化粧品產品資訊檔案(範例)

<肌膚調理凝膠>

＜PIF **無特定之格式**，本範例**僅提供參考用**＞

中華民國 112 年 10 月

目　　錄

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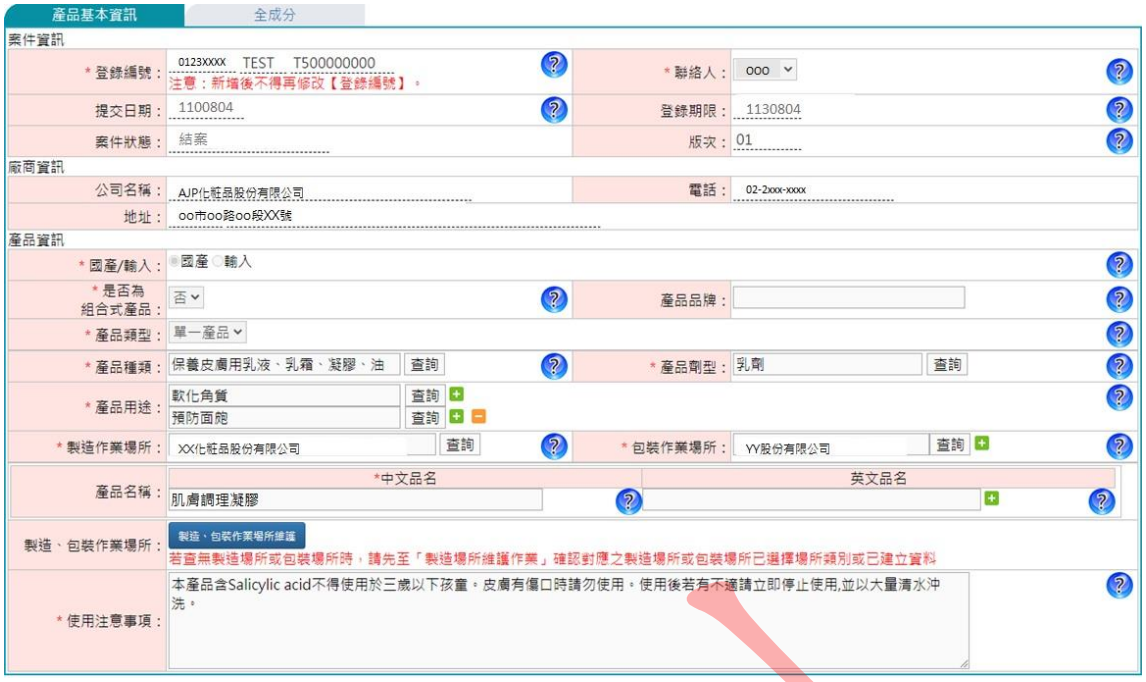
I. 產品敘述

(1) 產品基本資料

項目	內容描述
產品名稱	肌膚調理凝膠
產品類別	保養皮膚用乳液、乳霜、凝膠、油
產品劑型	液劑
用途	軟化角質、預防面皰。
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	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：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：	ooo
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化粧品股份有限公司	電話：	02-2xxx-xxxx
地址：	oo市oo路oo段XX號		

產品資訊

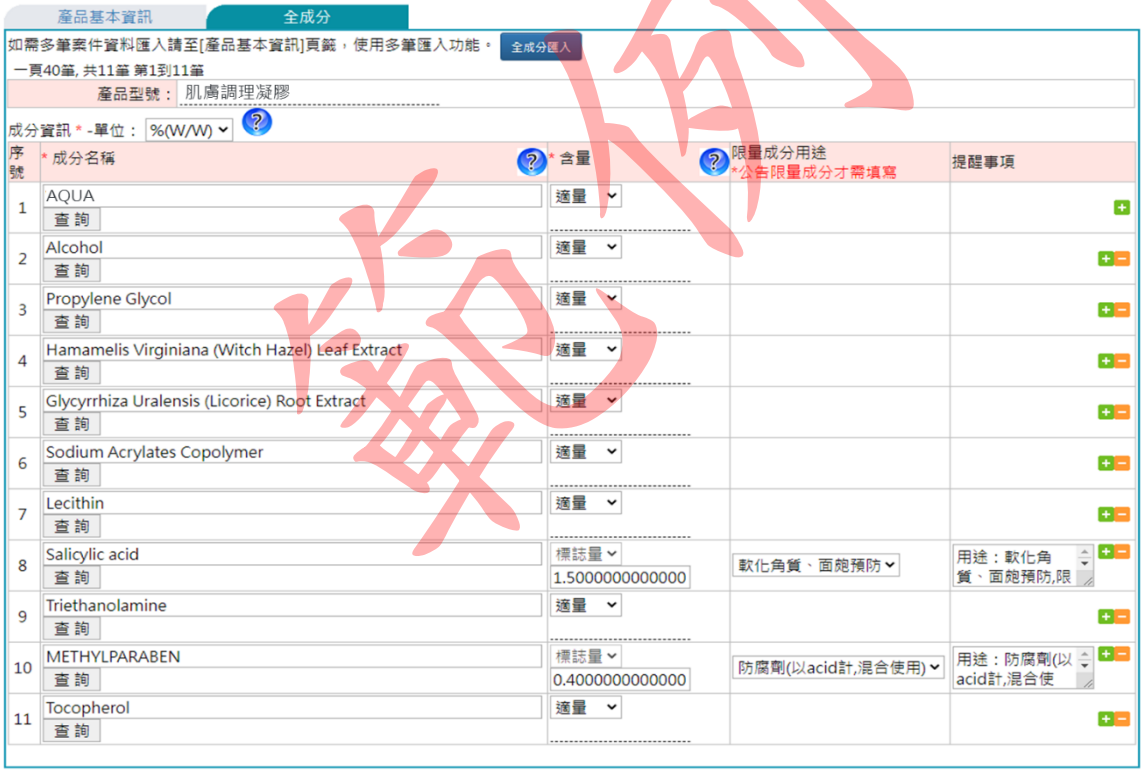
* 國產/輸入：	國產 輸入		
* 是否為組合式產品：	否	產品品牌：	
* 產品類型：	單一產品		
* 產品種類：	保養皮膚用乳液、乳霜、凝膠、油 查詢	* 產品劑型：	乳劑 查詢
* 產品用途：	軟化角質 查詢 預防面皰 查詢		
* 製造作業場所：	XX化粧品股份有限公司 查詢	* 包裝作業場所：	YY股份有限公司 查詢

產品名稱：	*中文品名	英文品名
	肌膚調理凝膠	

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

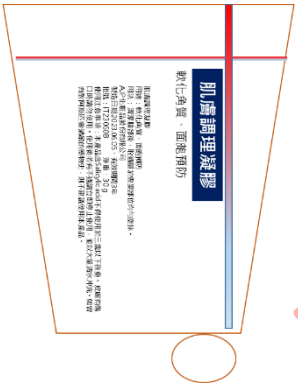
成分資訊 * -單位： %(W/W)

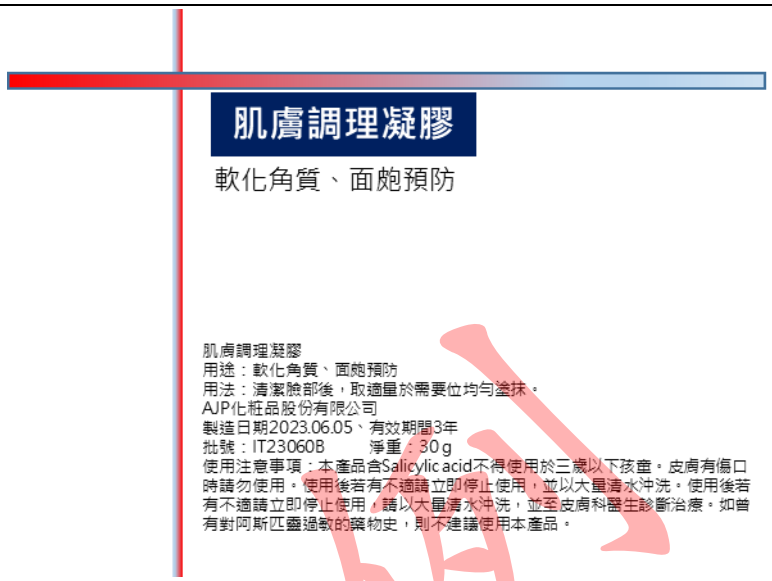
序號	* 成分名稱	* 含量	限量成分用途 *公告限量成分才需填寫	提醒事項
1	AQUA 查詢	適量		
2	Alcohol 查詢	適量		
3	Propylene Glycol 查詢	適量		
4	Hamamelis Virginiana (Witch Hazel) Leaf Extract 查詢	適量		
5	Glycyrrhiza Uralensis (Licorice) Root Extract 查詢	適量		
6	Sodium Acrylates Copolymer 查詢	適量		
7	Lecithin 查詢	適量		
8	Salicylic acid 查詢	標誌量 1.5000000000000	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	 品名：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。 全成分名稱(W/W)：Aqua、Alcohol、Propylene Glycol、Hamamelis Virginiana (Witch Hazel) Leaf Extract、Glycyrrhiza Uralensis (Licorice) Root Extract、Sodium Acrylates Copolymer (and) Lecithin、Salicylic acid(1.5%)、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：2023.06.05 有效期間：3 年 批號：IT23060B 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/本廠生產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

申請廠商蓋公司章

負責人/代表人：(Signature)

Person in charge

負責人或代表人章

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

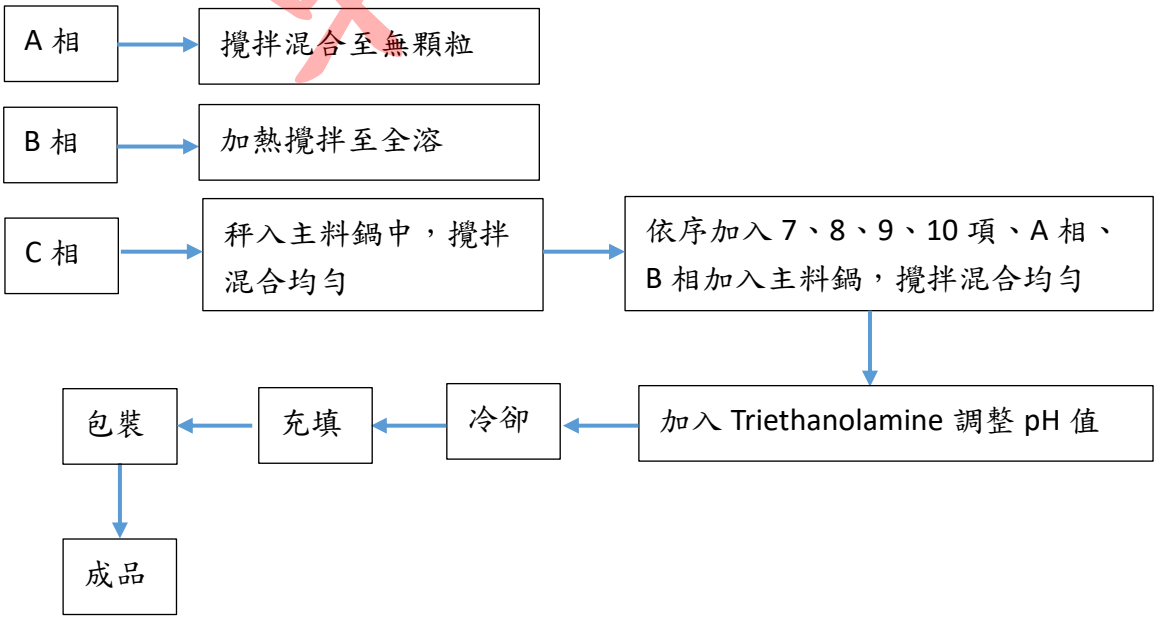
(6) 製造方法、流程

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，取適量於需要部位均勻塗抹。

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

肌膚調理凝膠 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 (at 25 °C)	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(at 25 °C)	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； 金黃色葡萄球菌 陰性； 綠膿桿菌 陰性； 白色念珠菌 陰性	參考衛生福利部食品藥物管理署 109.07.28 及 111.04.21 公布建議檢驗方法-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 (at 25 °C)	6.0~8.5	7.48	使用已校正之線上(on line) pH meter 測定
導電度(at 25 °C)	<10 µS/cm	6.4 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)

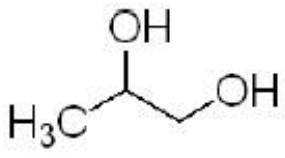
Characteristics	Specifications	Results
Specific Gravity @ 60°F (15.56°C)	NMT 0.7962	0.7959
Proof	NLT 199.0	199.12
Ethyl Alcohol, % volume	NLT 99.5	99.3
Appearance	Bright and clear, free from suspended matter	Pass
Order	Characteristic ethanol	Pass
Water, wt. %	0.7 max	0.6
Color, Pt-Co	0.0	Pass
Chloride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

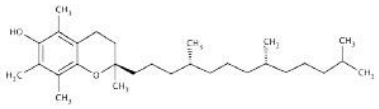
Chemical & Physical Properties

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℃

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 ($AUC_{0\text{-}24}$ 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 $AUCs_{0\text{-}24}$ 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：LD_{50}> 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 6.25cm²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.
2. α-tocopherol Registration Dossier ECHA 網頁：https://echa.europa.eu/registration-dossier/-/registered-dossier/11202/6/2/1
3. Risk profile Vitamin E . Version date: 28 Jun 2012.
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 (at 25 °C)	4.32	4.46	4.38	4.65
黏度(at 25 °C)	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	IT23060B		
產品製造日期	2023.06.06		
包裝材質	HDPE	**試驗日期**	112.06.07
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): 衛福部食藥署 110.05.13 公告之化粧品防腐效能試驗指引					
測試菌種 (Microbial strains)					
分析時間點 (Assay Time)	大腸桿菌 *Escherichia coli* (ATCC 8739) (CFU/g or ml)	金黃色葡萄球菌 *Staphylococcus aureus* (ATCC 6538) (CFU/g or ml)	綠膿桿菌 *Pseudomonas aeruginosa* (ATCC 9027) (CFU/g or ml)	白色念珠菌 *Candida albicans* (ATCC 10231) (CFU/g or ml)	黑麴菌 *Aspergillus brasiliensis* (ATCC 16404) (CFU/g or ml)
第 0 天	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，如抗痘試驗等。

(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 2023 年 5 月發布之歐盟消費者安全科學委員會(Scientific Committee on Consumer Safety, SCCS)化粧品成分測試及其安全性評估指引第 12 版(SCCS/1647/22)，並依用途、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	1.00

每日皮膚暴露量($E_{product}$)

對於此肌膚調理凝膠，參考 2023 年 5 月發布之 SCCS 化粧品成分測試及其安全性評估指引第 12 版(SCCS/1647/22)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 12 版 (SCCS/1647/22) 提及 90 天口服毒性試驗是化粧品成分最常用的重複劑量毒性試驗，當有科學合理的 90 天研究確認明確的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	28480
Tocopherol	0.2	100	293.5	0.0483	6079

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，對人體健康傷害風險低。

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%)未超過我國之規定。
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。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，建議上市後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符合衛福部食藥署 110.05.13 公告之化粧品防腐效能試驗指引標準 A，表示產品微生物汙染風險受到管控，可保護產品避免受到潛在微生物汙染之風險。

5. 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℃。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 12 版，計算化粧品中產品各別成分的暴露程度。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 # :

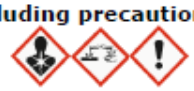
SECTION 2: Hazards identification

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.

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	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:

For the preliminary and the final Opinion

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Dr. N. von Goetz

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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The Opinions of the Scientific Committees present the views of the independent scientists who are members of the committees. They do not necessarily reflect the views of the European Commission. The Opinions are published by the European Commission in their original language only.

http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm

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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.

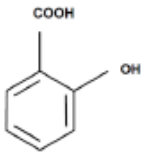
Ref: https://pubchem.ncbi.nlm.nih.gov/compound/338#section=Depositor-Supplied-Synonyms

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)	µg/g	< 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/cm^3 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/cm^2 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 cm² 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/cm²)**
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 cm² 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					Nagelschmitz 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.

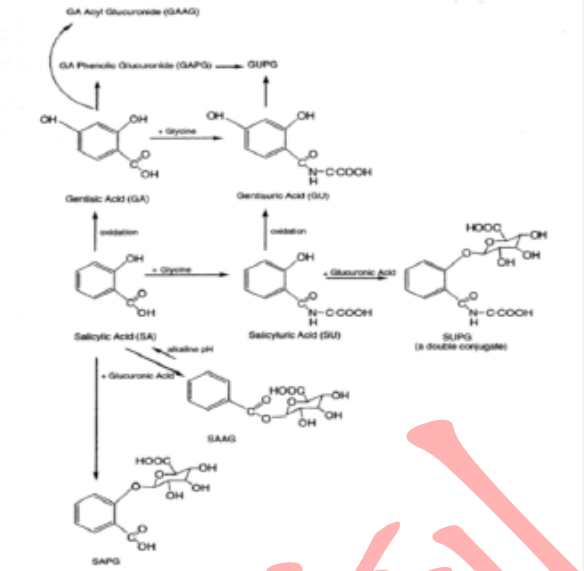


Figure 1. Scheme of the possible major metabolites of salicylic acid, Ref: CIR 2003 review

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, (Schardein *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

/

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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7. GLOSSARY OF TERMS

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8. LIST OF ABBREVIATIONS

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