318, H361	<= 100 %

For the full text of the H-Statements mentioned in this Section, see Section 16.

SECTION 4: First aid measures

4.1 Description of first-aid measures

General advice
Show this material safety data sheet to the doctor in attendance.

If inhaled
After inhalation: fresh air. Call in physician.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower. Consult a physician.

In case of eye contact
After eye contact: rinse out with plenty of water. Immediately call in ophthalmologist. Remove contact lenses.

If swallowed
After swallowing: immediately make victim drink water (two glasses at most). Consult a physician.

4.2 Most important symptoms and effects, both acute and delayed
The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed
No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

5.2 Special hazards arising from the substance or mixture
Nature of decomposition products not known.
Combustible.
Vapors are heavier than air and may spread along floors.
Forms explosive mixtures with air on intense heating.
Development of hazardous combustion gases or vapours possible in the event of fire.

5.3 Advice for firefighters
Stay in danger area only with self-contained breathing apparatus. Prevent skin contact by keeping a safe distance or by wearing suitable protective clothing.

5.4 Further information
Prevent fire extinguishing water from contaminating surface water or the ground water system.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures
Advice for non-emergency personnel: Avoid inhalation of dusts. Avoid substance contact. Ensure adequate ventilation. Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions
Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up
Cover drains. Collect, bind, and pump off spills. Observe possible material restrictions (see sections 7 and 10). Take up dry. Dispose of properly. Clean up affected area. Avoid generation of dusts.

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
Tightly closed. Dry.

Light sensitive.

Storage class
Storage class (TRGS 510): 13: Non Combustible Solids

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters
Contains no substances with occupational exposure limit values.

8.2 Exposure controls

Appropriate engineering controls
Change contaminated clothing. Preventive skin protection recommended. Wash hands after working with substance.

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU). Tightly fitting safety goggles

Skin protection
Handle with gloves. Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

The selected protective gloves have to satisfy the specifications of Regulation (EU) 2016/425 and the standard EN 374 derived from it.

Full contact
Material: Nitrile rubber
Minimum layer thickness: 0.11 mm

Break through time: 480 min
Material tested:Dermatril® (KCL 740 / Aldrich Z677272, Size M)

Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0.11 mm
Break through time: 480 min
Material tested:Dermatril® (KCL 740 / Aldrich Z677272, Size M)

data source: KCL GmbH, D-36124 Eichenzell, phone +49 (0)6659 87300, e-mail sales@kcl.de, test method: EN374
If used in solution, or mixed with other substances, and under conditions which differ from EN 374, contact the supplier of the EC approved gloves. This recommendation is advisory only and must be evaluated by an industrial hygienist and safety officer familiar with the specific situation of anticipated use by our customers. It should not be construed as offering an approval for any specific use scenario.

Body Protection
protective clothing

Respiratory protection
Where risk assessment shows air-purifying respirators are appropriate use a full-face particle respirator type N100 (US) or type P3 (EN 143) respirator cartridges as a backup to engineering controls. If the respirator is the sole means of protection, use a full-face supplied air respirator. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Control of environmental exposure
Do not let product enter drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Appearance	Form: powder, crystalline Color: white
b)	Odor	odorless
c)	Odor Threshold	Not applicable
d)	pH	2.4 at 20 °C
e)	Melting point/freezing point	Melting point/range: 158 - 161 °C - lit.
f)	Initial boiling point and boiling range	211 °C at 27 hPa 211 °C - lit.
g)	Flash point	157 °C - closed cup
h)	Evaporation rate	No data available
i)	Flammability (solid, gas)	The product is not flammable.
j)	Upper/lower flammability or	Lower explosion limit: 1.1 %(V)

	explosive limits	
k)	Vapor pressure	1 hPa at 114 °C
l)	Vapor density	No data available
m)	Density	1.44 g/cm3 at 20 °C
	Relative density	No data available
n)	Water solubility	No data available
o)	Partition coefficient: n-octanol/water	log Pow: 2.25 at 25 °C - Bioaccumulation is not expected.
p)	Autoignition temperature	No data available
q)	Decomposition temperature	No data available
r)	Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: No data available
s)	Explosive properties	No data available
t)	Oxidizing properties	none

9.2 Other safety information
No data available

SECTION 10: Stability and reactivity

10.1 Reactivity
Forms explosive mixtures with air on intense heating.
A range from approx. 15 Kelvin below the flash point is to be rated as critical.
The following applies in general to flammable organic substances and mixtures: in correspondingly fine distribution, when whirled up a dust explosion potential may generally be assumed.

10.2 Chemical stability
The product is chemically stable under standard ambient conditions (room temperature) .

10.3 Possibility of hazardous reactions
Risk of ignition or formation of inflammable gases or vapours with:
Fluorine
iodine
Violent reactions possible with:
Strong oxidizing agents
iron/iron-containing compounds

10.4 Conditions to avoid
Light.
Strong heating.

10.5 Incompatible materials
No data available

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Rat - male - 891 mg/kg
(OECD Test Guideline 401)
Oral: Behavioral:Muscle weakness.
Inhalation: No data available
LD50 Dermal - Rat - male and female - > 2.000 mg/kg
(OECD Test Guideline 402)

Skin corrosion/irritation
Skin - Rabbit
Result: No skin irritation - 4 h
(OECD Test Guideline 404)

Serious eye damage/eye irritation
Eyes - Rabbit
Result: Risk of serious damage to eyes.
(Draize Test)

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
Test Type: In vitro mammalian cell gene mutation test
Test system: mouse lymphoma cells
Metabolic activation: with and without metabolic activation
Method: OECD Test Guideline 476
Result: negative
Test Type: Chromosome aberration test in vitro
Test system: Chinese hamster ovary cells
Metabolic activation: with and without metabolic activation
Method: OECD Test Guideline 473
Result: negative
Test Type: Ames test
Test system: Escherichia coli/Salmonella typhimurium
Metabolic activation: with and without metabolic activation
Method: OECD Test Guideline 471
Result: negative

Test Type: Chromosome aberration test
Species: Mouse
Cell type: Bone marrow
Application Route: Intraperitoneal
Method: OECD Test Guideline 475
Result: negative

Test Type: sister chromatid exchange assay
Species: Mouse
Cell type: Bone marrow
Application Route: Oral
Method: US-EPA
Result: negative

Carcinogenicity
No data available

Reproductive toxicity
Suspected of damaging the unborn child.

Specific target organ toxicity - single exposure
No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information

Repeated dose toxicity - Rat - male and female - Oral - 2 yr - NOAEL (No observed adverse effect level) - 50 mg/kg
Remarks: (in analogy to similar products)
(ECHA)
The value is given in analogy to the following substances: methyl salicylate

RTECS: VO0525000
Cough, Shortness of breath, Headache, Nausea, Vomiting
Mild chronic salicylate intoxication is termed salicylism. Symptoms include: headache, dizziness, ringing in the ears, difficulty in hearing, dimness of vision, mental confusion, lassitude, drowsiness, sweating, thirst, hyperventilation, nausea, vomiting, and occasionally diarrhea. A more severe degree of salicylate intoxication is characterized by more pronounced CNS disturbances (including generalized convulsions and coma), skin eruptions, and marked alterations in acid-base balance.
To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

SECTION 12: Ecological information

12.1 Toxicity

Toxicity to fish	flow-through test LC50 - Pimephales promelas (fathead minnow) - 1,370 mg/l - 96 h (OECD Test Guideline 203) Remarks: (in analogy to similar products) The value is given in analogy to the following substances: Sodium salicylate
Toxicity to daphnia and other aquatic invertebrates	static test EC50 - Daphnia magna (Water flea) - 870 mg/l - 48 h (OECD Test Guideline 202)
Toxicity to algae	Growth inhibition ErC50 - Desmodesmus subspicatus (green algae) - > 100 mg/l - 72 h (OECD Test Guideline 201)
Toxicity to bacteria	static test EC50 - Pseudomonas putida - 380 mg/l - 16 h Remarks: (ECHA) The value is given in analogy to the following substances: methyl salicylate

12.2 Persistence and degradability

Biodegradability	aerobic - Exposure time 4 d Result: > 90 % - Inherently biodegradable. (Regulation (EC) No. 440/2008, Annex, C.9)

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
PBT/vPvB assessment not available as chemical safety assessment not required/not conducted

12.6 Endocrine disrupting properties
No data available

12.7 Other adverse effects
No data available

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product
Waste material must be disposed of in accordance with the national and local regulations. Leave chemicals in original containers. No mixing with other waste. Handle uncleaned containers like the product itself. See www.retrologistik.com for processes regarding the return of chemicals and containers, or contact us there if you have further questions. The chemical must be disposed or recycled in accordance with Waste Disposal Act. See www.epa.gov.tw for the information of chemical waste disposal companies and their contacts.

SECTION 14: Transport information

14.1 UN number
ADR/RID: - IMDG: - IATA-DGR: -

14.2 UN proper shipping name

ADR/RID:	Not dangerous goods
IMDG:	Not dangerous goods
IATA-DGR:	Not dangerous goods

14.3 Transport hazard class(es)
ADR/RID: - IMDG: - IATA-DGR: -

14.4 Packaging group
ADR/RID: - IMDG: - IATA-DGR: -

14.5 Environmental hazards
ADR/RID: no IMDG Marine pollutant: no IATA-DGR: no

14.6 Special precautions for user

14.7 Incompatible materials

Further information
Not classified as dangerous in the meaning of transport regulations.

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture
No data available

SECTION 16: Other information

Full text of H-Statements referred to under sections 2 and 3.

H302	Harmful if swallowed.
H318	Causes serious eye damage.
H361	Suspected of damaging fertility or the unborn child.

Further information
The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

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Literature references	About detail information, please refer to each section The information contained herein is based on the present state of our knowledge. It characterises the product with regard to the appropriate safety precautions. It does not represent a guarantee of any properties of the product.		
Organization that prepared the SDS	Name:Merck KGaA LS-QH		
	Address/Telephone number:64271 Darmstadt Germany/+49 6151 72-0		
Date that the SDS was prepared	24.11.2021	Print Date	27.01.2022

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：Salicylic acid

SCCS/1601/18
Final Opinion
Corrigendum of 20-21 June 2019

European Commission

Scientific Committee on Consumer Safety

SCCS

OPINION ON

salicylic acid (CAS 69-72-7)
Submission I

Scientific Committees
on Consumer Safety
on Health, Environmental and Emerging Risks

The SCCS adopted the final Opinion
by written procedure on 21 December 2018

Corrigendum of 20-21 June 2019

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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All Declarations of Working Group members are available on the following webpage:
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 10 September until 14 November 2018). Comments received during this time were considered by the SCCS.
For this Opinion, comments received resulted in the following main changes: *sections 3.3.1.1. - 3.3.2.1 - 3.3.6.2. (SCCS comment), 3.3.2.2. (SCCS conclusion), 3.3.10, and 3.4.1. Changes in the discussion part and in the SCCS conclusions have been made accordingly.*
Corrigendum made in the conclusion number 2, only for clarity of SCCS position regarding percentage and coverage of oral products (lipstick).

1. ABSTRACT

The SCCS concludes the following:

1. *In light of the new data provided, does the SCCS still consider Salicylic acid (CAS 69-72-7) safe when used as a preservative in all cosmetic products up to a maximum concentration of 0.5% (acid) considering its current restriction as reported above?*

   The SCCS considers salicylic acid (CAS 69-72-7) safe when used as preservative at a concentration of 0.5 % in cosmetic products considering its current restrictions in place.
   This Opinion is not applicable to any oral product (such as toothpaste and mouthwash) with the exception of lipsticks. Sprayable products that could lead to exposure of the consumer's lung by inhalation are also excluded. The provided information shows that salicylic acid is an eye irritant with the potential to cause serious damage to the eye.

2. *In addition, does the SCCS still consider Salicylic acid (CAS 69-72-7) safe when used for purposes other than inhibiting the development of micro-organisms at a concentration up to 3.0 % for the cosmetic rinse-off hair products and up to 2.0 % for other products considering its current restrictions as reported above?*

   Based on the data provided and available literature, the SCCS considers salicylic acid (CAS 69-72-7) safe when used for purposes other than preservative at a concentration up to 3.0 % for the cosmetic rinse-off hair products and up to 2.0 % for other products, considering its current restrictions in place. However, in body lotion, eye shadow, mascara, eyeliner, lipstick and roll on deodorant applications, salicylic acid is considered safe up to 0.5 %. The SCCS position is that these levels are inclusive of any use of salicylic acid, i.e. should not exceed the stated levels with additional use as a preservative.
   This Opinion is not applicable to any oral product (such as toothpaste and mouthwash) with the exception of lipsticks. Sprayable products that could lead to exposure of the consumer's lung by inhalation are also excluded.

3. *Does the SCCS have any further scientific concerns with regard to the use of Salicylic acid (CAS 69-72-7) in cosmetic products?*

   Salicylic acid is also used as a preservative in food and as a biocide in some consumer products (see section 3.2.3) or in various pharmaceutical formulations such as anti-acne products. As no specific exposure data were made available to SCCS to assess exposure following these non-cosmetic uses, it was not possible to include them in the aggregated exposure scenarios. Therefore, the actual total exposure of the consumer may be higher than exposure from cosmetic products alone.
   The conclusions of this Opinion refer only to Salicylic Acid and should not be applied to other salicylates or salicylic acid salts.

Keywords: SCCS, scientific opinion, salicylic acid, Regulation 1223/2009, CAS 69-72-7, EC 200-712-3, SCCS/1601/18

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on salicylic acid (CAS 69-72-7) - Submission I, SCCS/1601/18, preliminary version of 10 September 2018, final version of 21 December 2018, CORRIGENDUM on 20-21 June 2019

About 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.

They are: the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and 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 all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

Scientific Committee members

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Salicylic acid (CAS 69-72-7) and its salts, as Calcium salicylate, Magnesium salicylate, MEA-salicylate, Sodium salicylate, Potassium salicylate and TEA- salicylate (CAS 824-35-1/ 18917-89-0/ 59866- 70-5/ 54-21-7/ 578- 36-9/ 2174-16-5) are currently listed in Annex V (entry 3) of the Regulation (EC) No. 1223/2009[1] (Cosmetics Regulation) as preservative to be used in all cosmetic products up to a maximum concentration of 0.5% (acid). The following restriction applies: Not to be used for children under 3 years old, except for shampoos.

Salicylic acid (CAS 69-72-7) is also listed in Annex III (entry 98) of the Cosmetics Regulation to be used up to a maximum concentration of 3.0 % for the cosmetic rinse-off hair products and of 2.0 % for other products.
The following restrictions apply:
Not to be used for children under 3 years old, except for shampoos.
For purposes other than inhibiting the development of micro-organisms in the products.
This purpose has to be apparent from the presentation of the product.

The SCCNFP published an opinion on the safety of Salicylic acid (CAS 69-72-7) in June 2002 (SCCNFP/0522/01)[2].

ECHA's Risk Assessment Committee (RAC) adopted its opinion on the harmonised classification for Salicylic acid (CAS 69-72-7) on 10 March 2016, with a proposed classification as CMR2 [3] under Regulation (EC) No. 1272/2008. This proposed classification does not cover the salts of Salicylic acid.[4]

Art. 15 (1) of the Cosmetics Regulation states that '*a substance classified in category 2 may be used in cosmetic products where the substance has been evaluated by the SCCS and found safe for use in cosmetic products. To these ends the Commission shall adopt the necessary measures in accordance with the regulatory procedure with scrutiny referred to in Article 32(3) of this Regulation*'.

In December 2017, Cosmetics Europe transmitted a safety dossier on Salicylic acid (CAS 69-72-7) intended to demonstrate the safety of the ingredient for its current uses and restrictions.

Terms of reference

1. *In light of the new data provided, does the SCCS still consider Salicylic acid (CAS 69-72-7) safe when used as a preservative in all cosmetic products up to a maximum concentration of 0.5% (acid) considering its current restriction as reported above?*

2. *In addition, does the SCCS still consider Salicylic acid (CAS 69-72-7) safe when used for purposes other than inhibiting the development of micro-organisms at a concentration up to 3.0 % for the cosmetic rinse-off hair products and up to 2.0 % for other products considering its current restrictions as reported above?*

3. *Does the SCCS have any further scientific concerns with regard to the use of Salicylic acid (CAS 69-72-7) in cosmetic products?*

[1] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:342:0059:0209:en:PDF
[2] http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out170_en.pdf
[3] Repr. 2; H361d (Suspected of damaging the unborn child) (ECHA 2016)
[4] Harmonized classification of salicylic acid was published in the official journal (L251) on 5 October 2018 (regulation 2018/1480). Salicylic acid is classified as Repr. 2 (H361d Suspected of damaging the unborn child), Acute Tox. 4 (H302 Harmful if swallowed), Eye Dam. 1 (H318 Causes serious eye damage).

3. OPINION

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

Salicylic acid

3.1.1.2 Chemical names

IUPAC: 2-hydroxybenzoic acid

3.1.1.3 Trade names and abbreviations

A. MeSH entry names:

1. 2 Hydroxybenzoic Acid
2. 2-Hydroxybenzoic Acid
3. Acid, 2-Hydroxybenzoic
4. Acid, o-Hydroxybenzoic
5. Acid, ortho-Hydroxybenzoic
6. Acid, Salicylic
7. o Hydroxybenzoic Acid
8. o-Hydroxybenzoic Acid
9. ortho Hydroxybenzoic Acid
10. ortho-Hydroxybenzoic Acid
11. Salicylic acid

B. Depository supplied synonyms can be found at the link provided below.

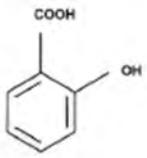
Ref: https://pubchem.ncbi.nlm.nih.gov/compound/338#section=Depositor-Supplied-Synonyms

3.1.1.4 CAS / EC number

CAS 69-72-7/ EC 200-712-3

Ref: Analytical Dossier; PubMed; ECHA, SigmaAldrich

3.1.1.5 Structural formula



3.1.1.6 Empirical formula

$C_7H_6O_3$

3.1.2 Physical form

Form: Crystalline powder Needles
Physical state: solid
Colour: white
Colourless

3.1.3 Molecular weight

138.12 g/mol

3.1.4 Purity, composition and substance codes

Purity: Salicylic acid is incorporated as an ultra-pure ingredient when used in cosmetics, and its typical purity level is 99.7-99.9%, with a minimum purity of 99% and maximum of 100%. Impurities could be phenol and sulphate, which are typically less than 0.02% and 0.04%, respectively.

Table 1. Physicochemical properties (purity) of salicylic acid

Property	Salicylic Acid
Purity	99.7-99.9%

Ref: https://echa.europa.eu/el/substance-information/-/substanceinfo/100.000.648
Novacyl Certificate of analysis

SCCS comment
The analytical methods used for the determination of purity of the test substance should be provided, according to the SCCS Notes of Guidance.

3.1.5 Impurities / accompanying contaminants

Salicylic Acid, Batch B14E099PHA

Characteristic	Unit	Value	Lower Limit	Upper Limit
Chlorides	% wt	< 0.0100	-	0.0100
Melting Range (FP)	°C	160.3	158.0	161.0
Melting Range (IP)	°C	159.9	158.0	161.0
Identification	-	Pass	-	-
Heavy Metals (as Pb)	ppg	< 20	-	20
Loss on Drying (KF)	% wt	0.066	-	0.500
Residue on Ignition	% wt	0.0140	-	0.0500
Sulphates	% wt	< 0.020	-	0.020
Assay	% wt	100.05	99.50	101.00
Related Compounds	% wt	0.0704	-	0.2000
Phenol	% wt	< 0.0010	-	0.0100
Other Impurities (sum)	% wt	< 0.0010	-	0.0500
4-Hydroxybenzoic Acid	% wt	0.0394	-	0.1000
4-Hydroxyisophthalic Acid	% wt	0.0310	-	0.0500
Sum of all Impurities	% wt	0.0704	-	0.2000

Ref: 24. 90916 SALICYLIC ACID%2c USP_COA

SCCS comment
Data on impurities of salicylic acid are provided in the specification sheets. The analytical methods used for the determination of impurities in the test substance along with the results of these studies should be provided, according to the SCCS Notes of Guidance. The SCCS is of the opinion that the method described in European Pharmacopoeia is the method of choice for the impurity testing of Salicylic Acid (EP7, pp2284-2285).

3.1.6 Solubility

In water: 2.24 mg/mL at 25 °C, 2 g/L at 20°C.
Readily soluble in acetone, oil of turpentine, alcohol, ether and benzene.
Solubility (weight percent): carbon tetrachloride 0.262 (25 °C); benzene 0.775 (25 °C); propanol 27.36 (21 °C); absolute ethanol 34.87 (21 °C); acetone 396 (23 °C)

Ref: ChemSpider (Royal Society of Chemistry); Lewis, 1993; Budavari 1989

3.1.7 Partition coefficient (Log P_{ow})

Octanol/water partition coefficient ($logP_{o/w}$)= 2.25

Ref: Sheu et al, 1975; US EPA Chemistry Dashboard

3.1.8 Additional physicochemical specifications

Table 2. Physicochemical properties of salicylic acid,

Property	Salicylic Acid
Molecular Formula	$C_7H_6O_3$
Molecular Weight (g/mol)	138.12
Physical Form	Solid at room temperature
Stability	Stable at room temperature
Boiling point (°C)	211 at 20mmHg; sublimes at 76°C[a]
Melting point (°C)	158-161[a]
pH of saturated aqueous solution	2.4 (saturated aqueous suspension)[b1], 2.4 (at 2 % m/v, aqueous suspension)[b2]
Vapour pressure	at 25°C: 0.000208 hPa[c]
pKa	2.9[d]
Density	1.44 g/cm³ at 20 °C[e]

a. Lewis, 1993
b. 1. Budavari, 1989; 2. 24. 90916 SALICYLIC ACID%2c USP__MSDS
c. ChemSpider (Royal Society of Chemistry)
d. Kamal et al 2005.
e. 24. 90916 SALICYLIC ACID%2c USP__MSDS
NR = not reported, a published value could not be found.

- organoleptic properties (colour, odour, taste if relevant)
- flash point: 157°C (salicylic acid)
- density: 1.443 g/cm² at 20°C (salicylic acid)
- viscosity:/
- refractive index:/

- UV/visible light absorption spectrum: UV max (4 mg percent in ethanol): 210, 234, 303 nm (molar extinction coefficient 8343, 5466, 3591).

Ref: Salicylic Acid Exposure FINAL 5 12 2017; 24. 90916 SALICYLIC ACID%2c USP__MSDS

3.1.9 Homogeneity and Stability

Stability: Salicylic acid gradually discolours in sunlight; when heated to decompose it emits acrid smoke and irritating fumes.

Ref: Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989., p. 1324; Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 3179

3.2 FUNCTION AND USES

3.2.1 Cosmetic product uses as per Cosmetic Products Regulation EC 1223/2009

Salicylic acid is used in cosmetic products as a denaturant, a hair and skin conditioning agent, an exfoliant, an anti-acne cleansing agent, an anti-dandruff agent and a product preservative.
Salicylic acid is currently listed in Annex V (entry 3) of the Cosmetics Regulation (EC) No. 1223/2009 as preservative to be used in all cosmetic products up to a maximum concentration of 0.5% (acid). The following restriction applies: Not to be used for children under 3 years old, except for shampoos.
Salicylic acid is also listed in Annex III (entry 98) of the Cosmetics Regulation to be used up to a maximum concentration of 3.0 % for the cosmetic rinse-off hair products and of 2.0 % for other products. The following restrictions apply: Not to be used for children under 3 years old, except for shampoos. Not to be used for purposes other than inhibiting the development of micro-organisms in the products. This purpose has to be apparent from the presentation of the product.

3.2.2 Cosmetic product uses as per Cosmetics Europe 2017 Survey

According to the survey, the salts of salicylic acid are used as preservatives in all cosmetic products except toothpaste or mouthwash products. Salicylic acid according to the survey is not used at all in mouthwash, toothpaste, eye liner and mascara.

In the submitted dossier, no data is provided to support the use of salicylic acid in sprayable products.

3.2.3 Other uses than cosmetics

Salicylic acid is used (at 15-40%) as a spot-treatment medication to treat warts and callouses because of its keratoplastic properties, and it is also used clinically as a skin peeling agent.

Ref: Arif, 2015

Salicylic acid is used as a preservative in food, as a chemical raw material for the synthesis of dyes and aspirin, and as an antiseptic and antifungal agent by topical application in veterinary medicine. Aspirin is metabolised to salicylic acid in the human body.

Taken from Biocide opinion/ ECHA:

- *The active substance is used in product-type 2 (PT2), ready-to-use product for* disinfection of dishwashing sponges between dishwashing sessions (and therefore prevention of spread of micro-organisms onto other kitchen utensils and surfaces) by non-professional users. Disinfection of sponges is considered as a PT2 use since the sponge itself will not come into contact with food. For the risk assessment the possible exposure via food is taken into account.
- The active substance is used in product-type 3 (PT3), ready-to-use product to disinfect teats of dairy cows in a pre- and/or post-milking application as a dip or spray. The product is intended for agricultural usage by farmers.
- The active substance is used in product-type 4 (PT4) by professional users as a disinfectant for surfaces in the (soft) drinks industry, including breweries, where drinks are prepared, processed and stored.

3.3 TOXICOLOGICAL EVALUATION

The toxicology evaluation is focused on the data available for salicylic acid.

3.3.1 Acute toxicity

3.3.1.1 Acute oral toxicity

From SCCNFP/0522/01/2002

Animal data

Acute toxicity has been investigated following various routes.
The oral LD50 of salicylic acid were 400-3700 mg/kg for the rat.

Ref.: Biofax 21-3/1971, McCann J., et al. 1975

The oral LD50 of formulations containing salicylic acid up to 2% were 10-20 g/kg for the rat, which is equivalent to 200 to 400 mg/kg bw for the pure substance.

Ref.: Procter & Gamble (1993a), (1993b) and (1989a)

New information

Animal Data

Guideline:	similar to OECD TG 401
Species/strain:	male Albino rats (strain not specified)
Group size:	5 per group (4 groups)
Test substance:	salicylic acid
Batch:	/
Purity:	/
Vehicle:	corn oil
Dose levels:	464, 681, 1000 and 1470 mg /kg bw
Route:	oral, unspecified
Administration:	single administration
GLP:	No

Observation period: 14 days
Study period: /

In the Biofax study (1971) which has been considered by RAC as the key study for assessing acute toxicity by oral route, salicylic acid (purity unknown) was tested in a test similar to OECD guideline 401. Five male Albino rats per group (4 groups) were administrated a single dose of the test substance in a corn-oil suspension. The doses were 464, 681, 1000 and 1470 mg/kg bw. The animals were then observed for 14 days. Under the conditions of this test, the LD50 was 891 mg/kg bw. Signs of intoxication were hypoactivity and muscular weakness. At necropsy, no significant findings were observed in survivors, whereas inflammation of the gastrointestinal tract was observed in deceased animals. Based on the results of this study, salicylic acid would be classified as harmful in male rats by oral route, according to the Directive (67/548/EEC) on dangerous substance.

Ref: Biofax, 1971;
https://echa.europa.eu/el/registration-dossier/-/registered-dossier/14544/7/3/2

In the more recent study from Hasegawa et al., 1989, n=10 Wistar rats were administrated a single dose of an aqueous solution of the test substance in a gum arabic. LD50 values were also in the range of 500 to 2000 mg/kg bw, demonstrating that salicylic acid is harmful *via* the oral route.

Ref: Hasegawa et al. (1989)

Human Data

In humans, the oral lethal dose for sodium salicylate or aspirin is estimated between 20 and 30 g in adults, but much higher amounts (130 g of aspirin in one case) have been ingested without a fatal outcome (Goodman & Gilman, 2006). Children under the age of 3 years are more sensitive than adults to salicylates.

SCCS comment
Salicylic acid was recently (Regulation 2018/1480) included in annex VI of CLP and as regards acute oral toxicity, it is classified as Acute Toxicity Category 4, H302 (Harmful if swallowed). Even though all the studies and publications submitted with this dossier have certain shortcomings, the available data support this classification.

3.3.1.2 Acute dermal toxicity

From SCCNFP/0522/01/2002

The topical application of acetylsalicylic acid powder at a dosage of 2 g/kg to rabbits did not induced any sign of erythema or oedema on both the intact and abraded skin of the animals. The dermal LD_{50} was estimated greater than 2 g/kg in rabbits.

Ref.: Procter & Gamble (1976b)

This submission
There is one animal study covering the acute dermal toxicity of salicylic acid.

Animal Data

Guideline:	OECD Guideline 402 (Acute Dermal Toxicity)
Species/strain:	female and male rats/ Wistar
Group size:	5 male and 5 female
Test substance:	salicylic acid
Batch:	/

Purity:	99.8 %
Vehicle:	cremophor EL®
Dose levels:	2000 mg/kg
Route:	dermal
Administration:	single administration
GLP:	Yes
Observation period:	14 days
Study period:	/
Year study completed:	1989

A single dose of 2000 mg/kg was occlusively applied to the intact clipped skin of 5 male and 5 female young adult rats (242/199g) for an exposure period of 24 hours. The animals were observed for mortality, body weights, clinical signs, and gross pathological changes for 14 days.

Results

No mortality and no local effects were noted. Clinical signs included poor general condition and piloerection. Onset of symptoms was 1 hour post administration. On day 2, all animals were free of signs. Necropsy on day 14 revealed slightly swollen liver in two females. The dermal LD50 in both sexes is greater than 2000 mg/kg bw.

Ref: Bomhard 1996;

https://echa.europa.eu/el/registration-dossier/-/registered-dossier/14544/7/3/4

SCCS comment
The SCCS considers salicylic acid as a low dermal acute toxicant.

3.3.1.3 Acute inhalation toxicity

The Applicant does not intend to use salicylic acid in spray or aerosol cosmetics.

SCCS comment
No data have been provided on acute toxicity by inhalation. According to the Applicant, salicylic acid is not intended for use in spray or aerosol cosmetics.

3.3.1.4 Acute toxicity by the intraperitoneal route

/

3.3.2 Irritation and corrosivity

SSCS general comment
In SCCNFP/0522/01, mostly product based information was evaluated for skin and eye irritation. However, risk assessment of cosmetic ingredients within the remit of the SCCS is based on the assessment of the ingredient and not of cosmetic formulations. Test results based on cosmetic formulations have therefore not been taken into consideration in this Opinion.

3.3.2.1 *Skin irritation*

SCCNFP/0522/01/2002
- Single dermal application for 4 hours of alcoholic solutions containing 2% salicylic acid was mildly to non-irritating to rabbit skin.
- Repeated open applications of 2.5 % and 5 % hydroalcoholic solutions of salicylic acid (3 hours exposure twice a day for 4 consecutive days) to guinea pig skin showed mild irritation.

Ref.: Procter & Gamble (1982a), (1979a), (1995a) and (1980)

This submission
Animal data

Guideline:	OECD 404 (2002)
Species/strain:	New Zealand White rabbit
Group size:	1 male and 2 females
Test substance:	Salicylic acid
Batch:	RAS0725500
Purity:	99.9%
Dose:	0.5 g
Exposure:	Single topical application for 4 hours and observation over 14 days
GLP:	In compliance
Study period:	2 April – 28 May 2008

Approximately 0.5 g of the test substance, spread over an area of 6.25 cm^2 and moistened with 0.5 mL of purified water was applied semi-occlusive to the test site for 4 hours. The skin was examined at 1, 24, 48 and 72 hours after patch removal, as well as 7, 10 and 14 days after the exposure.

Results
No death and no clinical signs of systemic toxicity were observed during the study. No staining of the treated skin by the test item was observed. The test item did not elicit any skin reactions at the application site of any animal at any of the observation times.

Conclusion
The study authors conclude that salicylic acid is not irritating to rabbit skin.

Ref: RCC, 2008a
SCCS comment
Based on previous animal skin irritation studies using alcoholic solutions of salicylic acid, the SCCNFP had considered in its Opinion (SCCNFP/0522/01 of 2002) that salicylic acid is mildly to non-irritating to skin. However, the new study provided in the current submission indicates that neat salicylic acid is not irritating to skin.

3.3.2.2 Mucous membrane irritation / eye irritation

This submission
Animal data
The primary eye irritation potential of salicylic acid was evaluated with a method similar to a Draize test. In this study, salicylic acid induced severe eye irritation. Mean scores for cornea, iris and conjunctivae were 51.5, 40.3 and 38.7 at 24 h, 48 h and 72 h, respectively.

Ref: BioFax 1971

Additionally, in a Draize eye irritation test available in open literature, salicylic acid induced severe irritation that did not recover within 21 days of treatment. Draize scores for cornea and conjunctivae were 54.1 and 10.3, respectively.

Ref: Sugai et al. 1991

***In vitro* data**

In an *in vitro* Bovine Corneal Opacity/Permeability (BCOP) test available in open literature, results for opacity but not permeability were reported for salicylic acid tested at up to 10% in MEM + 1% FBS. Based on the following opacity readings in this study, salicylic acid was considered by the RAC as a severe eye irritant: 0.1%: 7.2±1.7; 1%: 70.2±8.4; 5%: 88.2±5.1; 10%: 98.7±7.4.

Ref: Gautheron et al. 1992

Applicants' conclusion on eye irritation

On the basis of a hazard assessment in animals, salicylic acid can induce severe irritation does not recover within 21 days of treatment (Sugai et al 1991). Salicylic acid has therefore been classified by the RAC as irritant for the eyes, with R41: risk of serious damage to eyes, according to EU criteria and is classified category 1 (irreversible effects on the eye) according to the GHS (EU).

SCCS comment

The reference BioFax, 1971 provided to SCCS is only a fax with test results and does not include any details about how the study was conducted.

SCCS conclusion on eye irritation

Based on all available data concerning ingredients, SCCS considers salicylic acid as being able to cause serious damage to the eye. Salicylic acid was recently classified as Eye Dam. 1 (H318 Causes serious eye damage) and was included in annex VI of CLP (Regulation 2018/1480).

3.3.3 Skin sensitisation

From SCCNFP/0522/01/2002

Animal data

Potential allergic contact sensitisation has been investigated according to the modified Buehler test protocol using the guinea pig:

- 20 animals had hydro-alcoholic solutions of salicylic acid, acetyl salicylate, methyl salicylate or hexadienyl acetyl salicylate (25% w/v) applied for 6 hours, once a week, for three weeks. After a 2-week rest period the animals were challenged with the same concentrations. Under the experimental conditions adopted none of the animals exhibited signs of sensitisation.

  Ref.: Procter & Gamble (1975), (1976d), (1976e), (1976f), and Robinson (1990)

Human data

The results of human repeated insult patch tests conducted with formulation containing up to 2 % salicylic acid confirm that topical application does not cause skin sensitisation. In 3 studies, some subjects were showing a positive response to an ingredient of the product formulation. None of the subjects were sensitive to salicylic acid.

Ref: Procter & Gamble (1988a), (1993g), (1994k) and Orris L. (1995)

SCCNFP/0522/01/2002 conclusions
-According to the modified Buehler test protocol using the guinea pig, salicylic acid was not considered as a sensitising agent. However, no data were provided about the experimental potential risk under maximising conditions or to the confirmation of absence of risk to humans.
- The results of human repeated insult patch tests conducted with formulation up to 2% salicylic acid confirm that topical application does not cause skin sensitisation. Salicylic acid is not known as a sensitiser.

This submission

Local lymph node assays (LLNA)

Guideline:	OECD 429
Species/strain:	Female CBA/J mice
Group size:	4 mice per group (except group 4 (25% salicylic acid): 3 mice per group)
Test substance:	Salicylic acid
Batch:	S2013607
Purity:	99%
Vehicle:	4:1 acetone/olive oil (AOO)
Concentration:	5, 10, 25%
Positive control:	Not included
GLP:	Not in compliance
Study period:	16 - 22 June 1993

Mice were treated by topical application to the dorsal surface of each ear with the vehicle alone or with salicylic acid (5, 10 and 25%) for three consecutive days. Five days after the first topical application, mice were administered with ^{3}HTdR. After sacrifice, the draining auricular lymph nodes were excised and pooled for each experimental group. Single cell suspensions (SCSs) of pooled lymph node cells (LNC) were prepared and ^{3}HTdR incorporation was measured. The proliferative responses of lymph node cells (LNC) was expressed as the number of radioactive disintegrations per minute per lymph node (DPM/NODE) and as the ratio of HTdR incorporation into LNC of test lymph nodes relative to that recorded for control lymph nodes. A test substance was regarded as "a sensitiser" in the LLNA if the test substance resulted in an incorporation of ^{3}HTdR at least 3-fold or greater than that recorded in the control mice.

Results

The ratio between test substance and control lymph node proliferation was: 0.8, 1.5 and 2.5 for 5, 10 and 25% salicylic acid, respectively. Salicylic acid failed to show positive proliferative responses at any of the concentrations assayed. The mice showed no visible signs of toxicity to salicylic acid throughout this study.

Conclusion

Salicylic acid is 'unlikely to be a strong sensitizer' in the LLNA.

Ref: Unilever, 1993

Non-guideline studies

Two publications were provided as well by the Applicant in which the skin sensitising potential of salicylic acid was tested in the LLNA. Gerberick *et al.* (1992) reported on an LLNA that was performed in groups of 5 CBA/J mice dosed once daily for 4 consecutive days

with 12.5 µL of 1, 10 or 20 % salicylic acid in acetone. Stimulation indices (treated vs control ratios) of 0.9, 1.8 and 7.2-fold were observed. This indicated that the test material was sensitising at 20%.

Ref: Gerberick et al., 1992

Boussiquet-Leroux et al. (1995) published an LLNA using 5% to 20% salicylic acid in 4:1 acetone:olive oil (AOO). Groups of four female CD1 mice were dosed for 3 days with 25 µL of test solution or vehicle only. The maximum treated/control (T/C) ratio was 1.74, indicating that the test material was not sensitising.

Ref: Boussiquet-Leroux et al., 1995

Human data

The Applicant provided a new human study in which salicylic acid was tested in a formulation. In SCCNFP/0522/01 as well, only human data were provided based on patch tests using salicylic acid in product formulations. Based on all human data, the Applicant concluded that topical application of formulations containing up to 2% of salicylic acid does not cause skin sensitisation.

Ref: TKL Research, 2008a and 2008b

The sensitising potential of salicylic acid has been studied in three different LLNA studies. Salicylic acid was positive in one LLNA at a concentration of 20% and negative in the other two LLNA studies. It is well known that strong irritants like salicylic acid can give a false-positive response in the LLNA, explaining the results observed by Gerberick *et al.* (1992). Together with the evidence from the Buehler test provided in Submission I (SCCNFP/0522/01, 2002), it can be concluded that salicylic acid has no skin sensitising potential.

3.3.4 Toxicokinetics

3.3.4.1 Dermal / percutaneous absorption

SCCNFP/0522/01/2002 conclusion
Salicylic acid is readily absorbed when applied on the skin. The absorption is strongly dependent on the vehicle composition, pH, and structure of the skin, as well as conditions of the application on the skin (single dose, repeated doses and occlusion). The absorption from topically applied 2 % salicylic acid containing products is in the range of 20 % of the applied dose. After topical administration on human skin of 1.25 to 1.5 g of a 2 % salicylic acid containing formulation (corresponding to 25 mg of salicylic acid) daily for 16 days, the peak salicylate levels were between 1/10th and 1/20th of those obtained after the oral administration of 81 mg of acetyl salicylic acid (baby dose aspirin).

This submission

Animal studies

***In vitro* data**

***In vitro* percutaneous absorption**
In vitro percutaneous absorption studies (OECD guideline 428) have been performed using Franz diffusion cells and porcine skin dermatomed to a thickness of 500 ± 50 µm. The receptor chamber was filled with a receptor fluid containing phosphate-buffered saline (pH 7.4) in distilled water, 1% bovine serum albumin, and 0.04% of gentamicin sulfate. The cells were placed in a circulating water bath to ensure that the skin surface was maintained

at 32 °C. The integrity of the skin was checked by measurements of transepidermal water loss. The diffusion experiment was initiated by applying 10 µL of ethanol–water (1:1) solution salicylic acid (about 3%, w/v) to the entire surface. After an exposure time of 24 hours, the test formulation remaining on the skin surface was removed with a specific wash. The *stratum corneum* of the treated area was removed by eight successive tape strippings. After that, the viable epidermis was separated from the dermis. The different compartments, for each active principle, were analysed using high-performance liquid chromatography. Six samples were used for each experimental assay. Dermal absorption of salicylic acid (epidermis, dermis and receptor fluid) on intact skin was found to be **34.48% ± 2.56** (n=6). Total recovery was 99.28% ± 4.31.

Ref: Rubio et al 2011

^{14}C-salicylic acid was topically dosed with either 10% solutions of natural extracts or ethanol (control) using a flow through *in vitro* porcine skin diffusion system. Porcine skin was dermatomed to a thickness of 500 µm. Each square section (1 cm^2) was placed into a two-compartment Teflon flow-through diffusion cell using a well-established protocol. The dermal side of the skin sections were perfused using the receptor fluid consisting of a Krebs–Ringer bicarbonate buffer spiked with dextrose and BSA (4.5% w/v). The temperature of the perfusate and the diffusion cells was maintained at 37 °C. The flow rate of the flow-through receptor solution was 4 mL/h. Salicylic acid was topically dosed either in 10% solution of eight natural extracts or ethanol at a concentration of 1.6 µg/µL as finite (25 µL) volumes to an area of 1 cm^2. Samples of the receptor fluid were collected at the following predetermined intervals post dose application: 0, 15, 30, 45, 60, 75, 90, 105, 120min and then 3, 4, 5, 6, 7, 8, 12, 16, 20 and 24h. At the end of experiment, the dose area was swabbed and then tape-stripped six times. Samples from the perfusate, swabs, stratum corneum tape strips, dosed skin and mass balance samples were analysed with liquid scintillation counter. The dermal absorption of ^{14}C-salicylic acid in ethanol was **40.05% (± 7.63**; n=3).

Ref: Muhammad et al. 2017

***In vivo* data**

***In vivo* percutaneous absorption in Rhesus Monkeys**

The effect of daily topical application on the *in vivo* percutaneous absorption of salicylic acid in rhesus monkeys has been investigated (female rhesus monkeys; n=4; aged 7 ± 3 yr; 5±2 kg). In both single- and multiple-dose experiments, salicylic acid was administered dissolved in a small volume of acetone, at a surface dose of 4 mg/cm2 to a lightly clipped area of the abdomen. In the single-dose study the 14C-labelled salicylic acid were applied and the dose site was washed, 24 hr after administration, with soap and water. To quantify absorption, urine was collected for 7 days after dosing and was assayed for 14C radioactivity by liquid-scintillation counting. Urine samples were collected, after dosing, according to the following schedule: day 1: 0-4, 4-8, 8-12 and 12-24 hr; days 2-7: urine for each 24-hr period was combined. In the multiple-application experiments, the animals received a chemical dose of 4 µg/cm2 applied to exactly the same site, every 24 hr for 14 days. The first and eighth applications used 14C-labelled salicylic acid; and other applications involved unlabelled compound at the same chemical dose. The skin site of application was not washed between dosings. No 'contamination' of the excretion kinetics of the second radiolabelled dose by the first was apparent. The kinetics observed are independent of the dosing method. Thus, under the conditions used, measurement of percutaneous absorption after a single application can be predictive of permeation when multiple skin contacts occur. The percutaneous absorption of 14C-salicylic acid after a single topical application was **59 % ± 32**. In the multiple dose study, cumulative absorption was **67 % ± 17** to **78 % ± 18** after the 1st and the 8th dose, respectively. According to the Applicant, this is unusually high, as the vehicle chosen for this study was acetone, which maximises skin penetration.

Ref: Bucks et al, 1990

Human studies

***In vitro* data**

***In vitro* Percutaneous Absorption of ^{14}C-salicylic Acid**

Guideline:	OECD 428/ OECD 28/ SCCS 1358/10
GLP:	No
Test system:	Human abdominal skin samples (Split-thickness)
Sample number:	12 human abdominal skin samples
Test substance:	[phenyl-^{14}C(U)]-Salicylic acid
Batch:	150924
Purity:	99.0 %
Vehicle:	ethanol: water (35% v/v)
Concentration:	2% (w/w)
Route:	topically, dermal
Dose:	40 µg/cm^2
Receptor fluid :	5%, v/v PBS with new-born calf serum, 2.5 µg/mL amphotericin B, 100 units/mL penicillin, and 0.1 mg/mL streptomycin.
Exposure:	Single application 2 mg/cm^2
Exposure period:	1, 2, 4, 6, 8, 10, 12 and 24 h post dose.
Method of analysis:	Liquid scintillation counting
Study period:	1 September 2015 – 11 November 2015

Four samples of full-thickness human skin (abdomen) were obtained from male and female donors. Split-thickness membranes were prepared by pinning the full-thickness skin, stratum corneum uppermost, onto a raised cork board and cutting at a setting equivalent to 200-400 µm depth using a Zimmer® electric dermatome. The surface area of exposed skin within the cells was 3.14 cm^2. Any skin sample exhibiting a resistance less than 4 kΩ was excluded from subsequent absorption measurements. The skin surface temperature was maintained at 32°C ± 1°C throughout the experiment. *Ca* 6.28 mg (2 mg/cm^2) of the test preparation was applied over the stratum corneum surface of the exposed skin of 12 skin samples obtained from four different donors. The exposure period was terminated at 24 h post dose. Receptor fluid was sampled at approximately 1, 2, 4, 6, 8, 10, 12 and 24 h post dose. The highest achievable concentration of the test item in receptor fluid (i.e. if 100% was absorbed) would be 12.6 mg/L. Since water solubility of the test substance is 2.2 µg/mL, the receptor fluid was considered to be acceptable for use. At 24 h post dose, the donor chamber was transferred to a pre-weighed pot containing ethanol. The skin was then removed from the static diffusion cells and dried. The stratum corneum was removed with 20 successive tape strips. The remaining skin was divided into exposed and unexposed skin. The exposed epidermis was separated from the dermis. The skin samples were solubilised with Solvable® tissue solubiliser. All samples were analysed by liquid scintillation counting.
The mass balance for all samples was within 100 ± 10%, with the exception of Cell 28 (mass balance: 89.66%). Similar absorption profiles were observed for all samples. The absorbed dose (50.09%) was the sum of the receptor fluid (47.97%) and the receptor chamber wash (2.12%). Dermal delivery (54.00%) was the sum of the absorbed dose, the epidermis (1.26%) and dermis (2.64%). A summary of the mean results are shown in Table 3.

Table 3. Mean results of salicylic acid application to human skin *in vitro* for 24 hours.		
Test Item	**[^{14}C]- salicylic acid**	
	(% Applied Dose)	**(µg equiv/cm^2)**
Dislodgeable dose	38.60 ± 4.8	15.72 ± 1.96
Unabsorbed dose	39.57 ± 4.88	16.11 ±1.99
Absorbed dose	50.09 ± 5.26	20.41 ± 2.14
Dermal delivery	54.00 ± 5.12	22.00 ± 2.09
Mass balance	93.57± 1.58	38.11 ± 0.61

According to the Applicant, the study provides a high-end estimate of skin absorption for use in risk assessment, as a worst case of **50.09 (±5.12;** n=12) % absorption of salicylic acid after a continuous 24 hours of topical exposure in ethanol:water (35% v/v).

Ref: Unilever, 2016.

A single dose of [^{14}C]-salicylic acid was applied onto human skin *in vitro* in diffusion cells under non-occlusion as well as various occlusive time periods (1, 4 and 8 h). The dermatomed human cadaver skin was clamped onto 1.77 cm^2 glass Franz cells in a diffusion cell system. A 12 mL of reservoir fluid volume was filled to capacity with receptor fluid PBS (0.01 M, pH 7.4). The temperature of the glass cell was maintained at 32 °C. A 5 µL dose of [^{14}C]-salicylic acid was applied to the surface of the skin. At regular intervals (1, 4, 8, 12 and 24 h), 1.0 mL of the receptor fluid in each cell chamber was manually collected. Upon reaching a pre-defined time of occlusion (1, 4 or 8h of occlusion), the wraps were removed. After 24 hours, skin samples were removed and the skin surface sites were tape-stripped 10 times. The radioactivity in the epidermis and dermis represented the dose absorbed in the skin. Mass balance was between 97-114%. The radioactivity recovery as percent of applied dose of [^{14}C]-salicylic acid was significantly higher under occlusion versus non-occlusion in the epidermis, dermis and receptor fluid after 24 h ($p < 0.05$). Occlusion increases salicylic acid absorption. The total amount of [^{14}C]-salicylic acid absorbed in the skin (epidermis + dermis + receptor fluid), as a percent of applied dose increased from 4.5% (8% including 1SD) under non-occlusion to **50.5%** (**85%** including 1SD) when under 8 h of occlusion.

Ref: Hafeez F, et al (2014)

A number of studies justify that salicylic acid is readily ionised and skin penetration is significantly affected by pH and other properties of the vehicle in which it is applied.

Ref: Harada K et al. (1993); Singh P & Roberts MS, 1994, and Leveque N. et al, 2004

In vivo data

Salicylic acid was applied daily over 14 days at 2% to the face and neck in different vehicles (a hydroalcoholic vehicle and a cream). The effect of facial skin condition (normal, acnegenic or photodamaged) on dermal delivery was also assessed. Subjects with acnegenic skin received topical treatment in a hydroalcoholic vehicle and those with aged or photodamaged skin were treated with salicylic acid in a cream.

Thirty-eight female volunteers, 18 to 65 years of age, were assigned to four treatment groups based on dermatologically assessed facial skin characteristics: two groups of subjects presented normal skin, one group presented mild to moderate acne, a fourth group was selected for evidence of moderate to severely aged or photo damaged skin, and a fifth group, which served as the reference control. The amount of the test material applied was approximately 1.25 to 1.5 g (25-30 mg salicylic acid). Subjects in the oral aspirin reference group received 81 mg of ASA with 8 ounces of water once daily. On day 15 of the study, all subjects were confined to the testing facility for 24 h. For the pharmacokinetic study, blood samples were collected on study days 0, 7, and 12; and for each day of analysis pre-dose

blood samples, as well as post-dose samples at 5, 15, 30, and 45 min, and 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h have been collected and total urine was also collected to determine salicylate excretion. Table 6 shows the estimated steady-state pharmacokinetic parameters (C_{max}, T_{max}, terminal half-life and AUC) for salicylic acid in plasma after both topical application and oral aspirin administration.

Table 4. Steady-state pharmacokinetic parameters in subjects with normal, aged or acnegenic facial skin after topical application of 2% salicylic acid or in subjects receiving one daily oral dose of 81mg aspirin.

Skin Type	Vehicle	C_{max} (µg/L)	T_{max} (h)	Terminal Half-Life (h)	AUC (µg h/L)
Normal	Cream	293 ± 37	4.30 ± 0.40	5.83 ± 0.73	3108 ± 293
Aged	Cream	275 ± 58	4.11 ± 0.58	5.93 ± 0.83	2636 ± 302
Normal	Hydroalcoholic	525 ± 66[a]	1.89 ± 0.35[a]	7.62 ± 0.82	4225 ± 425[a]
Acnegenic	Hydroalcoholic	487 ± 41	1.67 ± 0.24	8.06 ± 1.12	3893 ± 329
N/A	Oral aspirin	5282 ± 457[b]	0.71 ± 0.25[b]	2.62 ± 0.46[b]	22010 ± 3907[b]

Data presented are mean ± SEM for n=10 (normal/cream) or n =9 (all others groups). a) Significantly different from 'normal' subjects ($p < 0.05$). b) Statistically different from all topical treatments. N/A = not applicable.

Data presented in Table 4 indicate that systemic exposure to salicylic acid from the use of a 2% topical product is approximately 15% of that following an oral administration of 81 mg aspirin. Relative bioavailability for topically applied salicylic acid among normal skin type subjects were 57.6 and 44 % for the hydroalcoholic and cream delivery vehicles, respectively.

According to the Applicant, the lower absorption of topically compared with orally administered salicylates observed in this study is in agreement with earlier reports by other investigators. Moreover, the slower half-life observed after topical compared with oral administration indicated that absorption is the rate limiting step for absorption of topically applied SA.

Ref: Davis et al (1997).

A single-centre, single-sequence, two-period crossover study has been performed to compare systemic exposures following facial application of a 30% salicylic acid cosmetic skin peel formulation applied for 5 min and an oral dose of 650 mg aspirin in nine subjects (2 healthy male and 7 non-pregnant females; age 35-53). For the topical application, a 30% SA /3% glycolic acid hydroethanolic skin peel solution was applied to the full face. The solution was kept on the face for 5 min, and was then removed with warm water using a gauze pad. After a 1-week washout period, the test subjects ingested two 325-mg buffered aspirin tablets with 8 oz. of water. Blood samples were collected at 0.5, 1, 1.5, 2, 2.5, 3.5, 6, 12, and 24 h. The pharmacokinetic parameters are shown in Table 5.

Table 5. Salicylic acid pharmacokinetic parameters in humans after topical skin peel application and oral aspirin

Parameter	Mean	Standard Deviation	Geometric Mean	Range
Topical 30% salicylic acid				
C_{max} (µg/ml)	0.81	0.32	0.77	0.43-1.57
T_{max} (h)	2.33	0.54	2.27	1.40-3.40
AUC_{0-n} (h. µg/ml)	6.22	2.56	5.76	3.01-11.40
$AUC_{0-\infty}$ (h. µg/ml)	6.39	2.58	5.97	3.32-11.65
λz (h^{-1})	0.19	0.05	0.19	0.14-0.30
$T_{1/2}$ (h)	3.82	0.83	3.72	2.29-4.90
650 mg oral aspirin				
C_{max} (µg/ml)	56.40	14.20	54.8	34.3-77.5
T_{max} (h)	1.03	0.39	0.95	0.47-1.50
AUC_{0-n} (h. µg/ml)	319.50	104.80	304.20	86.7-464.1

$AUC_{0-\infty}$ (h. µg/ml)	319.90	105.10	304.50	186.8-464.4
λ_z (h^{-1})	0.32	0.04	0.31	0.26-0.38
$T_{1/2}$ (h)	2.23	0.27	2.21	1.84-2.72

The mean (SD) maximum SA concentration (C_{max}) was 0.81 (0.32) µg/mL and 56.4 (14.2) µg/mL. The AUC-based safety margin ratio was 50:1. A depot effect was observed during topical application of the skin peel solution as the absorption of SA continued beyond the 5 min application period. Plasma SA C_{max} values were achieved from 1.4 to 3.5 h after topical application and from 0.5 to 1.5 h after oral aspirin.

Ref: Fung et al (2008)

According to the Applicant, the plasma concentrations in the Fung et al. study (30%; 5 min) were similar to that of a low concentration (2%) applied in a leave-on product to the same body surface area. Reviews of the safety of skin peeling agents have been performed by Bari et al., (2005) and Arif et al., (2015).

The percutaneous penetration of salicylic acid was studied after topical application to the forearm of human volunteers. The penetration through the skin was quantitated by measuring ^{14}C salicylic acid appearance in urine. In the experiments, a 4 µg/cm² solution of ^{14}C salicylic acid dissolved in acetone was applied to a 13 cm² area of the ventral forearm (n=17). The skin site was not protected, and the subjects were asked not to wash the area for 24 hours. The urinary excretion was then measured for 5 days. Total absorption of ^{14}C salicylic acid after topical application was **22.78%** ± 13.25 of the applied dose.

Ref: Feldmann & Maibach 1970

A study compares percutaneous absorption of salicylic acid in the isolated perfused porcine skin flap (IPPSF) system with that in humans *in vivo*. *In vivo* human study included five or six normal volunteer outpatients per group. ^{14}C-salicylic acid was dissolved in 50 µL ethanol and a dose of 39.7 µg/cm² was spread over a 10 cm² skin surface area, 24 hours, n=6, unoccluded. The subjects were instructed to collect all urine in the containers provided for that day and the subsequent 6 days. At 7 days after application the skin dosing site was tape-stripped 10 times for residual chemical. Percutaneous absorption was determined from the 14C-urinary excretion. The percutaneous absorption values were, for human skin and the isolated perfused porcine skin flap system **6.5%** ± 5.0 and **7.5%** ± 2.6, respectively.

Ref: Wester et al 1998

SCCS comment
Salicylic acid is readily ionised and skin absorption is significantly affected by pH and other properties of the vehicle in which it is applied. In view of the high variability of dermal penetration values reported in the different studies, the SCCS estimates **a dermal absorption rate of 60 %** for salicylic acid. This value corresponds to the value of 60% absorption rate used by RAC (March 2016).

3.3.4.2 Non-dermal absorption

Oral route

Salicylic acid is well absorbed across the GI tract and is rapidly distributed throughout the extracellular fluids and most tissues.

Ref: Goodman & Gilman, 2006

A comparison between rat and human oral kinetics is presented in Table 6.

Table 6. Data from a range of kinetics studies in rat and humans, comparing oral dose (in mg/kg/day) with reported C_{max} (µg/mL) values.

Substance	Species	Dose mg/kg	C_{max} (µg/mL) SA	T_{max}	$T_{1/2}$	AUC mg / L hr	Clearance	Source
Salicylic Acid	Rat	150	246.6 ±20.6	No data	No data	No data	No data	Tanaka et al 1973
Aspirin	Rat	150 mg/kg twice daily	238 ±20	No data	No data	No data	No data	Wilson et al., 1977
Aspirin	Human	16	49					Kershaw et al 1987
Aspirin	Human	0.83	4.35					Bochner et al 1988
Aspirin	Human	1.35	5.28	0.71±0.25 (hr)	2.62± 0.46 (hr)	220.1		Davis et al 1997
Aspirin	Human	Single oral administration of 650 mg	56.4±14.2	1.03±0.39	2.23±0.27	319.8±105		Fung et al 2008
Aspirin	Human	8.3	22.85					Nageisch mitz et al 2014

*median values from a range of observed values.

SCCS comments

The SCCS notes that to compare toxicokinetics between different species at least T_{max} associated with C_{max} is needed, along with half-life, AUC and clearance (ref: Miaskiewicz et al 1982). No robust data have been provided on salicylic acid kinetics for both species (rat and human) to enable comparison of the kinetic parameters. Therefore, the SCCS disagrees with the Applicant that a factor of 4 accounting for inter-species toxicokinetic differences is not required.

Inhalation

Salicylic acid is neither volatile nor airborne and therefore, there are no studies on lung ADME. There are no spray or aerosol products containing salicylic acid in current use (Crème Global, 2017).

3.3.4.3 Distribution

Salicylic acid is a weak acid and after oral administration it is found in the unionised form in the stomach. Salicylic acid is well absorbed in humans from the gastrointestinal tract and rapidly distributed throughout the extracellular fluid and most tissues. High concentrations are found in the liver and the kidneys and 50 to 80 % of salicylic acid in plasma is bound to albumin and other proteins.

Placental absorption

Whole body autoradiography analysis of pregnant mice revealed that ^{14}C-salicylic acid is able to pass through the placenta to reach the fetus (Tjalve et al. 1973; Koshakji & Schulert, 1973). Placental absorption of salicylic acid using a non-standardised *in vitro* model procedure has been studied by Shintaku et al. (2007) so as to devise a pharmacokinetic model of human placental absorption. *In vitro* human placental perfusion was carried out based on the method reported by Schneider et al. (1972). Salicylic acid at

8 µg/mL was dissolved into the maternal perfusate on the maternal side of the placenta. Maternal and 'fetal'-side effluents were sampled for 60 min. The study shows **the potential of salicylic acid to cross the placenta.**

SCCS comment
SCCS agrees that salicylic acid has the potential to cross the placenta.

Parenteral route
All available sub-cutaneous (SC) and intravenous (i.v.) ADME studies for salicylic acid are outlined in Table 7.

Table 7. Parenteral route studies on salicylic acid in animals and in humans.

Number/ species	Dose	Application	Observations	Reference
Salicylic acid				
Rat - Sprague Dawley	300 mg/kg	Sub-cutaneous injection to gravid rats terminated after 1h	4.06% of the injected dose was found in fetal tissue	Koshakji & Schulert, 1973
Male Fischer 344 Rat	5 or 50 mg/kg	3 and 25 months animals; i.v. in 4:1:1 solution Emulphor:ethanol:water	5 mg/kg: Plasma SA conc. 17-28 µg/ml $T_{1/2}$(3mth) 4.08h $T_{1/2}$(25mth) 21.3h 50 mg/kg: Plasma SA conc. 100-120 µg/ml $T_{1/2}$(3mth) 30.1h $T_{1/2}$(25mth) 21.9h	McMahon et al 1990
Dog	1g	i.v. in sodium bicarbonate	>90% recovered in urine over 30-36hr; 50% unchanged as salicylic acid; 25% glucuronates; 10% salicyluric acid; 4-5% gentisic acid	Alpen et al 1951
Human	Not reported	i.v.	89% recovered in urine after 4h	Feldmann & Maibach, 1970

3.3.4.4 Metabolism

Salicylic acid is the principal metabolite of acetylsalicylic acid (ASA, aspirin) which is a common analgesic medicine. A scheme of the major possible metabolites of salicylic acid, as identified in mammals, is presented in Figure 1.

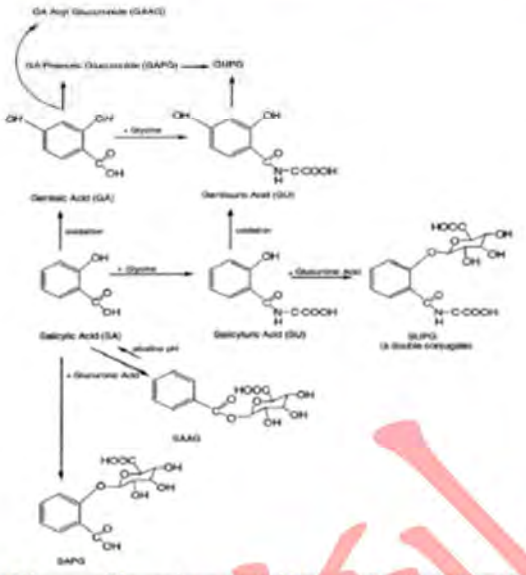


Figure 1. Scheme of the possible major metabolites of salicylic acid, Ref: CIR 2003 review

These metabolites have been detected and in some cases quantified in the ADME/PK studies described in this section. These metabolites are formed mainly as the result of hepatic microsomal cytochrome P450 enzymes and phase 2 glucuronosyl transferase (UGT) conjugation enzymes.

Studies reported by McMahon et al. (1990), performed on rats, demonstrated that salicylic acid can be metabolised to salicyluric acid, salicyl-glucuronic acid, oxidative metabolites (2,3-dihydroxybenzoic acid (gentisic acid) and 2,5-dihydroxybenzoic acid) and other glucuronides and glycine conjugates. All these metabolites, as well as unchanged salicylic acid, are eliminated almost entirely and rapidly via the urine.

Experiments in rats (McMahon *et al.*, 1990) showed that following single salicylic acid doses of 5 or 50 mg/kg bw, the compound is excreted in urine, predominantly as salicylic acid and salicyluric acid, and to a lesser extent oxidative metabolites (2,3- dihydroxybenzoic acid and 2,5 -dihydroxybenzoic acid), and other conjugated salicylic acid compounds (as salicyl ester glucuronide or salicyl ether glucuronide).

In humans the major metabolic pathway for elimination of salicylates is via conjugation. The principal metabolite in humans is salicyluric acid. A minor oxidative pathway leads to the production of 2,5-dihydroxybenzoic acid (gentisic acid, 25DHBA) and 2,3-dihydroxybenzoic acid.

SCCS comments
Based on the studies provided by the Applicant, the SCCS is of the opinion that metabolism for salicylic acid in rats and humans is at least similar. It is metabolised mainly to salicyluric acid and conjugated salicylic acid compounds, with a small proportion of oxidative metabolites.

3.3.4.5 Excretion

McMahon et al. (1990) showed that oral salicylic acid is excreted almost exclusively in the urine in rats. Less than 1 % was found in bile (as unmetabolised salicylic acid), as exhaled carbon dioxide or in feces. This study reported a shift in urinary excretion at high concentrations, towards a higher proportion of oxidative metabolites in older rats. Salicylic acid is excreted by renal excretion as an unchanged chemical entity (10 %) or after conjugation with glycine (salicyluric acid 75 %), with glucuronic acid (salicyl acyl and phenolic glucuronides 5 %) and/or after hydroxylation (gentisic acid < 1 %) (Goodman & Gilman 2006). Excretion is almost complete in rats within 24 hours, irrespective of the route of administration. Similarly, in humans, excretion is almost all in urine, and almost complete within 24 hours after all routes of exposure.

3.3.5 Repeated dose toxicity

No OECD guideline repeat dose 28-day or 90-day sub-chronic study data are available on salicylic acid via the oral and inhalation routes.

3.3.5.1 Repeated dose (28 days) oral / dermal / inhalation toxicity

SCCNFP/0522/01/2002

- No systemic toxicity was noted from sub-chronic dermal toxicity studies conducted in the rabbit at the highest dosage of 120 mg/kg/day salicylic acid formulations; dermal irritation was the main recorded observation.
- The chronic oral toxicity study performed in rat with acetylsalicylic acid at a concentration of 200 mg/kg/day during 200 days showed no significant toxic effects compared to the control group at this dose level.
- In humans, toxic effects were reported when 10 g or more of salicylates were given orally in single dose or divided doses within a period of 12 to 24 hours. Children are more sensitive than adults to salicylates. Reye's syndrome in children is associated with the ingestion of acetylsalicylic acid.

Repeated dose dermal toxicity

Animal data

14-days sub-chronic percutaneous toxicity/irritation study

Guideline:	in accordance with IRDC SOPs
Species/strain:	female and male rabbits/ New Zealand
Group size:	4 groups of 3 male and 3 female rabbits
Test substance:	salicylic acid
Physical form:	liquid
Batch:	/
Purity:	/
Vehicle:	8% propylene glycol butyl ether in ethanol
Dose levels:	2 mL/kg day
Route:	topical application for 13 days
Administration:	once daily
GLP:	Yes (1987)
Observation period:	14 days
Study period:	8 April 1993- 8 July 1993

A 14-day sub-chronic percutaneous study was performed in four groups of 3 male and 3 female New Zealand White rabbits administered topically at 2 mL/kg/day of salicylic acid-containing solutions. The concentrations tested were 0%, 2%, 10% and 25% (corresponding to 0, 40, 200 and 500 mg/kg/day) of salicylic acid in a vehicle solution. After a 7-hour period of daily exposure, the application site was washed with water and dried.

Results

No deaths were observed during the study. Dose-related slight to marked erythema and oedema were noted for all dosage groups. Desquamation was most often noted in the 25 % salicylic acid group; fissuring of varying degree was observed in all dosage groups. Eschar was noted in the 10 % and 25 % dosage groups; exfoliation was noted on day 13 in a 25% dosage group. Atonia was predominantly observed in the animals treated with 10 and 25 % salicylic acid. These signs were generally noted between days 7 to 14. The changes in the body weights of animals were considered as not remarkable during the study. Concerning clinical findings, no visible abnormalities were noted at necropsy in any animal beyond the dermal irritation observed at the test sites. Under the experimental conditions adopted, the test articles were considered as dermal irritants by the investigators.

Ref: Procter & Gamble, 1993f

All animals survived after 28 days of treatment. There were no test article-related effects on appearance, behaviour, body weights or ophthalmoscopic examinations. Slight to marked erythema, desquamation, fissuring, oedema and slight to moderate atonia were noted at the site of application. The greatest severity for all findings, particularly scab formation, and desquamation, was observed most predominantly in the high-dose group and during the first 28 days of the treatment. The differences noted in body weight gain and in the body weight change values were not considered treatment-related. No test article-related toxicologic findings were detected in any haematological, biochemical or urological parameters. Serum salicylate was noted in all groups at 1 hour after dosing; the maximum levels occurred between 2.5 and 7 hours after dosing. A low incidence of trace to mild myocardial degeneration was observed in all treatment groups and the vehicle control group at the terminal sacrifice. However no dose-response relationship was retained with respect to either lesion incidence or severity. Under the experimental conditions adopted, the tested formulations were considered irritant.

Ref: Procter & Gamble, 1994&1994d;

Human data

Mild chronic salicylate intoxication is defined as salicylism and cases of this and metabolic acidosis have been described after topical application of salicylic acid. Salicylism can be severe and depends among various factors such as the age of the patient, the intensity of the skin damage, the concentration of salicylic acid in the formulation, and the surface of application. Salicylism symptoms can appear within a short period of treatment.

Ointments containing salicylic acid 3 to 6 % have caused nausea, dyspnoea, loss of hearing, confusion and hallucinations in three patients with extensive psoriasis. The cream was applied six times a day and combined with UV therapy. Salicylism symptoms developed in 4 days and were associated with significant salicylic acid plasma levels of 46 to 64 mg/100 mL. Symptoms disappeared rapidly after discontinuation of the ointment applications (Von Weiss & Lever, 1964). Another salicylism case was reported in a man with a widespread psoriasis that covered 80% of his body surface. The patient was treated with 10% topical salicylic acid on the first 2 days of hospitalization and 20% salicylic acid on the 3rd day on all involved areas of the skin. The serum level of salicylic acid was 93 mg/100 mL (Jabarah et al 1997).

The signs and symptoms of intoxication with salicylic acid vary according to the level of salicylic acid in the plasma. Symptoms may be present with levels of salicylic acid in the plasma as low as 10 mg/100 mL (Von Weiss & Lever, 1964). Ordinarily, symptoms that occur at levels below 35 mg/100 mL are quite mild. Salicylism can be acute or chronic and

usually develops when blood concentrations of salicylate are greater than 35 mg/mL (Madan and Levitt 2014). The most common early symptoms are difficulty in hearing, tinnitus, nausea, and hypernea. The clinical manifestations of intoxication with salicylic acid include gastrointestinal, respiratory, renal, metabolic, neural, and psychic disturbances. Systemic effects of topical salicylic acid are minimal when it is applied to intact skin in low to moderate doses. Conversely, with a break in the stratum corneum, measurable levels of salicylic acid can be found in the body even after application of low concentrations in hydrophilic ointment. Toxicity from the application of as little as 1% to 2% salicylic acid has been reported in neonates. (Madan and Levitt 2014).
In humans, severe salicylism by the dermal route is normally associated with a diseased state of the skin compounded by the multiple applications to large areas of the body. The application of salicylic acid to extensive areas, particularly in children, may involve a risk of toxicity from high levels of dermal absorption (Galea & Goel, 1989; Chiaretti et al., 1997). Children are particularly susceptible.

Repeated dose inhalation toxicity

/

Salicylic acid is not used in spray or aerosol cosmetics. This was verified by Crème Global (2017).

SCCS comment
No robust data have been provided to enable proper assessment of the repeated dose toxicity by inhalation. Since the Applicant does not intend to use salicylic acid in spray/aerosol products, inhalation toxicity is not considered in this Opinion.

3.3.5.2 Sub-chronic (90 days) oral / dermal / inhalation toxicity

Animal data

Sub-chronic dose dermal toxicity
Two 91-day studies were performed in New Zealand White rabbits in order to assess the sub-chronic cutaneous and systemic toxicity of two cleansing formulations containing 0.5% salicylic acid (Procter & Gamble 1990a, 1990b). 2 mL/kg of the test article, corresponding to 10 mg/kg, was applied to intact skin of the rabbits, with 7 hours daily exposure, 5 times a week. The neat or 50% w/v in distilled water diluted product was applied. Controls were treated with distilled water. The following observations were performed during both studies: clinical data (food consumption, faeces, behaviour), daily dermal irritation observations, body weights records, mean haematology values (neutrophil, monocytes, basophil, leucocytes and lymphocytes counts), gross pathology findings (organ lesions, skin lesions), organ weights and histopathology findings. No deaths were observed during the study. No statistical differences were found in mean body weight or in organ weight. Transient dermal irritation including erythema, oedema, atonia, desquamation and fissuring, varying up to moderate intensity and transient slight to moderate desquamation were observed and considered related to the treatment. No systemic toxicity was observed as confirmed by the clinical evaluation, the clinical chemistry, haematological and histopathological examinations. The tested products were considered slightly and transiently irritating to the skin when applied neat or at a concentration of 50% w/v to the intact rabbit skin.

A 91-day sub-chronic cutaneous toxicity study was performed in New Zealand White rabbits treated with cleansing formulations containing 0.5% to 6% of salicylic acid in propylene glycol butyl ether/ethanol (vehicle), corresponding to topical doses of 10, 20, 40 or 120 mg/kg of salicylic acid (Procter & Gamble, 1994, 1994d). Two controls group were included, one with untreated animals, one with vehicle treated animals. The tested product was applied once daily during a seven hour period, five days per week at a dosage volume of 2

ml/kg to the intact skin of the animals. A first 28-day period was followed by an interim sacrifice of five animals per group; the remaining animals continued to be observed until the end of the 91-day treatment. The observations recorded during the study were: clinical signs, dermal irritation, body weights, opthalmoscopic examinations, haematological parameters (haematocrit, haemoglobin, erythrocyte/leucocyte and platelet counts, coagulation times), biochemical parameters (ASAT, ALAT, alkaline phosphatase, glucose, urea nitrogen, bilirubin, cholesterol, albumin, globulin, total protein, creatinine, electrolytes, phosphorus, calcium), urological parameters (volume, specific gravity), serum salicylate analysis, macroscopic and microscopic examinations, organ weights.

All animals survived after 91 days of treatment. There were no test article-related effects on appearance, behaviour, body weights or ophthalmoscopic examinations. Slight to marked erythema, desquamation, fissuring, oedema and slight to moderate atonia were noted at the site of application. After 91 days of treatment, the severity and frequency of hyperkeratosis, acanthosis and dermal inflammation were greatest in the high-dose group. The differences noted in body weight gain and in the body weight change values were not considered treatment-related. No test article-related toxicologic findings were detected in any haematological, biochemical or urological parameters. Serum salicylate was noted in all groups at 1 hour after dosing; the maximum levels occurred between 2.5 and 7 hours after dosing. A low incidence of trace to mild myocardial degeneration was observed in all treatment groups and the vehicle control group at the terminal sacrifice. However no dose-response relationship was retained with respect to either lesion incidence or severity. Under the experimental conditions adopted, the tested formulations were considered irritant.

3.3.5.3 Chronic (> 12 months) toxicity

No chronic data have been submitted.

SCCS overall conclusion of repeated dose toxicity
SCCS considers that the assessment from SCCNFP (2002) concerning the toxicity of salicylic acid after repeated exposure remains valid.
In particular:
- No systemic toxicity was noted from sub-chronic dermal toxicity studies conducted in the rabbit at the highest dosage of 120 mg/kg/day salicylic acid formulations; dermal irritation was the main recorded observation.
- In humans, toxic effects have been reported after topical application of salicylic acid to extensive areas of the body in diseased skin. Children are more sensitive than adults to develop salicylism, thus the topical application of salicylic acid may involve a risk of toxicity. Reye's syndrome in children is associated with the use of acetylsalicylic acid during a viral illness.

3.3.6 Reproductive toxicity

3.3.6.1 Fertility and reproduction toxicity

There is no standard guideline two-generation reproductive toxicity study available for salicylic acid by any route. As per the SCCNFP 2002 Opinion, the REACH dossier for salicylic acid and the RAC 2016 Opinion, evidence on fertility and reproductive parameters following oral exposure to sodium salicylate or acetylsalicylic acid (aspirin) are used to support the conclusion that salicylic acid does not have significant effects on fertility. This is on the basis that sodium salicylate and aspirin ingested orally are readily converted to systemic salicylic acid, and so in essence the reproductive organs are actually exposed to salicylic acid following intake.

A detailed analysis of reproduction in humans exposed to aspirin was conducted by Novacyl, including review of a new epidemiology literature analysis by an external expert. In 2013, a CLH dossier was provided by industry with an update including this new data analysis of human exposures and the lack of reproductive effects for the fertility endpoints observed following widespread exposures to aspirin.

Taken from RAC (March 2016)

The assessment of salicylic acid is based on read-across data from studies on methyl salicylate (MeS) and acetylsalicylic acid (ASA). The studies used in the assessment are summarised in the table below.

Table 8. Summary of fertility studies

Summary of the fertility studies taken into assessment

Study design, test material, species	Doses	Conclusions
3-generation study (Collins et al., 1971), MeS, male and female Osborne-Mendel rats	500, 1500, 3000 and 5000 ppm (equivalent to 22.5, 67.5, 135, 225 mg/kg bw/d as salicylic acid) in the diet	No statistically significant decrease in fertility index was reported at any dose for any generation.
2-generation study (Abbott & Harrisson, 1978), MeS, male and female Wistar rats	2500 and 5000 ppm (equivalent to 113 and 225 mg/kg bw/d as salicylic acid) in the diet	Non-significant decrease in mating performance for the first generation.
2-generation study (Abbott & Harrisson, 1978), MeS, male and female mice	2500 and 5000 ppm (equivalent to 324 and 648 mg/kg bw/d as salicylic acid) in the diet	No adverse effects were reported on any reproductive parameter.
2-generation study,(NTP, 1984a) continuous breeding protocol , MeS, CD-1 mice	25, 50 and 100 mg/kg bw/d (22.5, 45 and 90 mg/kg bw/d as salicylic acid) by gavage	No effects on fertility were reported.
1-generation study (NTP, 1984b), continuous breeding protocol , MeS, CD-1 mice	100, 250 and 500 mg/kg bw/d (90, 225 and 450 mg/kg bw/d as salicylic acid)	No effect on fertility index.
Fertility test, (Gilhardein et al., 1969), ASA , male and female rats	A single dose level of 0.4% in the diet (210 mg/kg bw ASA, equivalent to 161 mg/kg bw as salicylic acid)	ASA did not significantly affect male or female fertility. This dose caused moderate bw depression in males and severe bw depression in females.

Note: all the studies in the table above have a Klimisch reliability score of 2.

None of these studies have been done with salicylic acid but with methyl salicylate or acetylsalicylic acid. These studies also showed a number of deficiencies in relation to current test guidelines in terms of parameters studied, but the results were consistent. No statistically significant effect on fertility was reported in any study. In addition, 2-year chronic toxicity studies in rats and dogs (Webb, 1963) showed no abnormalities in sexual organs (testes/prostate or ovaries/uterus). The adverse effects on reduced viability of offspring reported primarily in rats represent developmental toxicity rather than a reduction in fertility in either males or females.

SCCS comments

SCCS agrees that salicylic acid should not be classified as a reproductive toxicant for the fertility endpoints.

3.3.6.2 Developmental Toxicity

In March 2016, the Committee for Risk Assessment of the European Chemical Agency proposed to classify salicylic acid as a category 2 reproductive toxicant (ECHA, 2016). The

classification is based on adverse developmental effects in two animal species (rat and monkey).
All developmental studies on salicylic acid have been performed in rats and are summarised in table 9.

Table 9. Reproductive and developmental animal studies with salicylic acid.

Species	Test article	Route of exposure	Dosage	Results	Reference
Wistar Rat 20 per group	Salicylic acid	Oral, days 8-14 of gestation	0.06, 0.1, 0.2 & 0.4 % in diet (50 to 200 mg/kg/day)	Maternal mortality 0%. **0.4%:** body weight loss, toxic symptoms, 71% neonatal mortality and growth retardation in foetuses. **0.2%:** growth retardation, skeletal abnormalities. **0.1%** and **0.06%** no significant adverse effects. **NOAEL 0.1% (approx. 75 mg/kg/day)**	Tanaka et al 1973a*
Wistar Rat 20 per group	Salicylic acid	Oral, days 8-14 of gestation	75, 150 or 300 mg/kg once daily	**300 mg/kg/day**: 3 dams died; 100% fetal mortality. **150 mg/kg/day**: 26% fetal mortality, reproductive effects. **NOAEL 75 mg/kg/day**	Tanaka et al 1973b*
Sprague Dawley Rat n = 10	Salicylic acid	Oral, 10 mg/kg twice daily, days 20 &21 of gestation	20 mg/kg/day	Increase in time of onset of parturition; duration of parturition increased in one animal; increased bleeding at parturition in 4 animals. No fetal deaths.	Waltman et al., 1973
Sprague Dawley Rat n = 17	Salicylic acid	Sub-cutaneous dose on day 9 of gestation	380 mg/kg/day	Marked maternal weight loss; decreased fetal weight; 46.6% resorption rate, 5.3% fetal malformations.	Koshakji & Schulert, 1973

*From this review, Tanaka et al 1973a is the pivotal study yielding the lowest NOAEL for the risk assessment.

Following review of the available toxicology data, the pivotal study (for deriving the point of departure (POD) as a toxicological benchmark for the safety evaluation of salicylic acid) remains the same in this dossier as was concluded by the SCCNFP in 2002, namely the developmental toxicity study on salicylic acid by Tanaka et al., 1973a. The POD is expressed as a no observed adverse effect level (NOAEL) of 75 mg/kg/day relating to the most sensitive toxic endpoint i.e. teratogenicity in the rat as the most sensitive species.

Tanaka et al., 1973 a

Guideline/method: Equivalent to OECD Guideline 414 (Prenatal Developmental Toxicity Study)
Species/strain: Rat/Wistar
Group size: 20 females per dose
Test substance: Test substance: salicylic acid; 0.5% in CMC (carboxymethyl cellulose); No other data
Batch:
Dose levels: 0.06%, 0.1%, 0.2% and 0.4% in the diet (50.7 ± 0.6, 77.4 ± 1.0, 165 ± 2.1, 205.9 ± 18.9 mg/kg bw/d, respectively)
Positive control: /
Route: Oral dietary administrations
Exposure period: Exposure was limited to the period of organogenesis (GD 8-14 only)
Exposure frequency: Daily
GLP: No
Study period: /

On day 20 of gestation, 15 of the 20 animals were sacrificed and 5 were allowed to deliver their offspring. The offspring were weaned on day 21 and their weight and growth recorded

every 3 days. After 56 days, the offspring were sacrificed and any visceral or skeletal abnormalities were recorded.

Results

In the 0.4% dose group (205 mg/kg bw/day):
- a marked body weight loss was observed in dams at the beginning of salicylic acid administration, but a gradual increase in body weight was then observed after GD 11 day. This decrease in body weight was assumed to be due to a decrease in food intake, but no deaths were observed.
- uterine and placental weights were significantly lower than controls, but there were no marked differences in the number of corpora lutea or in the rate of nidation in all groups. There was 71.2% neonatal mortality in this group. One dam gave birth to six offspring and all died within a day.
- litter size and body weight and length as well as tail length were statistically significantly decreased. Effects observed at 56 days in offspring were 29.6% external anomalies, 13.6% internal organ anomalies and 46.8% skeletal anomalies.
- maternal effects expressed as temporary body weight loss with toxic symptoms (salivation, piloerection) and the following fetal effects: high fetal mortality (no live fetuses in 9/15 dams examined), high frequency of complex anomalies (cranioschisis, myeloschisis, pes varus, oligodactyly etc.) and dose-related fetal growth retardation.

In the 0.2% dose group (165 mg/kg bw/d):
- fetal effects (fetal anomalies and growth retardation) were seen in the absence of maternal effects. This dose resulted in a maternal serum concentration of about 116 microgram/mL.
- the body weight and length and the tail length were statistically significantly decreased. Effects observed at 56 days in offspring were 3.8% external anomalies, no internal organ anomalies and 14.6% skeletal anomalies.

In the 0.1 and 0.06% dose (approximately 75 and 50 mg/kg bw/d, respectively) groups:
- the two lower doses caused neither maternal nor fetal effects.

In conclusion, this academic non-GLP compliant study illustrates the potential of salicylic acid to induce embryofetal toxicity at dose levels equal to or higher than 0.2% and malformations at the maternally toxic dose level of 0.4% following dietary administration in Wistar rats between days 8 and 14 of gestation.

The no observed adverse effect levels (NOAELs) were defined at 0.2% (165 mg/kg bw/d) for maternal toxicity and 0.1% (75 mg/kg bw/d) for developmental toxicity.

Tanaka et al., 1973 b

Guideline/method:	Equivalent to OECD Guideline 414 (Prenatal Developmental Toxicity Study)
Species/strain:	Rat/Wistar
Group size:	20 females per dose
Test substance:	Test substance: salicylic acid; 0.5% in CMC (carboxymethyl cellulose); No other data
Batch:	
Dose levels:	75, 150 and 300 mg/kg in a 0.5% solution of sodium carboxymethylcellulose
Positive control:	/
Route:	Oral gavage
Exposure period:	Exposure was limited to the period of organogenesis (GD 8-14 only)
Exposure frequency:	Daily

GLP:	No
Study period:	/

Results
In the 300 mg/kg groups of salicylic acid, the body weight gains were inhibited with toxic symptoms such as salivation and piloerection, and some animals died within a few days after the beginning of the administration and high fetal mortality prevailed. Decreased uterine weight was observed in animals of the 150 and 300 mg/kg dose groups as compared to controls; these groups had 25.7% and 100% fetal mortality, respectively.

Litter size and neonatal body weight, body length, and tail length were significantly decreased in the 150 mg/kg dose group.

The incidences of external, internal, and skeletal anomalies in offspring autopsied at the 56th day were 1.8%, 0%, and 2.5%, respectively, for the 75 mg/kg group and 27.8%, 12.7%, and 65.7%, respectively; for the 150 mg/kg group. The offspring from animals of 150 mg/kg salicylic acid group had decreased body length and tail length compared to controls.
The thyroid weight of male offspring from the 75 mg/kg group was significantly decreased compared to controls. The incidences of external organ, internal organ, and skeletal anomalies in offspring were 0%, 5.0% and 0% respectively, for the 75 mg/kg group and 13.7%, 17.2% and 79.2% respectively, for the 150 mg/kg group.

Under the conditions of the present experiment, salicylic acid administered by gavage is embryotoxic in the rats and induces malformations at maternally toxic doses. The teratogenic effect of salicylic acid may be considered as possibly due to direct action of the agent on the foetus, since a relative distribution of the agent was found in the foetus through the placental barrier.

The NOAEL (maternal): 150 mg/kg and the NOAEL (development): 75 mg/kg were identified.

Taken from RAC (March 2016)

The results of the studies demonstrated that salicylic acid has an embryo-/foetotoxic effect in **rats** with dose-dependent growth delays, fetal death and malformations. Early developmental effects were clearly seen in the absence of maternal effects. The teratogenicity of salicylic acid may be attributable to a direct action of the compound. This finding is further supported by the mechanistic study of Greenaway (1982) in which teratogenicity of salicylate in rat embryos was shown independent of maternal factors after exposure *in vitro*.
However, although there was a general resemblance in terms of skeletal and internal organ abnormalities observed, the pattern of malformations following exposures to salicylic acid and acetylsalicylic acid is slightly different, as described in the studies of Tanaka and Gupta. One explanation could be the differences in the experimental protocol, such as the moment of exposure during organogenesis. However, differences in effects following exposure to salicylic acid and acetylsalicylic acid were shown in *in vitro* cultured rat embryos (Yokoyama, 1984): the anomalies induced by acetylsalicylic acid were systemic (e.g. crown-rump length significantly reduced) while those induced by salicylic acid were more localised (e.g. facial anomalies).
The study **in monkeys** also showed teratogenic properties with acetylsalicylic acid but with lower magnitude.
By contrast, the effects **in rabbits** were limited to slight growth retardation and were present only at doses much higher than in the rats and monkeys. No skeletal malformations were reported and at the highest dose only one kit of a dam had hydrocephaly.

Overall, salicylic acid was shown to have teratogenic properties but with species differences in potency: strong in rats and lower in monkeys. In contrast, the teratogenic potential in rabbits was practically non-existent. The data from humans are considered inconclusive.
In conclusion, taking into account the available data, including pharmacokinetics, *in vitro* tests with acetylsalicylic acid and salicylic acid, developmental studies in animals (positive findings in rat and monkey studies and a negative rabbit study), human epidemiology and medical experience, the RAC considered classification of salicylic acid as Repr. 2; H361d (Suspected of damaging the unborn child) to be justified.

SCCS comments
SCCS agrees with RAC that salicylic acid is a developmental toxicant. Harmonised classification of salicylic acid was recently published in Regulation 2018/1480 and is classified as Repr. 2 (H361d Suspected of damaging the unborn child).

For MoS calculation, SCCS uses the developmental NOAEL of 0.1% (75 mg/kg bw/day) derived from Tanaka et al. (1973a). The developmental effects observed in this study are the most sensitive effects after repeated exposure to salicylic acid. This is also in agreement with the previous SCCNFP Opinion (2002) and is also supported by Tanaka et al. (1973b).

3.3.7 Mutagenicity / genotoxicity

3.3.7.1 Mutagenicity / genotoxicity in vitro

From SCCNFP/0522/01/2002

Studies have been performed in order to assess the mutagenic/genotoxic potential of salicylic acid and acetylsalicylic acid. These results are summarised in the following tables 10, 11 and 12.

Table 10. *In vitro* mutagenicity in Bacteria and Yeast

Methods	Test article	Metabolic activation	Results	Reference
Ames tests	• salicylic acid acetylsalicylic acid 500 µg/mL	With without	negative	McCann, 1975 Kawachi, 1979
Ames tests	salicylic acid 3 to 8 10^{-5} M	No data available	negative	McCann J., 1975
Bacillus subtilis assay	salicylic acid acetylsalicylic acid	Without	positive	Kawachi T., 1979

Table 11. *In vitro* mammalian clastogenicity

Methods	Test article	Metabolic activation	Results	Reference
Cultured CHO cells (*3 hour exposure*)	salicylic acid 1.5 to 25 mg/mL	With and without	negative	Stich HF, 1981

Chinese hamster lung cells (*48 hour exposure*)	salicylic acid 1.0 and 1.25 mg/mL	Without	positive	Ishidate MR, 1983

The *in vitro* studies for salicylic acid and for acetylsalicylic acid that were submitted include results of experiments whose methodology is not reported: they are mainly represented by a list of results related to many chemicals. The results reported do not comply with the guidelines defined by the SCCNFP.

Table 12. *In vivo* clastogenicity/mutagenicity

Method	Test article	Animal species	Results	Reference
Drosophila sex-linked recessive lethal assay	Acetylsalicylic acid 10 mM	*Drosophila Melanogaster*	negative	King MT 1979

This submission

A range of studies have been performed in order to assess the mutagenic/genotoxic potential of salicylic acid. These results are summarised in the following sections.

Mutagenicity / genotoxicity *in vitro*
Available *in vitro* data for mutagenicity and genotoxicity for salicylic acid and sodium salicylate are presented in Tables 13 and 14.

Table 13. Bacteria and yeast assays for salicylic acid and sodium salicylate

Methods	Test Article	Metabolic activation	Results	Reference
Ames test: TA100, TA98, TA1535, TA1537.	Salicylic acid	With and without	negative	McCann et al 1975
Ames TA98	Salicylic acid 2.5 to 10 mg/mL	With and without	negative	San & Chan, 1987
Ames	Salicylic acid 0.1 mg/disc	With and without	negative	Kuboyama & Fujii, 1992
B subtilis rec assay H17(Rec$^+$0 and M45(Rec$^-$)	Salicylic acid (5mg/disc)	NR	positive	Kuboyama & Fujii, 1992
Ames: TA98, TA100.	Sodium salicylate	With and without	negative	Kuboyama & Fujii, 1992
B subtilis rec assay H17(Rec$^+$0 and M45(Rec$^-$)	Sodium salicylate 5mg/disc	NR	negative	Kuboyama & Fujii, 1992
OECD guideline 471 Ames: TA1535, TA1537, TA98 and TA100	Salicylic acid 1.22 to 5000	With and without	negative	(Ministry of Labour/Japan, 2000) Reliability 1, Key

and WP2uvrA/pKM101 of *E. coli*	µg/plate			study in REACH dossier.

Applicant's conclusion: On the balance of evidence and giving the OECD guideline test study the most weight, salicylic acid is not genotoxic in bacterial assays.

Table 14. *In vitro* mammalian clastogenicity and gene mutation

Methods	Test Article	Metabolic activation	Results	Reference
Chinese Hamster Ovary Cells (cultured for 3 hours) equivalent to OECD guideline 473	Salicylic acid 1.5 to 25 mg/mL	With and without	negative	Stich et al 1981
Chinese Hamster Lung Cells (cultured for 48 hours)	Salicylic acid 1 and 1.25 mg/mL	Without	positive	Ishidate, 1983
OECD Guideline 476 Mouse lymphoma assay	Salicylic acid 87.5, 175.0, 350.0, 1400.0 µg/mL	With and without (4h); without (24h)	Salicylic acid did not induce mutations	RCC, 2008b; key study in REACH dossier.

Applicant's conclusion: In an OECD guideline 476 study, salicylic acid did not induce mutations. Salicylic acid also did not lead to chromosome aberrations in an OECD guideline 473 equivalent study.

3.3.7.2 Mutagenicity / genotoxicity in vivo

From SCCNFP/0522/01/2002

One study by Giri et al. (1996) has investigated mutagenicity / genotoxicity *in vivo*, the findings of which are illustrated in Table 15.

Table 15. Summary of results on chromosomal damage by Giri et al. 1996.

Methods	Test Article	Results
Sister chromatid exchange (SCE) assay*, n=5 Swiss albino mice	25, 50 or 100 mg/kg salicylic acid in DMSO, injected intraperitoneally. Oral dosing with 350 mg/kg salicylic acid in gum acacia and distilled water.	Salicylic acid did not induce SCE
Chromosome aberration assay**, n =4 or 5 Swiss albino mice	50, 100 or 200 mg/kg salicylic acid in DMSO (n=4), injected intraperitoneally. Oral dosing with 350 mg/kg salicylic acid in gum acacia and distilled water (n =5)	No increase in chromosomal aberration. A significant increase in mitotic index was seen only with the lowest dose (50 mg/kg) *i.p.* and the oral dose.
Sister chromatid	25, 50 or 100 mg/kg sodium	Salicylic acid did not induce

exchange (SCE) assay*, n=5 Swiss albino mice	salicylate in DMSO, injected intraperitoneally. Oral dosing with 350 mg/kg salicylic acid in gum acacia and distilled water.	SCE
Chromosome aberration assay**, n =4 or 5 Swiss albino mice	50, 100 or 200 mg/kg sodium salicylate in DMSO (n=4), injected intraperitoneally. Oral dosing with 350 mg/kg SA in gum acacia and distilled water (n =5)	A significant increase in chromosomal aberrations was seen with 200 mg/kg *i.p.* and the oral dose.
*IP and oral dosing studies taken together, these studies are acceptable, satisfying the requirement of Test Guideline OPPTS870.5915 (*In vivo* Sister Chromatid Exchange Assay). **These tests were carried out according to a scientifically acceptable standard which is similar to EPA OPPTS 870.5915. Although each of these key studies had minor deviations from current guidelines, IP and oral dosing taken together, they are considered as acceptable, satisfying the requirement for Test Guideline OECD 475 (Mammalian Bone Marrow Chromosomal Aberration Test).		

The study by Giri et al 1996, is the key *in vivo* study for mutagenicity cited in the REACH dossier for salicylic acid. Salicylic acid neither induced sister chromatid exchanges (SCE) nor chromosomal aberrations (CA) in *i.p.* or oral studies *in vivo* in mice. This indicates that salicylic acid is not genotoxic in the bone marrow cells of mice.

Applicants' conclusion: The overall conclusion from the weight of evidence *in vitro* and *in vivo* is that salicylic acid is not mutagenic/genotoxic.

SCCS evaluation studies on salicylic acid submitted by the Applicant in SCCNFP/0522/01/2002:

1. Gene mutation assays using bacteria

Guideline: /
Test system: Salmonella typhimurium strains TA100, TA1535, TA98, TA1537
Escherichia coli strain WP2*uvr*A/pKM101
Replicates: Two experiments, duplicate plates
Test substance: Salicylic acid
Batch: GE01 (Tokyo Kasei Kogyo Co, Ltd.)
Purity: >99.5%

Concentrations: Experiment 1:
±S9 mix: all *S. typhimurium* strains and *E. coli*: 0, 1.22, 4.88, 19.5, 78.1, 313, 1250, 5000 µg/plate

Experiment 2:
±S9 mix: all *S. typhimurium* strains: 0, 9.77, 19.5, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 µg/plate
±S9 mix: *E. coli* strain: 0, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 µg/plate

Vehicles: DMSO

Positive Controls:	-S9 mix: 2-aminofluorene (AF-2) for TA100, TA98 and WP2*uvr*A/pKM101; sodium azide (NaN_3) for TA1535; 9-aminoacridine (9-AA) for TA1537 +S9 mix: 2-aminoanthracene (2-AA): for all *S. typhimurium* and WP2*uvr*A/pKM101 strains
Negative controls:	Vehicle control (DMSO)
GLP:	/
Study period:	/

Material and methods
Salicylic acid was tested for mutagenicity in the reverse mutation assay with and without metabolic activation in *S. typhimurium* strains TA100, TA1535, TA98, TA1537, and *Escherichia coli* strain WP2*uvr*A/pKM101, in duplicates, in two separate experiments, both with and without the addition of a S9-mix system (no data on the metabolic system).

Results
There are no data on a preliminary toxicity assay.

Experiment 1
In this experiment, the dose levels tested were 1.22, 4.88, 19.5, 78.1, 313, 1250, 5000 µg per plate in the presence and absence of S9 activation system. No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation.
Toxicity was observed beginning at 78.1 µg/plate (TA100 strain), 313 µg/plate (TA1535, TA98 or TA1357 strains) or 1250 µg/plate (*E. coli* WP2*uvr*A/pKM101).

Experiment 2
In this experiment, the dose levels tested were 9.77, 19.5, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 µg per plate for all *S. typhimurium* strains and 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 µg/plate for *E. coli* strain, in the presence and absence of S9 activation system. No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation.
Toxicity was observed beginning at 78.1 µg/plate (TA100 and TA1537 strains), 156 µg/plate (TA98 strain), 313 µg/plate (TA1535 strain) or 2500 µg/plate (*E. coli* WP2*uvr*A/pKM101).

Ref.: Ministry of Labour/Japan, 2000

SCCS comment
The results of the study are presented in the pdf file provided to the SCCS in the form of two tables and indicate no mutagenic effect of salicylic acid in the absence or presence of S9 mix in all bacterial strains used.
The SCCS noted that from the information provided it is not certain if the study was performed under GLP standard. Furthermore, it is not clear who performed the study or when it was performed, what concentrations of the positive control substances were used and what the historical values of revertants number for control and positive substances were.

Other studies submitted by the Applicant and available from the open literature are presented in Table 16. They are of limited value for hazard identification.

Table 16. Studies on gene mutations of salicylic acid in bacteria

	Type of test	Tester strain	Test concentrations	S9-mix	Result	Reference	SCCS remarks
1.	Ames test	S. typhimurium: TA100, TA98,	≤ 500 nM/plate	With and without	negative	McCann et al. 1975	- non-GLP study

		TA1535, TA1537					
2.	Ames test	S. typhimurium: TA98	2.5, 5, 10 mg/mL	Without	negative	San & Chan, 1987	- non-GLP study - limited value
3	Ames test Pre-incubation for 30 min	S. typhimurium: TA98, TA100	0.1 mg/plate	With and without	positive	Kuboyama & Fujii, 1992	- non-GLP study - salicylic acid tested positive with rat S9, but sodium salicylate negative; - only one concentration of salicylic acid and two bacterial strains were tested - no TA98 revertants after the exposure to salicylic acid –S9 (probably due to excessive cytotoxicity) - limited value
4	Rec-assay	Bacillus subtilis strains H17 (Rec+) and M45 (Rec-)	1, 2, 3, 4, 5 mg/disc	-	positive	Kuboyama & Fujii, 1992	- Non-GLP study - salicylic acid tested positive (evident concentration-effect relationship) but sodium salicylate was tested negative - Rec-assay is not validated OECD test - limited value

2. *In vitro* gene mutations in mammalian cells

Guideline: OECD 476 (adopted July 21, 1997)
Test system: L5178Y mouse lymphoma cells (Thymidine Kinase Locus $Tk^{+/-}$)
Replicates: Two independent experiments, each two parallel cultures
Test substance: Salicylic acid pharmaceutical grade; CAS: 69-72-7
Batch: RAS0725500 made on Sept. 12th 2007 (purity: >99%)

Concentrations: Preliminary test:
+S9 mix (4 h exposure) and -S9 mix (4 and 24 h exposure): 7.97, 15.94, 31.88, 63.75, 127.5, 255, 510, 1020, 2040 µg/mL

Main test:
Experiment I:
±S9 mix (4 h exposure): 43.8, 87.5, 175, 350, 700, 1400 µg/mL
Experiment II:
-S9 mix (24 h exposure): 43.8, 87.5, 175, 350, 700, 1400 µg/mL
Vehicle controls: deionised water
Positive Controls: -S9 mix: methyl methanesulfonate (MMS), 19.5 µg/mL
+S9 mix: cyclophosphamide (CP), 3 and 4.5 µg/mL
GLP: Yes
Study period: May 2008 – Aug 2008

Material and methods

The *in vitro* mammalian cell gene mutation assay was conducted to investigate the potential of salicylic acid dissolved in water to induce gene mutations at the $TK^{+/-}$ locus of the L5178Y mouse lymphoma cell line.
Prior to the main study, a preliminary toxicity test was performed on cell cultures using a 4-hour exposure time both with and without metabolic activation (S9, liver post mitochondrial supernatant of rats treated with phenobarbital/β-naphthoflavone) and using a 24-hour exposure without S9-mix. The dose range used was 10.9 to 1400 µg/mL for all three exposure groups. The main assay was performed in two independent experiments, using

two parallel cultures each. The first main experiment was performed with and without liver microsomal activation and a treatment period of 4 h. The second experiment was solely performed in the absence of metabolic activation with a treatment period of 24 hours.

Results

In the **pre-test**, following 4 h (±S9-mix). no relevant toxic effects leading to RSG (% Relative Survival Growth) values below 50% were observed up to the maximum concentration (1400 µg/mL, i.e. 10 mM). After continuous treatment (24 hours), a relevant toxic effect occurred at the maximum concentration of 1400 µg/mL. The test medium was checked for precipitation at the end of each treatment period (4 or 24 hours) before the test item was removed. No precipitation occurred with and without metabolic activation.

In the **first experiment**, no relevant toxic effects indicated by a relative cloning efficiency 1 or a relative total growth of less than 50% of survival were observed up to the maximum concentration with and without metabolic activation. In the **second experiment** (24 h treatment solely without metabolic activation) relevant toxic effects were noted at 700 µg/mL and above. The data at the maximum concentration of 1400 µg/mL are considered valid even though the relative total growth fell short of the lower limit of 10 %. The corresponding relative cloning efficiency 1 however, was in a toxic but fully acceptable range. The recommended toxic range of approximately 10 – 20% of survival or RTG was covered in experiment II.

No substantial and reproducible dose dependent increase of the mutation frequency was observed in both main experiments. The threshold of 126 above the corresponding solvent control was not reached at any of the test points. Two minor increases exceeding the historical control range occurred in the second experiment following 24 h exposure at 700 and 1400 µg/mL in culture I. However, no comparable increase of the mutation frequency was noted in the parallel culture under identical conditions. A linear regression analysis (least squares) was performed to assess a possible dose dependent increase of mutant frequencies using SYSTAT® statistics software. A significant dose dependent trend of the mutation frequency indicated by a probability value of <0.05 was solely determined in the first culture of experiment II. However, a certain increase of the mutation frequency is common at cytotoxic concentrations and the threshold of 126 above the corresponding negative control was not reached. Therefore, the isolated significant trend described above was considered as biologically irrelevant.

Conclusion

In conclusion it can be stated that under the experimental conditions reported the test item did not induce mutations in the mouse lymphoma thymidine kinase locus assay using the cell line L5178Y in the absence and presence of metabolic activation.

Ref: RCC, 2008b

SCCS comment

In the first culture of the second experiment a significant trend (p=0.001) was observed, and mutation frequency for the two highest concentrations was outside the historical control range. The RSG at the highest concentration of 1400 µg/mL was below 10% meaning a strong cytotoxic effect. Considering this and also the fact that this effect was not repeated in the second culture (although significance level was at p=0.052), the significant trend should be regarded as not biologically meaningful. Hence, the study indicates no mutagenic effect of salicylic acid in the mouse lymphoma assay.

3. *In vitro* chromosomal aberrations

SCCS comment

1. Only one study on chromosomal aberrations *in vitro* with salicylic acid is available in the open literature and which was submitted by the Applicant. In this study (Stich et al., 1981) Chinese Hamster Ovary cells were exposed to salicylic acid for 3 hours, with and without S9-mix. The result of the study is negative. However, the SCCS emphasizes that the study

is not GLP-compliant, and is of limited value since apparently only one concentration of salicylic acid was tested (25 mg/mL) in the main experiment, and no result with a positive control without S9-mix was provided. Moreover, for each sample 200 metaphase plates were analysed for chromosome aberrations, which is in contrast to the current recommendation of scoring at least 300 well-spread metaphases per concentration and control to conclude a test chemical as clearly negative (OECD TG 473 adopted 29 July 2016).

2. In the second study, i.e. Ishidate et al. (1983) on chromosomal aberration test *in vitro* a Chinese hamster fibroblast cells were exposed to 1 and 1.25 mg/mL salicylic acid for 48h. Although, the result was positive as claimed by the Applicant, the original publication was not provided for verification in the submission II.

4. *In vivo* chromosomal aberrations

SCCS comment
The SCCS considers the result of the submitted *in vivo* study (Giri et al., 1996) on chromosomal aberrations and sister chromatid exchanges of salicylic acid as negative.

Overall SCCS comments on mutagenicity
The SCCS comments are based on available, i.e. previously and currently submitted data on mutagenicity testing of salicylic acid. The genotoxicity of salicylic acid was investigated with valid genotoxicity tests for *in vitro* gene mutations, in both bacterial (Ministry of Labour/Japan, 2000) and mammalian test system (RCC, 2008b). Although no valid *in vitro* test results on chromosomal aberrations were provided, the *in vivo* chromosomal aberration and sister chromatid exchange tests in mice showed no mutagenic activity of salicylic acid (Giri et al., 1996).
Based on the results provided salicylic acid can be considered to pose no genotoxic hazard.

3.3.8 Carcinogenicity

From SCCNFP/0522/01/2002

Animal data

- Salicylic acid was tested as part of a skin tumour promotion study using uninitiated mouse skin. Salicylic acid 20% in a dioxane solution was applied topically (one drop of about 25 µl) to 31 female "Sutter" mice, 2-3 months of age, treated twice weekly for 12 weeks. There were no deaths or papillomas throughout the study. However, as no post-mortem examination was performed at the end of the treatment period, the results were considered of limited value for the evaluation of possible carcinogenic properties of the substance.

  Ref.: Boutwell, 1959

- Carcinogenicity studies have been performed to assess the carcinogenic potential of acetylsalicylic acid in mice at 1 and 5% and in rats at 0.25% and 2% in drinking water. The results were negative on both studies. Considering these results, salicylic acid, a metabolite of acetylsalicylic acid, was considered to be devoid of such a potential.

  Ref.: Odashima, 1979

- Salicylic acid is the main metabolite of acetylsalicylic acid (aspirin) and there is sufficient evidence in animal models that acetylsalicylic acid prevents cancer.

  Ref.: Vaino, 1997

Human data
No data are available for salicylic acid.

- Salicylic acid is the main metabolites of aspirin (acetylsalicylic acid). Epidemiological studies have shown that acetylsalicylic acid reduces the risk of colorectal cancer.

  Ref.: Vaino, 1997
- Thun et al. reported that chronic use of acetylsalicylic acid decreases susceptibility to bowel cancer.

  Ref.: La Du, 1971
- In another report, salicylic acid has been shown to interact with phenolsulphotransferase and it has been proposed that this could be one of the pathways by which acetylsalicylic acid reduces cancer risk.

  Ref.: Levy, 1972
- Recently it has also been reported that users of acetylsalicylic acid had a moderately reduced risk of gastric cancer.

  Ref.: Akre, 2001

Hazard evaluation
Only one animal study on the carcinogenicity of salicylic acid has been found. The study is of limited value for evaluation of possible carcinogenic properties of the substance. However, it has been found both in epidemiological studies and in animal experiments that acetylsalicylic acid reduces skin cancer risk. Since salicylic acid is the main metabolite of acetylsalicylic acid, the cancer preventive effect of acetylsalicylic acid may be caused by its metabolite salicylic acid.

Ref: Boutwell and Bosch, 1959

This submission

Animal data
Salicylic acid was tested as part of a skin tumour promotion study using uninitiated mouse skin (Boutwell & Bosch, 1959). Salicylic acid 20% in a dioxane solution was applied topically (one drop of about 25 µL) to 31 female "Sutter" mice, 2-3 months of age, treated twice weekly for 12 weeks. There were no deaths or papillomas throughout the study. However, as no post-mortem examination was performed at the end of the treatment period, the results were considered of limited value for evaluation of possible carcinogenic properties of the substance.
There are no oral carcinogenicity studies on salicylic acid. Carcinogenicity studies have been performed to assess the carcinogenic potential of acetylsalicylic acid in mice at 1 and 5% and in rats at 0.25% and 2% in drinking water (Odashima et al 1979). The results showed acetylsalicylic acid was not carcinogenic in both studies. Considering these results, salicylic acid, a major metabolite of acetylsalicylic acid, is also considered not to be carcinogen. Salicylic acid is the main metabolite of acetylsalicylic acid (aspirin) and there is evidence in animal models that acetylsalicylic acid helps to prevent cancer (Ma et al., 2017).

Human data
Salicylic acid is the main metabolite of aspirin (acetylsalicylic acid). Epidemiological studies have shown that acetylsalicylic acid can reduce the risk of cancer (Ma et al 2017). Thun et al. (1991) reported that chronic use of acetylsalicylic acid decreases susceptibility to bowel cancer. It has also been reported that users of acetylsalicylic acid had a moderately reduced risk of gastric cancer (Akre et al 2001).

Applicant's conclusion: There are no reports of aspirin or salicylic acid acting as a carcinogen. Reported studies discuss the potential anticancer properties of these substances.

Overall SCCS comment on carcinogenicity
No additional studies have been provided by the Applicant in submission II. However, on the basis of the evidence available on negative results of genotoxicity and some evidence on the absence of carcinogenicity, the SCCS considers salicylic acid as unlikely to be a carcinogen.

3.3.9 Photo-induced toxicity

3.3.9.1 Phototoxicity / photo-irritation and photosensitisation

In the previous SCCNFP Opinion, no photo-induced toxicity data have been provided.

This submission
Salicylic acid has been investigated for phototoxic and photosensitising potential, as outlined in the Table below.

Table 17. Phototoxicity studies for salicylic acid

Method	Observations	Reference
5 albino outbred ICR mice Days 0 and 1: 50 µL 50% salicylic acid in acetone applied to clipped abdominal skin, and site irradiated for 2.5 h at 15 cm. Day 5: 50 µL 25% salicylic acid in alcohol applied to either side of the pinna, and site irradiated for 2.5 h at 15 cm.	The degree of the sensitivity was assessed by measuring the ear thickness 24 hours after challenge. Ear thickness was not increased after 24 h. Not photosensitising	Miyachi & Takigawa, 1983
2% salicylic acid in a cream; 2 male and 5 female human subjects. 0.2 g cream applied to lower back. Irradiated with UVA 24 h after application.	No phototoxic potential.	Ivy Laboratories (1993a)
2% salicylic acid in a cream: 8 male and 17 female human subjects. 100 mg applied to lower back (25 mg/cm^2) for 24 h. Solar simulator applied to treated area. 48 hrs later process was repeated. Induction phase, twice weekly exposures over 3 weeks. Challenge patch was applied 10 days after last induction.	Not photosensitising.	Ivy Laboratories (1993b)
2% salicylic acid in gel; 1 male, 9 female human subjects. 0.2g volar forearms. One forearm exposed to UVA 24 h after application.	No phototoxic potential	HRL Inc (1993c)
2% salicylic acid in gel; 4 male and 24 female human subjects. 0.2g volar forearms. One forearm exposed to UVA 24 h after application. Induction phase, twice weekly exposures over 3 weeks. 0.2 g volar forearms. UVA (15 min) and UVB irradiated (135 sec).	Not photosensitising	HRL Inc (1993d)
2% salicylic acid in gel; 2 male and 8 female human subjects. 0.2 g volar forearms. One forearm exposed to UVA 24 h after application. Induction phase, twice weekly exposures over 3 weeks. 0.2 g volar forearms. UVA (17 min) and UVB irradiated (120 sec).	Not photosensitising	HRL Inc (1997b)
2% salicylic acid in gel; 5 male and 23 female human subjects. 0.2 g volar	Not photosensitising	HRL Inc (1997c)

forearms. One forearm exposed to UVA 24h after application. Induction phase, twice weekly exposures over 3 weeks. 0.2 g volar forearms. UVA (17 min) and UVB irradiated (120 sec).		
2 or 4% salicylic acid in cream applied in the morning; 18 male mice, 18 female mice. In the afternoon, skin was exposed to synthetic solar light for four hours, 5 days per week, 40 weeks.	Not photocarcinogenic; photoprotective	National Toxicology Program, 2007

Applicants' conclusion: Salicylic acid is not phototoxic.

SCCS comment
Although risk assessment of cosmetic ingredients in the remit of the SCCS is based on the assessment of the ingredient and not of cosmetic formulations, test results of phototoxicity studies which use commercial (probably cosmetic) formulations have been reviewed by the SCCS. The SCCS agrees that, based on the submitted studies (in human and in mice), salicylic acid does not have photo-irritant, photosensitising or photocarcinogenic properties.

3.3.9.2 Photomutagenicity / photoclastogenicity

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3.3.10 Special Investigations

Although, the literature search performed by the SCCS has shown some evidence that some salicylates, such as homosalate, may have endocrine properties, only a few studies have investigated the endocrine properties of salicylic acid itself.

Salicylic acid is not listed as an endocrine disrupter candidate in the priority list published in 2007 by the European Commission. This working list of chemicals was compiled from lists of "suspected endocrine disruptors" published by various organisations, supplemented by a search of the scientific literature to identify reports and papers describing effects suggestive of endocrine disrupting activity for specific chemicals.
(http://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm).

Salicylic acid has also not been identified as an endocrine disrupter by the Pesticide Action Network Pesticide DataBase.
Ref: http://www.pesticideinfo.org/Docs/ref_toxicity5.html#EDSummary

In a newly published report from the Danish Centre on Endocrine Disrupters researchers from the National Food Institute, Technical University of Denmark, and the University of Southern Denmark have evaluated that there is solid scientific evidence that salicylic acid is an endocrine disruptor. In this report different derivatives of Salicylic acid have been used, e.g. acetylsalicylic acid (Aspirin), sodium salicylate and methyl salicylate.
Ref: http://cend.dk/files/DK_ED-list-final_appendix1_2018.pdf

SCCS is also aware that in the framework of the Biocide regulation, specific tests are currently on-going to assess whether salicylic acid has endocrine disrupting

properties. Depending on the outcome of these tests, the potential endocrine disrupting properties of salicylic acid in cosmetics may need to be considered.

3.4 EXPOSURE ASSESSMENT

3.4.1 Single and aggregate exposure to salicylic acid as cosmetic ingredient

The Applicant used three different scenarios and approaches for the consumer exposure assessments, two of which (A and B) are further described and considered in this Opinion. Both scenarios assume 100% occurrence of salicylic acid in all cosmetics products used by an individual in a day. The product concentrations used in both approaches are based on the current legislation that allows SA for use as preservative up to 0.5% and in other applications up to 2 or 3% (Table 18). They are further based on an industry survey provided by the Applicant on concentrations actually used to date (see Appendix). The concentrations used in the assessments are for all products larger than the maximal concentrations found in the survey. In the assessment of the Applicant, all scenarios also factor in a value of 50% for skin penetration of the dermally applied substance from all products, which, according to the Applicant, is likely to be a significant overestimate for most products at neutral pH.
There are literature reports about the use of salicylic acid in toothpaste and mouthwash, however, according to the survey presented by the Applicant, it is not used in any oral products, and therefore not considered in the exposure assessments. Furthermore, the Applicant did not consider any sprayable products for the exposure assessment. Values for the % level of salicylic acid in each of the 17 product types, which were used in the exposure assessment, are presented in Table 18.

Table 18. Salicylic acid concentration values used in the exposure assessment

Product Type (Crème C&C)	Concentration (% w/w)
Shower gel	2
Liquid hand soap	2
Shampoo	3
Rinse-off conditioner	3
Hair styling	2
Body lotion (mass market, prestige, other)	0.5
Face moisturiser	2*
Hand cream	2
Liquid make-up foundation	2
Make-up remover	2
Eye shadow	0.5
Mascara	0.5
Eye pencil	0.5
Lipstick	0.5
Deodorant roll-on	0.5

Deodorant aerosol spray (ethanol-based)	0**
Deodorant spray	0**
Toothpaste	0***
Mouthwash	0***

* For face moisturiser products in Scenario 1, the concentration data and frequency of use of face cream products has been used.
** For both the deterministic and the probabilistic exposure assessment, these products have been excluded, since the Applicant does not intend to use salicylic acid in spray/aerosol products and claims that spray products containing salicylic acid do not exist on the European market.
*** For both the deterministic and the probabilistic exposure assessment, these oral products have been excluded, since the Applicant stated that SA is currently not used in such products on the European market.

The survey of SA use in cosmetic products on the European market also reports the number of formulations with SA on the European market in relation to the total number of respective formulations (see Table 19). This information was NOT used in the approaches A and B that have been selected for SCCS conclusions. It is included in this opinion only for illustrating that to date the assumption of 100% occurrence in cosmetics products in approaches A and B with reference to a whole population is highly conservative. However, considering brand loyalty and possible formulation change in the future, the SCCS considered only the conservative scenarios A and B appropriate for risk assessment.

Table 19. Occurrence (%) of salicylic acid in cosmetic formulations on the European market calculated from tonnage data.

Product Type (Creme C&C)	Formulations total	Formulations with SA[1]	Occurrence (fraction)
Showergel	2985	386	0.121
Liquid hand soap	409	33	1.436
Shampoo	2692	575	6.754
Rinse-off conditioner	2071	39	7.516
Hair styling	2311	20	0.019
Body lotion	3200	61	0.013
Face moisturizer	5218	432	0.958
Hand cream	641	8	0.220
Liquid make-up foundation	8336	194	0.274
Make-up remover	1454	163	0.710
Eye shadow	6140	4	<0.001
Mascara	906	10[2]	0.009[2]
Eye pencil	1599	6[2]	0.029[2]
Lipstick	9751	4	0.001

Deodorant roll-on	1374	16	<0.001
Mouthwash	68	0	0
Toothpaste	517	0	0

[1]Except mascara, eye pencil
[2]No salicylic acid in product type. Refers to formulations containing magnesium salicylate

A) **Deterministic approach according to the SCCS Notes of Guidance, 2016:** This consumer exposure assessment uses maximum allowed % levels of salicylic acid in 17 cosmetic product types (including a calculation of aggregate exposure) according to the deterministic additive methods referred to in the SCCS Notes of Guidance 9th revision (April 2016). This method assumes that everybody in the population uses all the products each day. This is a highly precautionary scenario.
In the SCCS Notes of Guidance 9th revision (April 2016), values are provided for the amount of product exposure an individual consumer could experience daily, for 17 different cosmetic products, and as calculated in mg/kg bw/day.
According to the Applicant, the cosmetics industry does not currently use salicylic acid in toothpaste or mouthwash. Salicylic acid has a bitter taste and is not likely to be palatable in oral care products nor is it likely to be the best preservative for these products. Therefore, oral care products were not included in the exposure assessment. If this situation was to change in the future and salicylic acid was used up to a maximum of 0.5% in an oral care product, the resulting exposures would be very low.

B) **Probabilistic approach:** a consumer exposure assessment using maximum allowed % levels of salicylic acid and taking into account habits and practices data for product use in the European population. Probabilistic distributions of product use data are used according to the Crème Care and Cosmetics exposure model (Ref: Crème Global 2017). This model uses a Monte Carlo approach to solve the exposure equations based on individual based habits and practices and is further described in the following publications: D. Comiskey et al. 2015 &2017, B. Safford et al. 2015 & 2017. The calculations for SA follow the same approach as described in these publications, only differ in the selection of parameter values (assumed occurrence: 100%; specific product concentrations in Table 20).
This approach differs from the deterministic approach only in that product exposure is not based on conservative point estimates for products amounts used, but is based on distributions of product usage data, thus allowing the analysis to reflect that not all subjects are high users of each product. The same concentration and retention values have been used as in the deterministic approach (see Table 18) and the model calculation for the probabilistic approach included also the assumption that salicylic acid is present in every product in the market for cosmetics (occurrence: 100%). Applying these parameters together with the habits and practices data in the Crème Care and Cosmetics exposure model yields the 95th percentile values for systemic exposure dose (SED) and MOS (see Table 20).

SCCS comment
The Applicant considers a dermal absorption fraction of **50%** as a "highly conservative value" to calculate the aggregate exposure. However, in light of the provided absorption studies, the SCCS is of the opinion that a dermal absorption value of **60%** should be used in the calculations (see chapter 3.3.5).

By multiplication with a correction factor, the SCCS updated the SEDs provided by the Applicant to be valid for an absorption fraction of 60%. The updated SEDs for the deterministic approach are given in Table 20 and for the probabilistic approach in Table 21.
The standard errors in Table 21could not be recalculated for uptake of 60%, they refer to the Applicant's calculation with an uptake of 50%.

Table 20. Approach A: Systemic exposure dose (SED) calculation of salicylic acid in various cosmetic products using the deterministic approach according to SSCS Notes of Guidance, 2016

Skin penetration (%):		**60**		
Product	**Maximum concentration (w/w %)**	**Calculated relative daily exposure to product[1] (mg/kg bw/day)**	**Total dermal exposure (mg/kg bw/day)**	**Calculated SED[2] (mg/kg bw/day)**
Shower gel	2	2.79	0.0558	0.0335
Hand wash soap	2	3.33	0.0666	0.0400
Shampoo	3	1.51	0.0453	0.0272
Hair conditioner	3	0.6	0.0180	0.0108
Hair Styling	2	5.74	0.1148	0.0688
Body lotion	0.5	123.2	0.616	0.369
Face cream	2	24.14	0.4828	0.2897
Hand cream	2	32.7	0.654	0.3924
Liquid foundation	2	7.9	0.158	0.0948
Make-up remover for face	2	8.33	0.1666	0.1000
Eye shadow	0.5	0.33	0.0017	0.0011
Mascara	0.5	0.42	0.0021	0.0012
Eyeliner	0.5	0.08	0.0004	0.0002
Lipstick, lip salve	0.5	0.9	0.0045	0.0028
Non-spray deodorant	0.5	22.08	0.1104	0.0662
Deodorant aerosol spray (ethanol-based)*	0			
Deodorant spray*	0			
Toothpaste**	0			
Mouthwash**	0			
Aggregate Exposure				**1.50**

[1]According to values in Table 4 on page 82 of the SCCS Notes of Guidance, 2016
[2]Total dermal exposure x 0.6
* The Applicant does not intend to use salicylic acid in spray/aerosol products.
**The cosmetics industry stated that it does not currently use salicylic acid or its salts in these products

Table 21. Approach B: Probabilistic approach: Estimated 95th percentile and standard error of the systemic exposure dose (SED) of salicylic acid from individual product types, and calculated aggregate exposure from all assessed products (consumers only).

Product	**Concentration (w/w %)**	**SED (95th percentile) (mg/kg bw/day)**	**Standard Error * (mg/kg bw/day)**

Shower gel	2	0.0316	0.0006
Liquid Hand Soap	2	0.0326	0.0003
Shampoo	3	0.0352	0.0005
Rinse-off Conditioner	3	0.0438	0.0013
Hair Styling	2	0.0780	0.0027
Body Lotion	0.5	0.3552	0.0119
Face Moisturiser	2	0.3017	0.0072
Hand Cream[1]	2	0.4130	0.0444
Liquid Makeup Foundation	2	0.1308	0.0072
Makeup Remover	2	0.0840	0.0044
Eye Shadow	0.5	0.0004	0.00001
Mascara	0.5	0.0011	0.00006
Eyeliner	0.5	0.00004	0.000001
Lipstick	0.5	0.0010	0.00005
Deo Roll On	0.5	0.0560	0.00087
Aggregate Exposure[2]		**0.384**	**0.0074**

[1]Note that the P95 of exposure across all products is sometimes exceeded within an individual product category. This is because high users of an individual product are not high users of all products.
[2]This is based upon a probabilistic assessment of habits and practices product use data, therefore this is not a straightforward addition of the SED values for individual products.
* note that the standard errors were not recalculated for uptake of 60%, they refer to the Applicant's calculation with an uptake of 50%.

The Applicant also provided two other probabilistic scenarios ("Scenario 2" and an "Additional Scenario"), where a survey among industry was used to derive distributions for currently used salicylic acid concentrations in products. Since Scenario 2 assumes distributions of current concentrations in products, which may be different in the future, this scenario is not precautionary enough to be used for the assessment of salicylic acid. The "Additional scenario" is even less precautionary as it is based on survey figures that represent actual occurrence of salicylic acid in products, and is therefore likewise not reported here.

According to the 9th revision of the Notes of Guidance (2016), a probabilistic approach can be accepted, if the robustness has been checked. The probabilistic approach presented above is precautionary in two ways: First, it is assumed that every consumer who uses a product category that may contain salicylic acid, uses salicylic acid containing products. Since there are a number of other preservatives that can be used instead of SA, this is a conservative assumption. Second, it is assumed that all the products contain maximum levels allowed as of today, which is another conservative assumption. Hence, the approach presented above is probabilistic only regarding the use data, which can be assumed to be stable over a longer period of time. The SCCS was given access to the general Crème Care and Cosmetics exposure model and assured that the model assumptions and the realisation are sound and according to the current state of the art.
However, whereas the assumptions and results of the model are clearly reported in the form of text, the presented report for salicylic acid does not include a dated output file of the

Crème Care and Cosmetics exposure model that would contain the major assumptions together with the results. Also, the SCCS would prefer the presentation of 95% confidence limits instead of the standard error.
Spray products and oral care products, such as mouthwash and toothpaste, have not been considered in the exposure assessments. Therefore, this Opinion excludes such product categories.

The Crème Care and Cosmetics exposure model uses habits and practices data for adults. The largest contributions were for hand cream, body lotion and face moisturiser. Garcia-Hidalgo et al, 2017 showed that children and adolescents in Switzerland generally use less of these product categories than adults. Therefore, the presented SEDs most probably are also protective for children and adolescents from 3-18 years of age.

3.4.2 Aggregate exposure with non-cosmetic uses

According to the Applicant, it is useful to consider how the SED for aggregate cosmetics exposures compares to everyday safe use of aspirin, assuming that 100% of aspirin is converted in a day to salicylic acid.
Aspirin is available over the counter for use as a low dose prevention treatment to improve cardiovascular functions and as a commonly used analgesic, used episodically at 1000 mg/day and maximally at 4000 mg/day (4 x 1000 mg/day). For a 60 kg adult, the intake for low dose is 1.35 mg/kg/day and for analgesic level aspirin up to a maximum of 67 mg/kg/day, and is considered safe at this level.
Systemic exposure to salicylic acid from cosmetics use is therefore significantly lower than the safe oral doses of aspirin used daily in the general population, including demonstrated safe use by pregnant women (Bard, 2012).

SCCS comment
The SCCS agrees that exposure to aspirin results in considerably larger doses of SA than the use as preservative in cosmetics. However, the use of a drug includes different risk-benefit considerations than the use in cosmetics, and in recent times also the deliberate use of aspirin has been questioned by medical doctors. Therefore, the fact that aspirin results in much larger doses of salicylic acid cannot be used as an argument for the safety of SA.

Salicylic acid is also used as a preservative in food and as a biocide in some consumer products (see section 3.2.3). As no specific exposure data were made available to SCCS to assess exposure following these non-cosmetic uses, it was not possible to include them in the aggregated exposure scenarios.

3.5 SAFETY EVALUATION (INCLUDING CALCULATION OF THE MOS)

The Margin of Safety is calculated by dividing the toxicological Point of Departure, POD, (in mg/kg/day) by an estimate of the systemic exposure dose (in mg/kg/day) following dermal exposure. The MOS's were updated by the SCCS to include a skin penetration of 60% in all calculations of systemic exposure dose.
The toxicological POD (75 mg/kg/day) is taken in this case as the NOAEL from the pivotal developmental study by Tanaka et al., 1973a, for the most sensitive toxic endpoint observed in the rat as the most sensitive species. Due to the evidence for high (100%) oral bioavailability in humans, the oral NOAEL of 75 mg/kg/day is defined as NOAELsys. The outcomes for aggregate exposures from the different risk assessment approaches are summarised in Table 22.

Table 22. MOS for aggregate systemic exposure to cosmetic products containing salicylic

acid			
Risk Assessment Scenario	**Basis for exposure assessment**	**Aggregate Systemic Exposure Dose (mg/kg/day)**	**Margin of Safety (using a NOAEL of 75 mg/kg/day)**
Scenario 1	Crème Care and Cosmetics model; probabilistic habits & practices; maximum % level	**0.384**	**195**
SCCS 2016 Notes of guidance Approach	SCCS Guidance 9th revision*; deterministic additive; maximum % level	**1.50**	**50**

* Assumes everybody in the population uses all the products each day, and all products contain salicylic acid, aggregate exposure is calculated on the basis of deterministic additive methods.

Applicant's Analysis

In the Applicant's dossier, evidence is presented to show that human and rat toxicokinetics are similar for salicylic acid. Therefore, according to the Applicant, the factor of 4 accounting for inter-species toxicokinetic differences is not required. This leads to a margin of safety of approximately 25 that is needed to account for the uncertainties in this risk assessment. Scenario 1 also ensures that when taking a maximal conservative approach to safety evaluation, the exposed population is safe. The most conservative deterministic approach according to SCCS 2016 Notes of Guidance leads to the conclusion that aggregate exposure is still greater than the required MOS of 25 to assure safety. This indicates that the current permitted uses of salicylic acid in cosmetic products are acceptable in terms of consumer health.

SCCS comment

The Applicant on the basis of the absorption studies considers a dermal absorption fraction of 50% as a "highly conservative value" to calculate the aggregate exposure. However, in light of the high variability of the dermal penetration values provided in the absorption studies, the SCCS considers 50% not conservative enough in this specific case but used a value of 60% instead. The Applicant excluded toothpaste and mouthwash in the aggregate assessment on the basis that the test substance is not used in these products, because of intrinsic product properties of salicylic acid. The SCCS accepts the argumentation of the Applicant. The Applicant also did not include spray applications in the aggregate exposure.

Regarding salicylic acid kinetics for rats and humans, no robust data have been provided to enable comparison of the kinetic parameters of the test substance between species (rats and human). In light of the above, the SCCS cannot compare the kinetics for rat to humans because of species' differences. Hence, the SCCS is of the opinion that the default acceptable **MoS of 100** should be applied.
The SCCS notes that the MoS of 50 derived on the basis of the deterministic approach according to the SCCS 2016 Notes of Guidance is therefore too low to conclude on the safety of salicylic acid.

The SCCS considers that for this case, the probabilistic approach can be used in the safety assessment of salicylic acid.
The probabilistic approach combines currently allowed maximal concentrations of salicylic acid with population data on habits and practices. For the assessment of the MOS, the 95th percentile is used. The derived MOS with this scenario is 195 and thus demonstrates the safety of salicylic acid for cosmetics, excluding oral products such as toothpaste and mouthwash. Sprayable products that could lead to exposure of the consumer's lungs by inhalation are also excluded.

3.6 DISCUSSION

Physicochemical properties

The analytical methods used for the determination of purity and impurities in the test substance along with the results of these studies should be provided, according to the SCCS Notes of Guidance. The SCCS is of the opinion that the method described in European Pharmacopoeia is the method of choice for testing the purity and the impurities of Salicylic Acid.

Function and uses

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Toxicological Evaluation

Acute toxicity

Acute oral

Harmonised classification of salicylic acid was recently published in regulation 2018/1480 and it was classified as Acute Toxicity Category 4, H302 (Harmful if swallowed).

Acute inhalation

No data have been provided on acute toxicity by inhalation. According to the Applicant, salicylic acid is not intended for use in spray or aerosol cosmetics.

Irritation and corrosivity

Skin irritation

Based on a previous animal skin irritation study, the SCCNFP had considered in its Opinion (SCCNFP/0522/01 of 2002) salicylic acid as mildly to non-irritating to skin. However, the new study provided in the current submission indicates that neat salicylic acid is not irritating to skin.

Mucous membrane irritation / eye irritation

Based on all available ingredient based data, SCCS considers salicylic acid as being able to cause serious damage to the eye. Salicylic acid was recently classified as Eye Dam. 1 (H318 Causes serious eye damage) and was included in annex VI of CLP (regulation 2018/1480). Salicylic acid is eye irritant.

Skin sensitisation

Based on the studies provided, SCCS considers that salicylic acid has no skin sensitising potential.

Toxicokinetics

In view of the high variability of dermal penetration values reported in the different studies, the SCCS estimates a dermal absorption rate of 60 % for salicylic acid.

Regarding salicylic acid kinetics for rats and humans, no robust data have been provided to enable comparison of the kinetic parameters of the test substance between species (rats and human). In light of the above, the SCCS cannot compare the kinetics for rat to humans because of species' differences. Hence, the SCCS is of the opinion that the default acceptable **MoS of 100** should be applied.

In addition and based on the studies provided, the SCCS is of the opinion that the metabolism for salicylic acid in rats and humans is at least similar. Salicylic acid is metabolised mainly to salicyluric acid and conjugated salicylic acid compounds, with a small proportion of oxidative metabolites. The SCCS agrees that salicylic acid has the potential to cross the placenta, based on the provided studies.

Repeated dose toxicity

Inhalation
No robust data have been provided to enable proper assessment of the repeated dose toxicity by inhalation. Since the Applicant does not intend to use salicylic acid in spray/aerosol products, inhalation toxicity is not considered in this Opinion.

Chronic (> 12 months) toxicity
SCCS considers that the assessment from SCCNFP (2002) concerning the toxicity of salicylic acid after repeated exposure remains valid.
In particular:
- No systemic toxicity was noted from sub-chronic dermal toxicity studies conducted in the rabbit at the highest dosage of 120 mg/kg/day salicylic acid formulations; dermal irritation was the main recorded observation.
- In humans, toxic effects have been reported after topical application of salicylic acid to extensive areas of the body in diseased skin. Children are more sensitive than adults to develop salicylism, thus the topical application of salicylic acid may involve a risk of toxicity. Reye's syndrome in children is associated with the use of acetylsalicylic acid during a viral illness.

Reproductive toxicity
SCCS concludes that there is insufficient evidence that salicylic acid has an adverse effect on sexual function and fertility.

Developmental Toxicity
SCCS agrees that salicylic acid can be considered as a developmental toxicant. Harmonised classification of salicylic acid was recently published in regulation 2018/1480 and is classified as Repr. 2 (H361d Suspected of damaging the unborn child).As the developmental effects are the most sensitive effects after repeated exposure to SA, the **NOAEL of 75 mg/kg bw/day** has been used for the calculation of the MoS.

Mutagenicity / genotoxicity
The genotoxicity of salicylic acid was investigated with valid genotoxicity tests for *in vitro* gene mutations, in both bacterial and mammalian test system. Although no valid *in vitro* test results on chromosomal aberrations were provided, the *in vivo* chromosomal aberration and sister chromatid exchange tests in mice showed no mutagenic activity of salicylic acid. Based on the submitted studies and available literature, the SCCS is of the opinion that salicylic acid does not pose risk of genotoxicity.

Carcinogenicity
No additional studies have been provided by the Applicant in submission II. However, on the basis of the evidence available on negative results of genotoxicity and some evidence on the absence of carcinogenicity, the SCCS considers salicylic acid as unlikely to be a carcinogen.

Photo-induced toxicity
The SCCS agrees that, based on the submitted studies, salicylic acid does not have photo-irritant, photosensitising or photocarcinogenic properties.

Special investigation

There is some evidence that some salicylates such as homosalate may have endocrine properties but few studies have investigated endocrine properties of salicylic acid itself. In a newly published report from the Danish Centre on Endocrine Disrupters researchers have evaluated that there is solid scientific evidence that salicylic acid is an endocrine disruptor. Salicylic acid is not listed as an endocrine disrupter candidate in the priority list published in 2007 by the European Commission. Salicylic acid has also not been identified as an endocrine disrupter in the Pesticide Action Network Pesticide DataBase.

Exposure Assessment

For the exposure assessment of salicylic acid, the SCCS has considered it appropriate to use the probabilistic scenario that assumes maximum allowed concentrations of salicylic acid in all cosmetics where it is used.

4. CONCLUSION

1. *In light of the new data provided, does the SCCS still consider Salicylic acid (CAS 69-72-7) safe when used as a preservative in all cosmetic products up to a maximum concentration of 0.5% (acid) considering its current restriction as reported above?*

   The SCCS considers salicylic acid (CAS 69-72-7) safe when used as preservative at a concentration of 0.5 % in cosmetic products considering its current restrictions in place.
   This Opinion is not applicable to any oral product (such as toothpaste and mouthwash) with the exception of lipsticks. Sprayable products that could lead to exposure of the consumer's lung by inhalation are also excluded. The provided information shows that salicylic acid is an eye irritant with the potential to cause serious damage to the eye.

2. *In addition, does the SCCS still consider Salicylic acid (CAS 69-72-7) safe when used for purposes other than inhibiting the development of micro-organisms at a concentration up to 3.0 % for the cosmetic rinse-off hair products and up to 2.0 % for other products considering its current restrictions as reported above?*

   Based on the data provided and available literature, the SCCS considers salicylic acid (CAS 69-72-7) safe when used for purposes other than preservative at a concentration up to 3.0 % for the cosmetic rinse-off hair products and up to 2.0 % for other products, considering its current restrictions in place. However, in body lotion, eye shadow, mascara, eyeliner, lipstick and roll on deodorant applications, salicylic acid is considered safe up to 0.5 %. The SCCS position is that these levels are inclusive of any use of salicylic acid, i.e. should not exceed the stated levels with additional use as a preservative.
   This Opinion is not applicable to any oral product (such as toothpaste and mouthwash) with the exception of lipsticks. Sprayable products that could lead to exposure of the consumer's lung by inhalation are also excluded.

3. *Does the SCCS have any further scientific concerns with regard to the use of Salicylic acid (CAS 69-72-7) in cosmetic products?*

   Salicylic acid is also used as a preservative in food and as a biocide in some consumer products (see section 3.2.3) or in various pharmaceutical formulations such as anti-acne products. As no specific exposure data were made available to SCCS to assess exposure following these non-cosmetic uses, it was not possible to include them in the aggregated exposure scenarios. Therefore, the actual total exposure of the consumer may be higher than exposure from cosmetic products alone.
   The conclusions of this Opinion refer only to Salicylic Acid and should not be applied to other salicylates or salicylic acid salts.

5. MINORITY OPINION

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6. REFERENCES

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7. GLOSSARY OF TERMS

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8. LIST OF ABBREVIATIONS

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