化粧品產品資訊檔案(範例)

<柔柔化粧水>

＜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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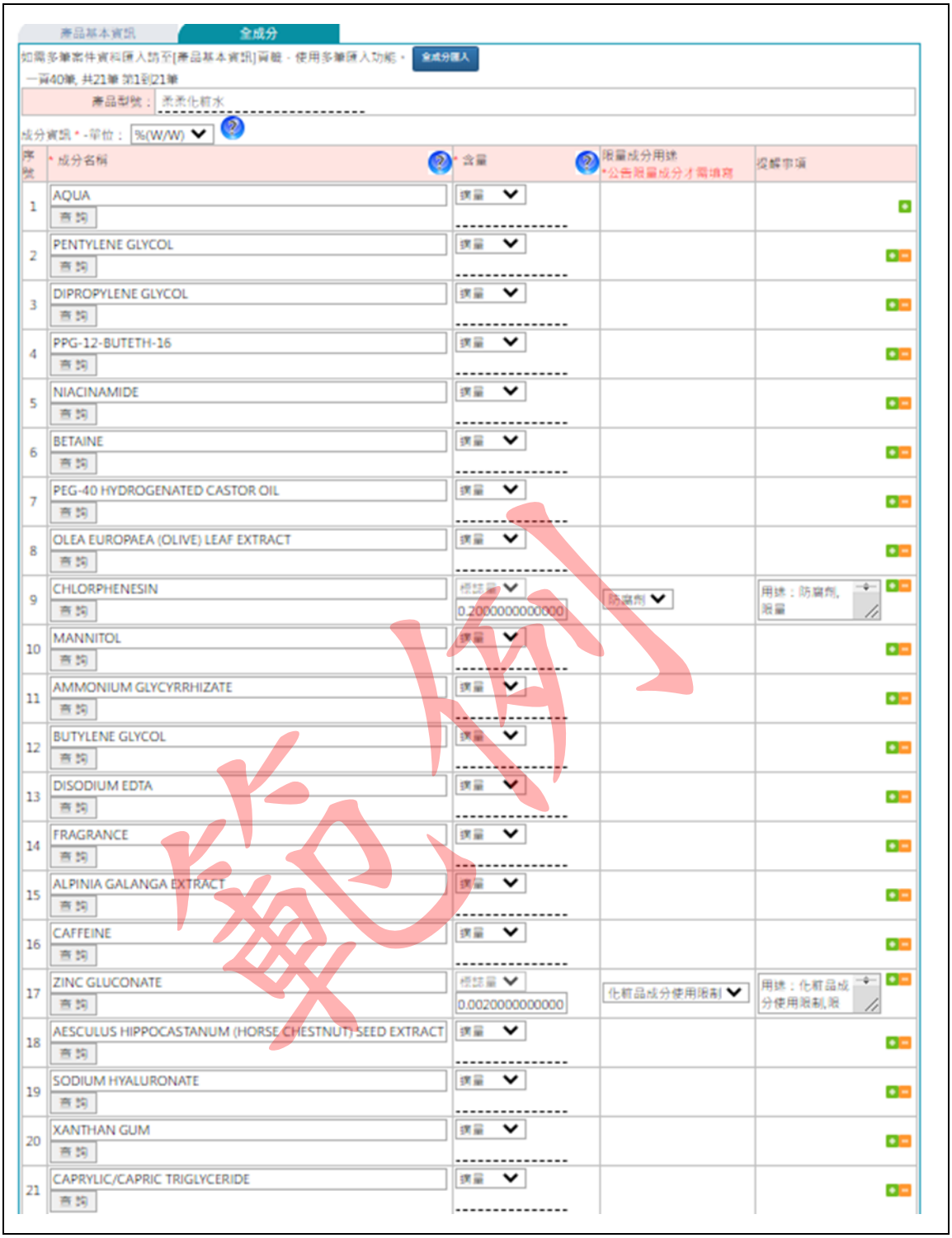
I. 產品敘述

(1) 產品基本資料

項目	內容描述
產品名稱	柔柔化粧水
產品類別	化粧水、化粧用油
產品劑型	液劑
用途	保濕
製造作業場所資訊	製造廠名稱：XX 化粧品股份有限公司 廠址：○○市○○區○○路○○號 國別：台灣
包裝作業場所資訊	包裝廠名稱：YY 股份有限公司 廠址：○○市○○區○○路○○號 國別：台灣
產品製造業者資訊	製造業者：AJP 化粧品股份有限公司 地址：○○市○○路○○段 XX 號 公司負責人：李○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：0123XXXX TEST 1000000012



商品基本資訊 | 全成分

如需多筆案件資料匯入請至[商品基本資訊]頁籤，使用多筆匯入功能。 全成分匯入

一頁40筆, 共21筆 第1到21筆

商品型號：柔柔化粧水

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	備註事項
1	AQUA 查詢	摘量		
2	PENTYLENE GLYCOL 查詢	摘量		
3	DIPROPYLENE GLYCOL 查詢	摘量		
4	PPG-12-BUTETH-16 查詢	摘量		
5	NIACINAMIDE 查詢	摘量		
6	BETAINE 查詢	摘量		
7	PEG-40 HYDROGENATED CASTOR OIL 查詢	摘量		
8	OLEA EUROPAEA (OLIVE) LEAF EXTRACT 查詢	摘量		
9	CHLORPHENESIN 查詢	標註量 0.2000000000000	防腐劑	用途：防腐劑, 限量
10	MANNITOL 查詢	摘量		
11	AMMONIUM GLYCYRRHIZATE 查詢	摘量		
12	BUTYLENE GLYCOL 查詢	摘量		
13	DISODIUM EDTA 查詢	摘量		
14	FRAGRANCE 查詢	摘量		
15	ALPINIA GALANGA EXTRACT 查詢	摘量		
16	CAFFEINE 查詢	摘量		
17	ZINC GLUCONATE 查詢	標註量 0.0020000000000	化粧品成分使用限制	用途：化粧品成分使用限制,限
18	AESCULUS HIPPOCASTANUM (HORSE CHESTNUT) SEED EXTRACT 查詢	摘量		
19	SODIUM HYALURONATE 查詢	摘量		
20	XANTHAN GUM 查詢	摘量		
21	CAPRYLIC/CAPRIC TRIGLYCERIDE 查詢	摘量		

(3) 全成分名稱及其各別含量

INCI Name	Cas No.	w/w%	功能
Aqua	7732-18-5	89.408	溶劑
Pentylene Glycol	5343-92-0	3.508	保濕劑
Dipropylene Glycol	25265-71-8	2.000	保濕劑
PPG-12-Buteth-16	9038-95-3	2.000	滋潤劑
Niacinamide	98-92-0	1.000	皮膚調理劑
Betaine	107-43-7	1.000	保濕劑
PEG-40 Hydrogenated Castor Oil	61788-85-0	0.400	助溶劑
Olea Europaea (Olive) Leaf Extract	8001-25-0	0.325	皮膚調理劑
Chlorphenesin	104-29-0	0.200	防腐劑
Mannitol	69-65-8	0.075	皮膚調理劑
Ammonium Glycyrrhizate	53956-04-0	0.020	皮膚調理劑
Butylene Glycol	107-88-0	0.020	皮膚調理劑
Sodium Hyaluronate	9067-32-7	0.010	保濕劑
Disodium EDTA	6381-92-6	0.010	螯合劑
Fragrance	-	0.010	香精
Alpinia Galanga Extract	84625-26-3	0.008	皮膚調理劑
Caffeine	58-08-2	0.002	皮膚調理劑
Zinc Gluconate	4468-02-4	0.002	皮膚調理劑
Aesculus Hippocastanum (Horse Chestnut) Seed Extract	8053-39-2	0.001	皮膚調理劑
Xanthan Gum	11138-66-2	0.0008	增稠劑
Caprylic/Capric Triglyceride	73398-61-5	0.0002	皮膚調理劑
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)	 
標籤/仿單	品名：柔柔化粧水 用途：保濕。 用法：早晚清潔肌膚後，取適量於手心或化粧棉上均勻塗抹於臉部肌膚。 全成分：Aqua、Pentylene Glycol、Dipropylene Glycol、PPG-12-Buteth-16、Niacinamide、Betaine、PEG-40 Hydrogenated Castor Oil、Olea Europaea (Olive) Leaf Extract、Chlorphenesin、Mannitol、Ammonium Glycyrrhizate、Butylene Glycol、Disodium EDTA、Fragrance、Alpinia Galanga Extract、Caffeine、Zinc Gluconate、Aesculus Hippocastanum (Horse Chestnut) Seed Extract、Sodium Hyaluronate、Xanthan Gum、Caprylic/Capric Triglyceride 保存方法：請置於室溫陰涼處並避免陽光直射。 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：2022.08.10 有效期間：3 年 批號：IT22080H 容量：200 mL 使用注意事項：使用時若有不適請立即停止使用，並以清水沖洗。

(5) 製造場所符合化粧品優良製造準則之證明文件或聲明書

衛 生 福 利 部

化 粧 品 優 良 製 造 證 明 書

證號：(C)GMPOOOO-OOO

製造廠（場所）名稱：

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

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

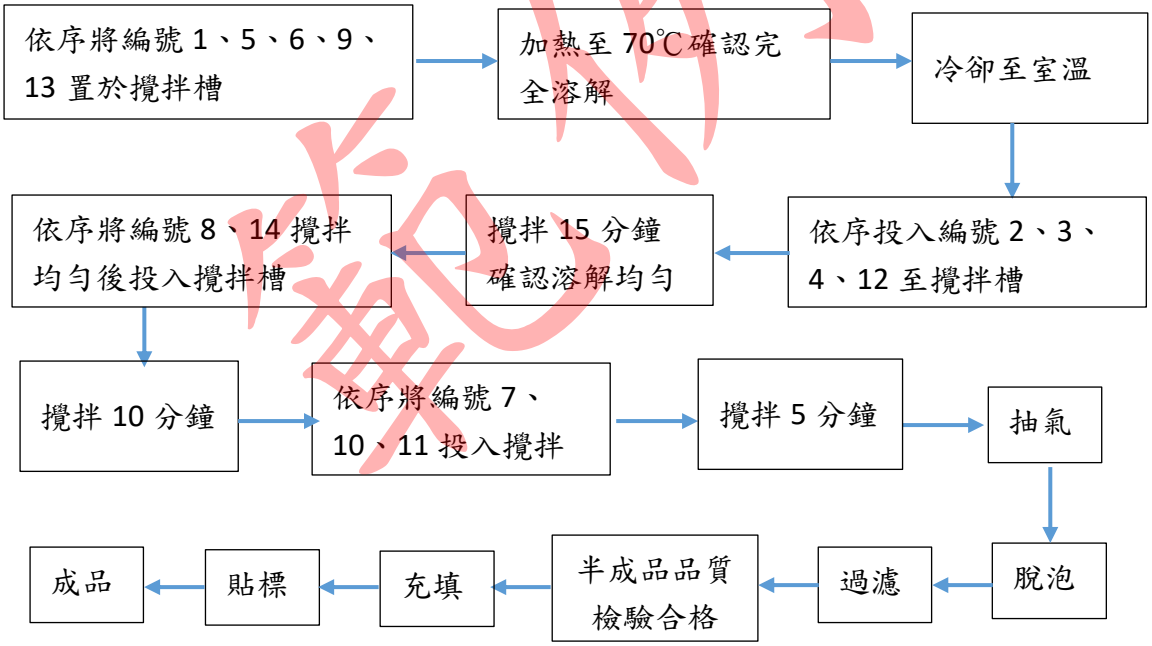
(6) 製造方法、流程

編號	Trade name (Product Name)	INCI name	Cas No.	w/w%
1	-	Aqua	7732-18-5	89.17
2	DIOL PD	Pentylene Glycol	5343-92-0	3.50
3	DPGFG	Dipropylene Glycol	25265-71-8	2.00
4	UCON™ 50-HB-660	PPG-12-Buteth-16	9038-95-3	2.00
5	Niacinamide PC	Niacinamide	98-92-0	1.00
6	AMINOCOAT™	Betaine	107-43-7	1.00
7	EUROL® BT	Olea Europaea (Olive) Leaf Extract(65%)	8001-25-0	0.50
		Aqua(35%)	7732-18-5	
8	PEG-40 Hydrogenated Castor Oil	PEG-40 Hydrogenated Castor Oil	61788-85-0	0.40
9	PROCARE CP-DEO	Chlorphenesin	104-29-0	0.20
10	Anasensyl® LS 9322	Mannitol(75%)	69-65-8	0.10
		Ammonium Glycyrrhizate(20%)	53956-04-0	
		Caffeine(2%)	58-08-2	
		Zinc Gluconate(2%)	4468-02-4	
		Aesculus Hippocastanum (Horse Chestnut) Seed Extract(1%)	8053-39-2	
11	Hyalufix® GL BC10095	Aqua(63%)	7732-18-5	0.10
		Butylene Glycol(20%)	107-88-0	
		Alpinia Galanga Extract(8%)	84625-26-3	
		Pentylene Glycol(8%)	5343-92-0	
		Xanthan Gum(0.8%)	11138-66-2	
		Caprylic/Capric Triglyceride(0.2%)	73398-61-5	
12	Sodium Hyaluronate	Sodium Hyaluronate	9067-32-7	0.01
13	EDTA.2Na.2H2O	Disodium EDTA	6381-92-6	0.01
14	-	Fragrance	-	0.01

製程簡述：

1. 依序將編號 1、5、6、9、13 置於攪拌槽加熱至 70℃確認完全溶解後降至室溫。
2. 依序投入編號 2、3、4、12 至攪拌槽攪拌 15 分鐘確認溶解均勻。
3. 依序將編號 8、14 攪拌均勻後投入攪拌槽中攪拌 10 分鐘。
4. 依序將編號 7、10、11 投入攪拌槽中攪拌 5 分鐘。
5. 抽氣。
6. 脫泡。
7. 過濾。
8. 完成半成品，品質檢驗合格後進行後續充填及貼標。

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：早晚清潔肌膚後，取適量於手心或化粧棉上均勻塗抹於臉部肌膚。

使用族群：青少年、成年人。

使用頻率：每日兩次。

(8) 產品使用不良反應資料

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

II. 品質資料

(9) 產品及各別成分之物理及化學特性

成品規格檢驗報告

柔柔化粧水 CoA			
檢測項目	**規格**	**實際檢驗結果**	**檢驗方法**
外觀	流動液體	流動液體	目視
顏色	淡黃色澄清透明	淡黃色澄清透明	目視
氣味	海洋清香	海洋清香	嗅覺
pH **(at 25 °C)**	5.5±0.5	5.8	使用已校正之 pH meter 依 pH meter 檢測方法測定
黏度**(at 25 °C)**	10±5 mPa·s	9.8 mPa·s	使用已校正之黏度計依黏度計檢測方法測定
密度	1.0±0.05 g/cm^3	1.0 g/cm^3	定量瓶
微生物規格	生菌數 < 1000 cfu/g 不得檢出： 大腸桿菌 綠膿桿菌 金黃色葡萄球菌 白色念珠菌	生菌數 未檢出 (<10 cfu/g)； 大腸桿菌 陰性； 綠膿桿菌 陰性； 金黃色葡萄球菌 陰性； 白色念珠菌 陰性	參考衛生福利部食品藥物管理署 109.07.28 及 111.04.21 公告建議檢驗方法-化粧品中微生物檢驗方法及化粧品中白色念珠菌之檢驗方法。
檢測人員/日期		(請簽名並加上日期)	
複核人員/日期		(請簽名並加上日期)	

各成分物理化學特性

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

1. INCI name：Aqua

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	6.8	使用已校正之線上(on line) pH meter 測定
導電度(at 25 °C)	<10 µS/cm	2.5 µS/cm	使用已校正之線上(on line)導電度計測定
微生物規格	生菌數 <100 cfu/ml	生菌數 未檢出 (<10 cfu/ml)；	參考環境保護署環境檢驗所公告之水中總菌落數檢測方法測定
檢測人員/日期		(請簽名並加上日期)	
複核人員/日期		(請簽名並加上日期)	

2. INCI name：Pentylene Glycol

No. 2772581

ISSUE DATE : 25.Aug.2020

CERTIFICATION OF ANALYSIS

COMMERCIAL NAME	:	
CHEMICAL NAME	:	1,2-PENTANEDIOL
LOT NO.	:	700774
Manufacturing date	:	2020/07/09
Expiration date	:	2023/07/08

DIOL PD contains not less than 95.0% of 1,2-pentanediol(C5H12O2:104.15).

	RESULTS	SPEC
Description	Pass	(*).
Identification	Pass	by J.S.Q.I. (*1).
Specific gravity (20/4℃)	0.970	0.966-0.976.
Purity test		
Heavy metals	Pass	Not more than 20 ppm.
Arsenic	Pass	Not more than 2 ppm.
Assay	Pass	by J.S.Q.I. (*1).
(Reference)		
Color (APHA method)	10	

(*) 1,2-Pentanediol is a colorless liquid. It has a characteristic odor.
(*1) The Japanese Standards of Quasi-Drug Ingredients

We hereby certify that above description of our manufacture is correct and true in every respect.
Yours faithfully,

Quality Control Division Manager

3. INCI name：Dipropylene Glycol

CERTIFICATE OF ANALYSIS

Head office :

Product Name : DPGFG

Lot No : B02541DP

Container No : WHSU2066852(10DRUMS)

Manufacturing Date :

EXPIRY DATE: 2

Property	Specification	Test Result	Test Method
Odor, Characteristic ,-	Min.Pass	Pass	Olfactory
DPG , wt.%	Min. 99.8	99.99	Current USP/ASTM E 202
MPG , wt.%	Max. 0.2	0.01	Current USP/ASTM E 202
Fe , ppm	Max. 0.1	0.04	ASTM E 394
Water , ppm	Max. 1000	60	Current USP/ASTM E 203
Color , APHA	Max. 10	3.0	ASTM D 1209
Acidity,0.01N , ppm	Max.30	9.0	Current USP/ASTM D 1613
IBP , DegC	Min.228	230.2	ASTM D 1078
Chloride , ppm	Max. 1	0.1	Current USP
DP , DegC	Max. 240	232.4	ASTM D 1078
SUSPEND,-	Min. Pass	Pass	SKC-M-107
Sp. Gr , 20/20 c	1.02 - 1.025	1.0238	Current USP/ASTM D 4052
As, ppm	Max. 2	LT0.1	Current USP
Heavy Metals as Pb , ppm	Max. 20	LT1.0	Current USP
Residue on Ignition , ppm	Max. 30	5.0	Current USP

I certify the above statements are true and correct .

Date Recorded :

4. INCI name： PPG-12-Buteth-16

Date 2020-03-23 (YYYY-MM-DD) Time 14:55:32 (Greenwich Mean Time) Page 1 of 2

分析證明/ Certificate of Analysis

產品編號/Product Number 00000247354

產品名稱/Product Name

UCON™ 50-HB-660 個人護理級

送貨單號/Delivery No.

訂單號/Order Number

裝運單號/Shipment No.

客戶資訊/Customer Information

客戶名稱/Customer Name

客戶訂單號/Customer PO number

規格編號/Specification Number 000000065140

產品名稱 (英語)/Product Name (English) UCON™ Fluid 50-HB-660 Personal Care Grade

批號/Batch Number D679K3CD04

復驗期/Retest Date 2022-03-05 (YYYY-MM-DD)

生產日期/Manufacturing Date 2020-03-05 (YYYY-MM-DD)

製造商地址/Manufacturer Address

測試/Test	單位/Unit	下限/Lower Limit	上限/Upper Limit	值/Value	方法/Method
粘度 @ 40攝氏度 Viscosity @ 40degC	cSt	124	136	127	ASTM D445
pH值 (10% , 在水裡) pH (10% in Water)		5.5	7.5	6.8	ASTM E70
水 Water	WT%	-	0.13	0.04	ASTM E203
顏色, Pt-Co Color, Pt-Co		-	50	21	ASTM D5386
外觀 Appearance	-	-	-	Pass	DOWM 101967

pH值的測定保證產品在製造和發運時是中性的。 由於偶發的氧化以及pH測定在重現性方面的難度，使用者的實驗室所測定的pH值一般均會低於檢驗證書上所報告的數值。
The pH determination assures that the product is neutral when manufactured and shipped. Because of adventitious oxidation and the difficulty in reproducing the pH determination, user laboratories will typically measure lower values than those reported on the Certificate of Analysis.

Quality Coordinator

質量協調員

若有問題諮詢請致電客戶服務中心或當地銷售人員
For inquiries please contact Customer Service or local sales

5. INCI name：Niacinamide

NIACINAMIDE PC

CERTIFICATE OF ANALYSIS

Productcode :
Lot No. :
Analysis No. :

Test	Result	Limits / Specifications	Dimension / Units
Appearance visual	crystalline powder	crystalline powder	
Colour visual	white	white	
Assay HPLC	99.5	99.0 to 101.0	% w/w
Related Substances:			
3-cyanopyridine HPLC	0.00	max. 0.10	% w/w
Any unknown impurity HPLC	0.04	max. 0.10	% w/w
Total of impurities HPLC	0.1	max. 0.2	% w/w
Nicotinic acid HPLC	67	max. 100	ppm
pH of solution Ph.Eur. of Nicotinamide	7.3	6.0 to 7.5	
Clarity of solution Ph.Eur. of Nicotinamide	0.32	max. 3.00	NTU
Colour values (CIELAB) L* Colour Instrument Measurement	98.1	90.0 to 101.0	
Colour values (CIELAB) a* Colour Instrument Measurement	0.0	-10.0 to 10.0	
Colour values (CIELAB) b* Colour Instrument Measurement	0.9	-10.0 to 10.0	
Colour of solution (calc./BY) Ph.Eur. of Nicotinamide	7	min. 7	
melting range start. point Ph. Eur. of Nicotinamide	129	128 to 131	°C
melting range end. point Ph. Eur. of Nicotinamide	130	128 to 131	°C
Particle Size Fraction			
min. 50 µm sieve analysis	99	min. 90	% w/w
min. 250 µm sieve analysis	<1	max. 8	% w/w
Sulphated Ash Ph.Eur. of Nicotinamide	0.03	max. 0.10	% w/w
Heavy Metals USP (method II) of Niacinamide	<10	max. 10	ppm

Date of issue : 29-Jun-2021

NIACINAMIDE PC

CERTIFICATE OF ANALYSIS

Productcode :
Lot No. :
Analysis No. :

Test	Result	Limits / Specifications	Dimension / Units
Chloride Limit test JP	<70	max. 70	mg/kg
Sulfate Limit test JP	<190	max. 190	mg/kg
Readily carbonizable substances USP of Niacinamide	passes test	passes test	
Identification UV, USP of Niacinamide	corresponds	0.63 to 0.67	
Identification IR, EP/USP of Niacinamide	corresponds	corresponds	
Loss on drying Ph.Eur. of Nicotinamide	0.0	max. 0.5	% w/w
Lead USP <730>	corresponds*	max. 1	ppm
Microbiology			
Total Aerobic Microbial Count Ph. Eur. 2.6.12	corresponds*	max. 100	CFU/g
Total Combined Yeast and Moulds Ph. Eur. 2.6.12	corresponds*	max. 100	CFU/g
Escherichia coli Ph. Eur. 2.6.13	corresponds*	negative in 1 g	
Staphylococcus aureus Ph. Eur. 2.6.13	corresponds*	negative in 1 g	
Pseudomonas aeruginosa Ph. Eur. 2.6.13	corresponds*	negative in 1 g	
Candida albicans Ph. Eur. 2.6.13	corresponds*	negative in 1 g	

*) checked at regular intervals

This lot has been analyzed and released. The manufacturing and control records have been reviewed by our authorized Quality organization. This lot meets substance specifications as given here above and has been produced in conformity with applicable Good Manufacturing Practices (GMP).

The product meets all requirements of the following valid compendia when tested accordingly:

USP and Ph. Eur.

6. INCI name：Betaine

CERTIFICATE OF ANALYSIS

Trade Name : AMINOCOAT™
Lot No. N10043
Manufacturing Date: April 28, 2021
Shelf life: 3 years after the date of manufacturing, on condition that a can has been kept unopened.

Test Parameter	Unit	Specification	Result
Appearance	—	White crystal	Conforms
Odor	—	Slightly specific odor	Conforms
Identification	—	Maximum absorption appear at around 525nm when measuring the absorbance by dissolving the Reinecke salt precipitates.	Conforms*
pH	—	5.0 to 7.0	6.2
Clarity and color of solution	—	Colorless, transparency when dissolved in water.	Conforms
Chloride	%	max.0.011	Conforms
Sulfate	%	max.0.01	Conforms
Pb	ppm	max.20	Conforms
Arsenic	ppm	max.2	Conforms
Loss on drying	%	max.5.0	1.1
Residue on Ignition	%	max.0.1	Conforms
Purity	%	min.98.0	99.9
Color value	—	max.30	5
Microbial Count	cfu/g	max.100	Conforms

*) checked at regular intervals

This lot was analysed and released by our authorized Quality Assurance Department and was found to meet the specification as given above.
The product meet requirement of the following valid compendia when tested accordingly:
JSQI

7. INCI name：PEG-40 Hydrogenated Castor Oil

Ethoxylated hydrogenated castor oil

Modify Date: 2022-01-11 11:52:00

	Common Name	Ethoxylated hydrogenated castor oil		
	CAS Number	61788-85-0 (/en/baike/1198760.html)	**Molecular Weight**	375.864
	Density	1.2±0.1 g/cm3	**Boiling Point**	529.0±50.0 °C at 760 mmHg
	Molecular Formula	$C_{21}H_{23}ClFNO_2$	**Melting Point**	N/A
	MSDS	USA	**Flash Point**	273.8±30.1 °C

Chemical & Physical Properties

Density	1.2±0.1 g/cm3
Boiling Point	529.0±50.0 °C at 760 mmHg
Molecular Formula	$C_{21}H_{23}ClFNO_2$
Molecular Weight	375.864
Flash Point	273.8±30.1 °C
Exact Mass	375.140137
LogP	3.01

Vapour Pressure	0.0±1.5 mmHg at 25°C
Index of Refraction	1.581

Safety Information

RIDADR	NONH for all modes of transport

8. Trade name (Product name)：EUROL® BT

INCI name：Olea Europaea (Olive) Leaf Extract (and) Aqua

Date: 27.07.2021 (DD.MM.YYYY) Time: 09:38:15 Page 1 of 2

	Ship to: 1001849
Certificate of Analysis	**Customer Information:**
Product Number:	**Customer P.O.#:**
Product Name:	**Customer Code:**
EUROL®BT-PLASTIC BOTTLE 1 KG	**Delivery Number:**
Lot Number:	**Order Number:**
	Date Shipped: 13.07.2021 (DD.MM.YYYY)

Manufacturing Date:	21.04.2021 (DD.MM.YYYY)	**Quantity:**	20.00	KG
Expiration Date:	20.04.2024 (DD.MM.YYYY)	**Net Weight:**	44.09	LB
Country of Origin:	Italy	**Net Weight:**	20.00	KG

Product Specification / Results of Analysis

Characteristic	Inspection Method	Value	Lower / Upper Limit	Unit
Appearance @ 20 °C Dense Liquid	BT-001-01/V02-08	Pass	- -	
Odor Strong Characteristic	BT002-02/V02-08	Pass	- -	
Color Dark Brown	BT003-01/V02-08	Pass	- -	
pH	BT005-01/V02-08	5,3	5,0 7,0	
Brix Grade	BT017-01/V02-08	71	65 -	Degrees
Bacterial Count < 100 CFU/ml	ISO 21149:2009	Pass	- -	
Fungal Count < 100 CFU/ml	ISO 16212:2011	Pass	- -	

Certificate is system generated, no signature is required.

9. INCI name：Chlorphenesin

CERTIFICATE OF ANALYSIS

PROCARE CP-DEO

DATE OF MANUFACTURED: Mar 07, 2022
USE BY DATE: Mar 06, 2025

Lot:

Items	Specification	Results
Appearance	White to pale yellow crystal	Passed
Odor	Almost odorless	Passed
Identification	IR Spectrum	Passed
Assay	Min. 99.0%	99.94%
pH	6.0~8.0	6.55
Loss of drying	Max. 1.0%	0.02%
Residue on ignition	Max. 0.1%	0.02%
Melting point	78.0~81.0℃	Passed
Heavy metals	Max. 20ppm	Passed
Arsenic	Max. 2ppm	Passed
Microbial count	Max.10^2 cfu/g	Passed

CONFORM: Mar 14, 2022

10. Trade name (Product name)：Anasensyl® LS 9322

INCI name：Mannitol (and) Ammonium Glycyrrhizate (and) Caffeine (and) Zinc Gluconate (and) Aesculus Hippocastanum (Horse Chestnut) Seed Extract

D-Mannitol

Modify Date: 2022-01-12 10:52:21

	Common Name	D-Mannitol		
	CAS Number	69-65-8 (/en/baike/962139.html)	Molecular Weight	182.172
	Density	1.6±0.1 g/cm3	Boiling Point	494.9±0.0 °C at 760 mmHg
	Molecular Formula	$C_6H_{14}O_6$	Melting Point	167-170ºC
	MSDS	Chinese USA	Flash Point	292.5±23.3 °C

Chemical & Physical Properties

Density	1.6±0.1 g/cm3
Boiling Point	494.9±0.0 °C at 760 mmHg
Melting Point	167-170ºC
Molecular Formula	$C_6H_{14}O_6$
Molecular Weight	182.172
Flash Point	292.5±23.3 °C
Exact Mass	182.079041
PSA	121.38000
LogP	-4.67
Vapour Pressure	0.0±2.8 mmHg at 25°C
Index of Refraction	1.597

Glycyrrhizic acid ammonium salt

Modify Date: 2022-01-11 08:37:54

	Common Name	Glycyrrhizic acid ammonium salt		
	CAS Number	53956-04-0 (/en/baike/831808.html)	**Molecular Weight**	839.96
	Density	1.43g/cm3	**Boiling Point**	971.4ºC at 760 mmHg
	Molecular Formula	$C_{42}H_{65}NO_{16}$	**Melting Point**	209ºC
	MSDS	Chinese USA	**Flash Point**	288.1ºC

Chemical & Physical Properties

Density	1.43g/cm3
Boiling Point	971.4ºC at 760mmHg
Melting Point	209ºC
Molecular Formula	$C_{42}H_{65}NO_{16}$
Molecular Weight	839.96
Flash Point	288.1ºC
PSA	272.70000
LogP	0.32860
Index of Refraction	49 ° (C=1.5, EtOH)
Storage condition	2-8°C
Water Solubility	Slightly soluble in water, very slightly soluble in anhydrous ethanol, practically in soluble in acetone. It dissolves in dilute solutions of acids and of alkali hydroxides.

Caffeine

Modify Date: 2022-06-25 18:37:39

	Common Name	Caffeine		
	CAS Number	58-08-2 (/en/baike/895838.html)	**Molecular Weight**	194.191
	Density	1.5±0.1 g/cm3	**Boiling Point**	416.8±37.0 °C at 760 mmHg
	Molecular Formula	$C_8H_{10}N_4O_2$	**Melting Point**	234-236.5 °C(lit.)
	MSDS	Chinese USA	**Flash Point**	205.9±26.5 °C
	Symbol	 GHS07 (/GHS.jsp#_pict)	**Signal Word**	Warning

Chemical & Physical Properties

Density	1.5±0.1 g/cm3
Boiling Point	416.8±37.0 °C at 760 mmHg

Melting Point	234-236.5 °C(lit.)
Molecular Formula	$C_8H_{10}N_4O_2$
Molecular Weight	194.191
Flash Point	205.9±26.5 °C
Exact Mass	194.080383
PSA	61.82000
LogP	-0.13
Vapour Pressure	0.0±1.0 mmHg at 25°C
Index of Refraction	1.679
Storage condition	2-8°C
Water Solubility	20 g/L (20 ºC)

Zinc dihexonate

Modify Date: 2022-01-11 17:36:03

	Common Name	Zinc dihexonate		
	CAS Number	4468-02-4 (/en/baike/895903.html)	**Molecular Weight**	455.704
	Density	N/A	**Boiling Point**	673.6ºC at 760 mmHg
	Molecular Formula	$C_{12}H_{22}O_{14}Zn$	**Melting Point**	131ºC
	MSDS	N/A	**Flash Point**	375.2ºC

Chemical & Physical Properties

Boiling Point	673.6ºC at 760 mmHg
Melting Point	131ºC
Molecular Formula	$C_{12}H_{22}O_{14}Zn$
Molecular Weight	455.704
Flash Point	375.2ºC
Exact Mass	454.030090
PSA	254.90000

Horse chestnut, Aesculus hippocastanum, ext.

Modify Date: 2022-01-22 22:51:14

	Common Name	Horse chestnut, Aesculus hippocastanum, ext.		
	CAS Number	8053-39-2 (/en/baike/154196 6.html)	**Molecular Weight**	N/A
	Density	N/A	**Boiling Point**	N/A
	Molecular Formula	N/A	**Melting Point**	N/A
	MSDS	N/A	**Flash Point**	N/A

Chemical & Physical Properties

No Any Chemical & Physical Properties

Fax No

Inspection Certificate 3.1 according to EN 10204

Anasensyl® LS 9322

10KG Fibre drums
Purchase Order/Customer Product#

Material
Order
Delivery
Lot
Lot/Qty 100.000 KG
Total 100.000 KG
Transport

Manufacturing Location:

Characteristic Method	Unit	Value	Lower Limit	Upper Limit
ORGANOLEPTIC CHARACTERISTICS PR.47		PASS		
TOTAL GERMS; <= 100 CFU/G PH. EUR. 2.6.12		<= 100 CFU/G		
PATHOGENS; ABSENT PH. EUR. 2.6.13		ABSENCE IN 1G		
GRAM NEGATIVE BACTERIA; ABSENT PH. EUR. 2.6.13		ABSENCE IN 1G		
WATER CONTENT, KARL FISCHER PR.58	%	1,0	0,0	3,0
PH; 1% PR.14		4,3	3,8	4,8
TOTAL ASHES; 700-800°C PR.78	%	0,2		1,0
INFRA-RED SPECTRUM PR.15		PASS		
ULTRA-VIOLET SPECTRUM; 261NM PR.13		OK		
PLANT EXTRACT/TLC		PASS		
GLYCYRRHYZINATE/HPLC PR.115	%	20,3	18,0	21,0
TOTAL NITROGEN PR.19	%	0,88	0,75	0,95
CAFFEINE/HPLC PR.103	%	1,98	1,70	2,20
MANNITOL/HPLC	%	74,9	72,0	80,0

The aforementioned data shall constitute the agreed contractual quality of the product at the time of passing of risk. The data are controlled at regular intervals as part of our quality assurance program. Neither these data nor the properties of product specimens shall imply any legally binding guarantee of certain properties or of fitness for a specific purpose. No liability of ours can be derived therefrom.

This is a computer-generated document. No signature is required.

11. Trade name (Product name)：Hyalufix® GL BC10095

INCI name：Aqua (and) Butylene Glycol (and) Alpinia Galanga Leaf Extract (and) Pentylene Glycol (and) Xanthan Gum (and) Caprylic/Capric Triglyceride

1,3-Butanediol

Modify Date: 2022-01-11 07:28:24

	Common Name	1,3-Butanediol		
	CAS Number	107-88-0 (/en/baike/593062.html)	Molecular Weight	90.121
	Density	1.0±0.1 g/cm3	Boiling Point	207.0±0.0 °C at 760 mmHg
	Molecular Formula	$C_4H_{10}O_2$	Melting Point	-54°C
	MSDS	Chinese USA	Flash Point	121.1±0.0 °C

Chemical & Physical Properties

Density	1.0±0.1 g/cm3
Boiling Point	207.0±0.0 °C at 760 mmHg
Melting Point	-54°C
Molecular Formula	$C_4H_{10}O_2$
Molecular Weight	90.121
Flash Point	121.1±0.0 °C
Exact Mass	90.068077
PSA	40.46000
LogP	-0.69
Vapour density	3.1 (20 °C, vs air)
Vapour Pressure	0.1±0.8 mmHg at 25°C
Index of Refraction	1.438
Stability	Stable. Flammable. Hygroscopic - protect from air and moisture. Incompatible with strong oxidizing agents.
Water Solubility	SOLUBLE

1,2-Pentanediol

Modify Date: 2022-01-14 16:38:47

	Common Name	1,2-Pentanediol		
	CAS Number	5343-92-0 (/en/baike/895760.html)	**Molecular Weight**	104.148
	Density	1.0±0.1 g/cm3	**Boiling Point**	206.0±0.0 °C at 760 mmHg
	Molecular Formula	$C_5H_{12}O_2$	**Melting Point**	N/A
	MSDS	Chinese USA	**Flash Point**	104.4±0.0 °C

Chemical & Physical Properties

Density	1.0±0.1 g/cm3
Boiling Point	206.0±0.0 °C at 760 mmHg
Molecular Formula	$C_5H_{12}O_2$
Molecular Weight	104.148
Flash Point	104.4±0.0 °C

Exact Mass	104.083733
PSA	40.46000
LogP	-0.28
Vapour Pressure	0.1±0.8 mmHg at 25°C
Index of Refraction	1.443
Water Solubility	miscible

Xanthan Gum

Modify Date: 2022-01-11 20:27:00

	Common Name	Xanthan Gum		
	CAS Number	11138-66-2 (/en/baike/1197547.html)	**Molecular Weight**	241.115
	Density	N/A	**Boiling Point**	N/A
	Molecular Formula	$C_8H_{14}Cl_2N_2O_2$	**Melting Point**	N/A
	MSDS	USA	**Flash Point**	N/A

Chemical & Physical Properties

Molecular Formula	$C_8H_{14}Cl_2N_2O_2$
Molecular Weight	241.115
Exact Mass	240.043228
Stability	Stable. Combustible. Incompatible with strong oxidizing agents.

glycerides mixed decanoyl and octanoyl

Modify Date: 2022-01-16 07:27:56

	Common Name	glycerides mixed decanoyl and octanoyl		
	CAS Number	73398-61-5 (/en/baike/1199077.html)	**Molecular Weight**	387.53076
	Density	N/A	**Boiling Point**	N/A
	Molecular Formula	$C_{21}H_{39}O_6$-	**Melting Point**	N/A
	MSDS	N/A	**Flash Point**	N/A

Chemical & Physical Properties

Molecular Formula	$C_{21}H_{39}O_6$-
Molecular Weight	387.53076

Certificate No 3180

Inspection Certificate 3.1 according to EN 10204

Hyalufix® GL BC10095

5KG Plastic jerricans
Purchase Order/Customer Product#

Material	
Order	
Delivery	
Lot	
Lot/Qty	30.000 KG
Total	30.000 KG
Transport	
RSPO Certificate	

Characteristic Method	Unit	Value	Lower Limit	Upper Limit
ORGANOLEPTIC CHARACTERISTICS PR.47		PASS		
TOTAL GERMS; <= 100 CFU/G PH. EUR. 2.6.12		<= 100 CFU/G		
GRAM NEGATIVE BACTERIA; ABSENT PH. EUR. 2.6.13		ABSENCE IN 1G		
PATHOGENS; ABSENT PH. EUR. 2.6.13		ABSENCE IN 1G		
PH; 100% PR.14		5.9	5.0	6.5
REFRACTIVE INDEX PR.61		1.364	1.340	1.380
DRY RESIDUE, SOLID CONTENT; 105°C; 15H PR.302	%	0.9	0.7	1.3
ASH PR.78	%	0.1	0.0	0.3
TOTAL SUGARS PR.303	%	0.33	0.10	0.60

Production date	06.02.2021
Retest date	05.02.2023

The aforementioned data shall constitute the agreed contractual quality of the product at the time of passing of risk. The data are controlled at regular intervals as part of our quality assurance program. Neither these data nor the properties of product specimens shall imply any legally binding guarantee of certain properties or of fitness for a specific purpose. No liability of ours can be derived therefrom.

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12. INCI name：Sodium Hyaluronate

Certificate of Analysis

Product Name	Sodium Hyaluronate	Report No.	
Batch No.		Test Date	2022.02.24
Quantity	43.66 kg	Report Date	2022.03.09
Origin	Fermentation	Manufacturing Date	2022.02.20
Grade	Cosmetic Grade	Retest Date	2024.02.19
Standard	In-house and customer standards		

Items	Specifications	Results
Characters	White or almost white granule or powder, odorless	White granule, odorless
Identification A. Infrared absorption B. Reaction of sodium	Complies with the Ph.Eur. reference spectrum of Sodium Hyaluronate Positive	Comply Positive
pH	6.0 ~ 8.0 (0.1% solution)	6.4
Light transmittance	≥ 99.0% (0.5% solution,550 nm)	99.9%
Intrinsic viscosity	2.90~3.42 m^3/kg	3.04 m^3/kg
Molecular weight	1.80×10^6 ~2.20×10^6 Da	1.91×10^6Da
Protein	The absorbance is NMT 0.5 at 280 nm	0.03
	≤ 0.3% (on the dried substance)	<LOD(0.03%)
Loss on drying	≤ 10.0%	6.8%
Ash	≤ 13.0%	11.4%
Residue on ignition	≤ 20.0% (on the dried substance)	17.6%
Heavy metals	≤ 20 ppm	< 20 ppm
Arsenic	≤ 2 ppm	< 2 ppm
Glucuronic acid	≥ 46.0% (on the dried substance)	48.0%
Assay	≥ 95.0% (on the dried substance)	99.1%
Total aerobic microbial count	≤ 80 cfu/g	< 10 cfu/g
Total combined yeasts / mould count	≤ 10 cfu/g	< 10 cfu/g
Escherichia Coli	Absent/g	Absent/g
Salmonella	Absent/10g	Absent/10g
Staphylococcus aureus	Absent/g	Absent/g
Pseudomonas aeruginosa	Absent/g	Absent/g
Conclusions	**The product complies with in-house and customer standards**	

Reported by

Date:

13. INCI name：Disodium EDTA

Dissolvine Na2, Nbo, 35 PE bags,25/875kg

Certificate of Analysis

Delivery Address

Order item
Delivery item
Material number

Customer ref.

Analysis	
Batch number	
Quantity	5.250KG
Production date	05.2020
Expiry date	05.2023
(Unless retested)	

Characteristic	**Unit**	**Values**	**Spec Limits**		**Method of Analysis**
			min.	**max.**	
Appearance		Free flowing white crystalline Pass			visual
Assay via Fe-pot	%	99,1	99,0	-	SMA 916.02
pH 1% solution	-	4,6	4,0	5,0	SMA 176.18

Our bv certify that the above product is samples taken from the production batches from which you have been supplied. This certificate of analysis does not exempt you from testing the suitability of the delivered product for your applications.

Page 1 of 1.

14. Fragrance

Issue date: 12/07/2021

Version: 2 (12/07/2021)

CERTIFICATE OF CONFORMITY

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

CERTIFYING PARTY:

CERTIFICATE DELIVERED TO:

SCOPE OF THE CERTIFICATE:

COMPULSORY INFORMATION:

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

We certify that the above mixture is in compliance with the Standards of the INTERNATIONAL FRAGRANCE ASSOCIATION (IFRA), up to and including the 50th Amendment to the IFRA Code of Practice (published January 2020) and the European Cosmetic Regulation (EC) 1223/2009 & its modifications, provided it is used in the following categories at a maximum concentration level of:

IFRA Categories [see Annex 1 below for details]	Maximum Level of use (%)
IFRA Category 1	Not approved
IFRA Category 2	2.42%
IFRA Category 3	4.44%
IFRA Category 4	45.29%
IFRA Category 5A	11.58%
IFRA Category 5B	6.86%
IFRA Category 5C	8.08%
IFRA Category 5D	2.26%
IFRA Category 6	Not approved
IFRA Category 7A	9.29%
IFRA Category 7B	9.29%
IFRA Category 8	2.26%
IFRA Category 9	21.81%
IFRA Category 10A	21.81%
IFRA Category 10B	48.48%
IFRA Category 11A	2.26%
IFRA Category 11B	2.26%
IFRA Category 12	Not limited

For other kinds of application or use at higher concentration levels, a new evaluation can be needed; please contact Gracefruit Limited

(10) 成分之毒理資料

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

1. INCI name：Pentylene Glycol

- 急性毒性：根據 OECD 401 進行的大鼠急性口服毒性試驗，結果顯示雌性和雄性的口服 LD_{50} > 5000 mg/kg bw。依 OECD 403 進行的大鼠急性吸入毒性，10 隻雄性和 10 隻雌性大鼠組分別在含 3380 和 7015 mg/m^3 Pentylene Glycol 的氣溶膠中僅用鼻子暴露 4 小時，儘管在所有動物中都觀察到輕微的呼吸困難和彎曲姿勢且在低劑量組和高劑量組中觀察到輕微和中度的褶皺皮毛，但沒有發現死亡率。因此吸入 LC_{50} >7015 mg/m^3 空氣。根據 OECD 402 進行的大鼠急性皮膚毒性，在 14 天的觀察期內於 2000 mg/kg bw 的劑量下沒有發現死亡，因此 LD_{50} > 2000 mg/kg bw。[1]
- 重複劑量毒性：根據 OECD 408 進行的大鼠口服重複劑量毒性研究中，Pentylene Glycol 以 50 mg/kg bw/d、250 mg/kg bw/d 和 1000 mg/kg bw/d 劑量給予 Wistar 大鼠，為期 3 個月。結果灌食 Pentylene Glycol 3 個月未引起受試物質相關的全身毒性不良跡象，NOAEL 為 1000 mg/kg bw/d。交叉參照 Pentylene Glycol 根據 OECD 411 進行的 90 天皮膚毒性研究，將 0、350、700 和 1000 mg/kg 的劑量施用於 Sprague Dawley 大鼠的剃毛皮膚上，研究包括額外的畸形大鼠生育參數(精子計數和精子活力和形態檢查)和行為活動參數。結果發現每日皮膚給藥 1000 mg/kg/day 於 91-93 天會有粗糙毛髮、毛皮染色和輕微皮膚刺激，顯微鏡下觀察到的表皮增生和角化過度，預計觀察到的微觀變化不會發展為潰瘍或慢性皮膚損傷。但在此劑量下行為活動參數或雄性生育力檢查和組織病理學未有任何不良反應。因此這項 90 天研究的全身皮膚 NOAEL 為 1000 mg/kg/day，而局部皮膚 NOAEL 為 700 mg/kg/day。[1]
- 皮膚腐蝕性/刺激性：根據 OECD 404 於維也納大白兔進行的皮膚刺激性評估，在半封閉條件下施用 0.5 ml Pentylene Glycol 24 h。由於水腫和紅斑評分均為 0，表示 Pentylene Glycol 對皮膚無刺激性。[1]
- 眼刺激性：根據 OECD 405 和歐盟方法 B.5 於維也納大白兔進行的

眼刺激性評估，兔眼施用 0.1 ml Pentylene Glycol 並評估了 21 天的反應。結果角膜混濁、虹膜、結膜紅斑和水腫的得分分別為 1.0、0.8、2.6 和 1.8。除虹膜外，所有反應在 21 天觀察期內均不可逆。在另一項根據 EPA OPP 81-4 於紐西蘭白兔進行的眼刺激性研究，結果刺激指數對於未沖洗和沖洗過的眼睛分別為 31.7 和 25.5。綜合兩項研究的結果，Pentylene Glycol 對眼睛有刺激性。[1]

- 皮膚致敏性：根據美國食品和藥物官員協會於食品、藥物和化粧品中的化學物質安全性評估所述，以 Maurer 優化測試評估對皮膚的敏感性，因此，Pirbright 白色天竺鼠接受十次皮內注射含 0.1% Pentylene Glycol 的生理鹽水和與完全 Bacto 佐劑的混合物，最後一次誘導注射後 14 天以 0.1% Pentylene Glycol 的生理鹽水激發，10 天後在封閉下經皮施用 10 %凡士林 24 小時。結果，測試動物和未處理的對照動物之間沒有觀察到差異。[1]
- 致癌性：沒有跡象顯示存在續發性癌症機制。因此，1,2 -戊二醇預計不會致癌。[1]
- 致突變性/遺傳毒性：Pentylene Glycol 在 Ames 試驗 (OECD 471)和小鼠淋巴瘤細胞試驗 (L5178Y TK +/-; OECD 476)中沒有致突變性，在體外哺乳類細胞染色體畸變試驗(OECD 473)中未發現染色體斷裂，Pentylene Glycol 被認為不具致突變性。[1]
- 生殖毒性：無 Pentylene Glycol 的生殖毒性的研究。結構相關的 1,2-丁二醇根據 OECD 422 進行生殖/發育毒性篩選測試，高達 1000 mg/kg 劑量下在親代動物和後代中未觀察到任何生殖毒性。交配、植入、懷孕、分娩和哺乳的參數與對照組沒有差異，表示 Pentylene Glycol 的生殖功能和發育毒性 NOAEL 為 1000 mg/kg/day。對於 Pentylene Glycol 也可以預期得到相同的結果。Pentylene Glycol 根據 OECD 414 以大鼠經口管飼研究進行發育毒性，高達 300 mg/kg 劑量下對懷孕大鼠或發育中的胎體沒有任何不利影響。懷孕女性和胚胎胎兒存活、生長和發育的 NOAEL 為 300 mg/kg/day。[1]
- 光毒性：無相關研究數據。
- 經皮吸收：根據 OECD 428 進行體外皮膚吸收試驗，在長達 24 小時的不同時間點測量局部施用含有 4% Pentylene Glycol 的防曬產品後 Pentylene Glycol 滲入和穿過豬皮膚的情況，此研究結果得知 24 小時後的生物利用度為 122.82 μg/cm^2，相當於施用劑量的 26.09%± 6.45%。[2]
- 毒理代謝動力學：無毒代動力學相關文獻。根據現有數據，Pentylene

Glycol 是一種具有低蒸氣壓的液體，在 20°C 時的 log Pow 為 0.06，可與水以任何比例混溶。從急性毒性研究中 Pentylene Glycol 可通過口服皮膚和吸入途徑進行生物利用。在大鼠暴露於 7 mg/L 氣溶膠約 4 小時後觀察到持續數天的中度呼吸窘迫。預設 100%再吸收計算出大鼠的全身內劑量為 2870 mg/kg，在皮膚暴露於 2000 mg/kg 劑量的大鼠中也觀察到持續數天的呼吸困難，大鼠經口暴露於 5000 mg/kg 劑量表現出類似或更嚴重的症狀。Pentylene Glycol 可能以原形排出或通過尿液與葡萄醣醛酸或硫酸鹽結合，由於沒有明確顯示在肝臟中具有首過效應，因此大量可能會以原形排出。由於高水溶性和可能的代謝，Pentylene Glycol 不太可能在體內聚積。[1]

- 人體數據：人類志願者進行 48 小時的封閉式表皮試驗進行評估。Pentylene Glycol 以 10% 的水溶液形式塗抹在 50 名志願者的背部，其中 14 名有過敏史或對皮膚敏感。測試部位立即評估和貼片去除 24 小時後評估，所有情況下都沒有觀察到刺激。[1] 另一人類反覆斑貼試驗進行 53 名受試者的結果無受試者有致敏現象。[1]
- 參考資料：

1. Registration Dossier. ECHA 網站: https://echa.europa.eu/registration-dossier/-/registered-dossier/2101/7/1
2. Margin of safety of pentylene glycol derived using measurements of cutaneous absorption and volatility. Regul Toxicol Pharmacol. Jul;87:106-111,2017.

2. INCI name：Dipropylene Glycol

- 急性毒性：根據 EPA OPP 81-1 進行且符合 GLP 的大鼠口服急性毒性研究，通過管飼法暴露 5.01 g/kg bw 二丙二醇(Dipropylene Glycol)沒有發生死亡，得出結論，大鼠的 LD_{50} > 5000 mg/kg bw。根據 EPA OPP 81-2 對兔子進行的急性皮膚毒性研究在閉塞下通過皮膚途徑暴露於 5.01 g/kg bw，沒有動物死亡亦無任何明顯的全身藥理或毒性作用跡象。根據測試結果確定大鼠的 LD_{50} > 5010 mg/kg bw。[1]
- 重複劑量毒性： NTP 對不同暴露時間(14 天、90 天和 2 年)的大鼠和小鼠進行飲用水研究，在大鼠 2 年研究中，在飲用水中暴露於 10000 和 40000 ppm 二丙二醇的雄性大鼠中觀察到慢性進行性腎病(CPN)和隨後的腎功能不全的發病率和嚴重程度增加，由於囓齒

動物 CPN 被認為在人類中沒有嚴格的對應物，因此這些發現被認為與人類風險評估無關。基於造成肝臟的膽管增生和鼻腔的嗅覺上皮萎縮和/或變性的發生率，確定雄性和雌性大鼠的重複劑量毒性 NOAEL 分別為 470 和 530 mg/kg bw/天(實際攝入劑量)。[1]

- 皮膚腐蝕性/刺激性：根據 EPA OPP 81-5 進行的一項符合 GLP 的兔子研究，將 0.5 ml 量的測試物質在封閉的情況下施於兔子測試部位 4 小時。貼片去除後 45 分鐘沒有觀察到刺激，除了一個部位 (1/6) 顯示出非常輕微的紅斑。在 24 小時內，所有測試區域看起來都正常，並在整個研究期間保持正常。紅斑和水腫的平均(24 + 48 + 72 小時)得分均為 0，另有兩項人類志願者研究結果均顯示二丙二醇不具有皮膚刺激性。[1]
- 眼刺激性：根據 EPA OPP 81-4 進行的一項符合 GLP 的兔眼刺激研究，沒有觀察到任何全身效應的證據。將測試物質施用於給藥的眼睛後沒有立即出現疼痛的跡象，例如長時間的眼瞼痙攣。根據結果二丙二醇對兔子眼睛沒有刺激性。[1]
- 皮膚致敏性：根據 GLP 和 EPA OPP 81-6 進行的 Buehler 天竺鼠試驗中，將 0.5 ml 新鮮製備的試驗溶液塗抹在 10 隻剃毛動物的表面上並保持 6 小時。接下來 2 週內在同一部位重複該誘導程序，總共進行 3 次 6 小時的暴露，誘導暴露之間間隔 5-9 天，最後一次誘導後兩週用 0.5ml 非刺激性濃度在每個部位進行激發並於 24、48 和 72 小時進行評分。5 隻動物中的 1 隻出現短暫的輕微片狀紅斑但沒有觀察到任何刺激，基於此結果二丙二醇被認為不具有皮膚致敏性。[1]
- 致癌性：NTP 為期 2 年大鼠和小鼠飲用水研究，大鼠暴露濃度分別為 0、2500、10000 和 40000 ppm(相當於雄性 115、470 和 3040 mg/kg bw/day 和雌性 140、530 和 2330 mg/kg bw/day)，小鼠暴露濃度為 0、10000、20000 和 40000 ppm (相當於雄性 735、1220 和 2390 mg/kg bw/day 和 575、1040 和雌性 1950 mg/kg bw/day)，在大鼠腎臟、肝臟和鼻子中發現了與二丙二醇相關的非腫瘤性病變，在小鼠沒有觀察到化合物相關的腫瘤或非腫瘤性病變僅減輕體重。大鼠或小鼠中均未觀察到二丙二醇致癌活性的證據。[1]
- 致突變性/遺傳毒性：在鼠傷寒沙門氏菌 TA98、TA98、TA100、TA1535 和 TA1537 菌株中無論是否有代謝活化且濃度高達 10000 µg/plate，以及小鼠淋巴瘤細胞中無論是否有代謝活化且濃度高達 5000

μg/ml，結果顯示二丙二醇不會導致突變率增加；另根據 OECD478 在劑量 2000 mg/kg bw 下進行的小鼠體內骨髓微核試驗結果呈現陰性。根據結果二丙二醇被認為是無基因毒性。[1]

- 生殖毒性：二丙二醇於大鼠或兔子進行的兩項發育毒性研究，在最高測試劑量(大鼠為 5000 mg/kg bw/day，兔子為 1200 mg/kg bw/day)均未觀察到對發育影響，此劑量遠高於重複劑量毒性的 NOAEL(470 mg/kg bw/day)。大鼠研究在 2000 和 5000 mg/kg bw/day 劑量下觀察到母體毒性，包括毒性臨床症狀、死亡率和相對肝臟重量增加(NOAEL 為 800 mg/kg bw/day)。[2] 尚無關於二丙二醇的生殖毒性研究，另一項與 OECD 416 兩代研究小鼠連續育種試驗用於單丙二醇，觀察對生育能力的 NOAEL 為 10100 mg/kg bw/day (測試的最高劑量)。[1]
- 光毒性：含有 7.2%二丙二醇的剃鬚製劑以 50 位受測者進行的重複斑貼試驗，增加紫外線照射無產生光毒性或光致敏反應。[2]
- 經皮吸收：關於二丙二醇根據經 OECD 428 進行的使用屍捐皮膚的體外皮膚滲透研究，專家判斷選擇 40%的皮膚吸收值用於風險評估 24 小時，暴露間隔結束時僅施用劑量的 0.075%純二丙二醇通過皮膚滲透到受體液中。[1]
- 毒理代謝動力學：無口服二丙二醇的基本毒代動力學研究，交叉參照二丙二醇結構類似物三丙二醇的現有毒代動力學研究計算通過口服途徑吸收三丙二醇的量為 86%。[1]
- 人體數據：24 小時半封閉貼片研究，用於比較包括二丙二醇等幾種測試物品的皮膚刺激性，將受試物質製成 25%的蒸餾水溶液，將 0.2 ml 溶液置於貼片上，塗抹在 33 名受試者背部的脊椎旁區域，受試者在整個測試期間沒有表現出任何皮膚刺激跡象，2 名受試者在 24 小時評估時表現出輕度紅斑。另一 14 天的累積刺激試驗中，大約 0.2 ml 的試驗材料在封閉敷料下以 50%溶液形式塗抹在 26 名人類志願者的上背部，週一至週五施用共 14 天，在研究前 4 天只有 1 名受試者有輕微紅斑，剩餘測試期間施用 25%二丙二醇紅斑消失，其他 25 名受試者在測試期間的任何時候都沒有表現出任何皮膚刺激跡象。一項針對濕疹患者的人體研究評估，503 名濕疹患者用 10%二丙二醇水溶液進行了貼片測試。貼片 2 天並在第 2、3 和 5-7 天評分反應，只有 1 例對二丙二醇的斑貼試驗呈陽性，結果顯示陽性反應，二丙二醇也僅有非常弱的致敏性。[2]

◆ 其他安全資料：三丙二醇和單丙二醇的結構及可比較的物理化學性質與二丙二醇相似，所有物質都是具有低蒸氣壓的粘性液體，相對密度約為 1，可與水混溶，log Pow 從丙二醇的-1.07 到-三丙二醇為 0.379。[1]

◆ 參考資料：

1. Registration Dossier. ECHA 網站: https://echa.europa.eu/registration-dossier/-/registered-dossier/16016/7/1
2. Final Report on the Safety Assessment of Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol. JACT 4(5):223-248, 1985.

3. INCI name：PPG-12-Buteth-16

- 急性毒性：PPG-12-Buteth-16 的大鼠急性經口 LD_{50} 為 18.3 g/kg。關於大鼠急性吸入毒性，PPG-12-Buteth-16 雄性和雌性的 LC_{50} 分別為 4670 mg/m^3 和> 5230 mg/m^3，PPG-7-Buteth-10 為 4.77 mg/m^3 (雄性和雌性) ，PPG-20-Buteth-30 為 330 mg/m^3 (雄性和雌性)，PPG-33-Buteth-45 為 147 mg/m^3；一般來說 PPG 丁基醚的致死率隨著分子量的增加而降低。[1]
- 重複劑量毒性：無 PPG- 12-Buteth- 16 的相關研究數據。PPG-24-Buteth-27 的大鼠 3 個月亞慢性口服毒性試驗，在飲食中濃度 0.01% 至 1.25%，在 0.05、0.25 或 1.25%實驗組的大鼠肝臟和腎臟中觀察到病變，0.05%實驗組觀察到的變化被認為是暫時的，0.01%組大鼠組織與對照組差異不大。另一項 PPG-33-Buteth-45 的大鼠 90 天亞慢性研究，在餵食劑量 0.7 和 4.0 g/kg/day 中觀察到肝和腎損傷，而較低劑量(0.03 或 0.15 g/kg/day)的大鼠中未觀察到這些損傷。[1]
- 皮膚腐蝕性/刺激性：在 PPG-12-Buteth-16、PPG-20-Buteth-30 和 PPG-33-Buteth-45 的皮膚刺激試驗中，僅施用 PPG-12-Buteth-16 後在兔子身上觀察到出血或充血現象(capillary Injection)，而另一項研究發現 PPG-26-Buteth-26 在紐西蘭白化兔中引起非常輕微到輕微的皮膚刺激。[1]
- 眼刺激性：PPG-12-Buteth-16 非兔子的眼部刺激物，此測試是將試驗物質(0.1ml)滴入受測動物一隻眼睛的結膜囊中。[2]
- 皮膚致敏性：針對 109 名受試者的 RIPT 研究發現在半封閉貼片下使用 0.75% PPG-12-Buteth-16 不會引起刺激或致敏性。另一含有 2.5% PPG-26-Buteth-26 剃鬚劑配方在兩次為期 21 天的家庭使用測試中分別以 52 和 54 受試者評估皮膚刺激或致敏性。根據 PPG-26-Buteth-26 和 PPG-12-Buteth-16 的刺激和致敏數據顯示這些 PPG Buteth 成分在目前的使用濃度下不會產生皮膚刺激或敏感性。[2]
- 致癌性：PPG-7-Buteth-10 和 PPG-33-Buteth-45 分別不會在小鼠體內誘發乳頭狀瘤或癌，在 1 至 2 次的 dimethylbenzanthracene (DMBA) 引發後給予 70% PPG-24-Buteth-27 將作為腫瘤促進劑，而 5% PPG-24-Buteth-27 則否。另一項為期 2 年的大鼠研究於飼料中添加濃度為 0.001%至 0.26%的 PPG BE800，結果無致癌性。[1]
- 致突變性/遺傳毒性：無 PPG-12-Buteth-16 的數據。Propylene Glycol

Butyl Ether、[(butoxymethylethoxy)methylethoxy]-propan-1-ol、poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy-及 1-(2-butoxy-1-methylethoxy)-propan-2-ol 以 Ames 測試結果均無致突變性，小鼠微核試驗中[(butoxymethylethoxy)methylethoxy]-propan-1-ol 和 1-(2-butoxy-1-methylethoxy)-propan-2-ol 經單次口服劑量 1875 mg/kg 和 2500 mg/kg 後的結果均為陰性；Propylene Glycol Butyl Ether 的多項基因毒性研究結果無致突變性。[1]

- 生殖毒性：無 PPG-12-Buteth-16 相關研究數據。大鼠在懷孕後第 6-16 天局部施用 PPG2 Butyl Ether 會產生局部皮膚反應，但不會產生生殖或致畸作用(NOEL > 1 ml/kg)。局部施用 Propylene Glycol Butyl Ether 對大鼠(懷孕 6-16 天施用≤1.0 ml/kg bw/day，相當於 880 mg/kg bw/day）或兔子(懷孕 6-16 天施用≤100 mg/kg bw/day)。局部施用 910 mg/kg bw/day 的 1-(2-butoxy-1-methylethoxy)-propan-2-ol 對大鼠沒有胚胎毒性、胎兒毒性或致畸性。大鼠以管飼法在懷孕 7-16 天給予高達 1000 mg/kg 的 Buteth-3，未觀察到與試驗物品相關的不良發育或生殖影響。大鼠在交配前和交配過程中口服 500 mg/kg bw/day 的 poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy-或 1000 mg/kg bw/day 的 1-(2-butoxy-1-methylethoxy)-propan-2-ol 沒有觀察到對生殖的影響。[1]
- 光毒性：無相關研究數據。
- 經皮吸收：無 PPG-12-Buteth-16 的數據。Buteth-3 通過人體皮膚於暴露 12 小時後的體外擴散速率為 22 μg/cm^2/h，對皮膚屏障功能沒有顯著影響。[1]
- 毒理代謝動力學：無 PPG-12-Buteth-16 的數據。Buteth-3 通過人體皮膚於暴露 12 小時後的體外擴散速率為 22 μg/cm^2/h，對皮膚屏障功能沒有顯著影響。propylene glycol ethers 在口服和吸入暴露後少量被迅速吸收並分佈到全身，排泄主要通過尿液和呼出的空氣，少量隨糞便排出。通過皮膚途徑吸收較慢但隨後分佈迅速。此外，Propylene Glycol Butyl Ether(一種單二醇醚)比二甘醇和三甘醇醚更容易通過皮膚吸收，然而二甘醇和三甘醇醚在皮膚上的存在時間可能比單甘醇醚長因為蒸氣壓較低。[1]
- 人體數據：針對 109 名受試者的 RIPT 研究發現，在半封閉貼片下使用 0.75% PPG-12-Buteth-16 不會引起皮膚刺激或致敏性。[1]
- 參考資料：

1. Amended Safety Assessment of Butyl Polyoxyalkylene Ethers as Used in Cosmetics. IJT 41(Suppl. 1):5-43, 2022.
2. Final Report on the Safety Assessment of PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35. Int J Toxicol. 2000;19(Suppl 1):47-67.

4. INCI name：Niacinamide

- 急性毒性：經口、吸入或皮膚途徑急性暴露後，Niacinamide(煙酰胺）被認為幾乎無毒。根據歐盟方法 B.1 tris 和 OECD 423 在大鼠進行的關鍵急性經口毒性研究，估計急性經口 LD_{50} > 2500 mg/kg bw，在大鼠、小鼠和兔的支持性研究證實，單次口服給藥後幾乎是無毒的。交叉參照 Niacine 的急性吸入毒性的研究，因為這兩種化合物都可在人體內轉化，根據 OECD 436 得知的 Niacine 暴露 4 小時的 LC_{50} 大於 3.8 mg/L 空氣(化學測定平均氣溶膠濃度)，此為最高氣溶膠濃度。根據歐盟方法 B.3 和 OECD 402 在大鼠進行的關鍵皮膚毒性研究，得知急性皮膚 LD_{50} > 2000 mg/kg bw。[1]
- 重複劑量毒性：根據歐盟方法 B.7 和 OECD 407 在大鼠進行的關鍵亞急性口服毒性研究，每天 1000 mg/kg/day 劑量給藥 4 週，作為主要標靶器官的肝臟也僅受到輕微影響，在暴露高劑量後所有變化都可逆的，而在 215 mg/kg/day 時未觀察到副作用。[1]
- 皮膚腐蝕性/刺激性：根據歐盟方法 B.4 和 OECD 404 以紐西蘭白兔進行的皮膚刺激性試驗，在三隻兔子的完整皮膚上單次 4 小時半封閉地施用，產生的主要刺激指數為 0.0，未產生皮膚刺激的跡象。也未發現腐蝕作用。[1]
- 眼刺激性：根據歐盟方法 B.5 和 OECD 405 以紐西蘭白兔進行的急性眼部刺激/腐蝕試驗，單次施用於三隻兔子未沖洗的眼睛，會導致角膜表面正常光澤變暗、瀰漫性角膜混濁、虹膜炎症和中度至重度結膜刺激。產生最大組平均分數為 34.3，根據 Modified Kay and Calandra 分類系統，將 Niacinamide 對兔眼的刺激分類為中度刺激物 (1 到 8 級的 5 級)。[1]
- 皮膚致敏性：根據 OECD 406 進行的天竺鼠最大化測試，給 20 隻 Pirbright White 天竺鼠皮內施用含有或不含有佐劑的 Niacinamide，然後在封閉貼片下單次暴露 48 小時。3 週後用 50% Niacinamide (50 mg) 的表皮貼劑在封閉包裹下對動物進行激發 24 小時。暴露的 9/20 動物在 24 小時時表現出微弱的紅斑跡象，其中 7 隻持續 48 小時，而對照組中的兩隻動物表現出紅斑，這在統計分析中被認為不顯著。[1]
- 致癌性：只有一項研究評估單用 Niacinamide 的致癌性，於瑞士白化小鼠的飲用水添加 1% 煙酰胺溶液，對生存率沒有實質性影響且

無致癌作用。所有其他報告都涉及某些方面 Niacinamide 與其他藥物合用的致癌性(腫瘤減少或促進)。[2]

- 致突變性/遺傳毒性：根據歐盟方法 B.13/14 和 OECD 471 進行的數個 Ames 測試中，使用鼠傷寒沙門氏菌菌株 TA98、TA100、TA1535、TA1537 和 TA1538，在有和無代謝活化的情況下測試高達 10000 ug/plate 的濃度，顯示 Niacinamide 是非致突變性的物質。根據歐盟方法 B.10 和 OECD 473 進行在體外培養的人淋巴細胞中誘導染色體畸變研究，濃度 5000 ug/mL 下且有和無代謝活化的情況在處理 21 和 44 小時後收集細胞，在該體外細胞遺傳學測試系統沒有顯示出染色體斷裂的證據。根據歐盟方法 B.12 和 OECD 474 進行的體內研究，在給藥後 24、48 和 72 小時檢查每組六隻小鼠，根據評估標準被認為是非致突變性的。[1]
- 生殖毒性：根據歐盟方法 B.31、OECD 414 和醫藥產品生殖毒性檢測指南(EC-Doc. 1111 3387/93)進行的一項使用 Niacinamide 的關鍵研究，每組 20 隻兔子以劑量 50、150 或 450 mg mg/kg bw/day 從懷孕的第 6 天到第 20 天通過口服管飼法給藥，在本研究的條件下母體及胎兒的 NOAEL 皆為 50 mg/kg bw/day。另一根據歐盟方法 B.31、OECD 414 使用 Nicotinic acid 進行的大鼠試驗可交叉參照至 Niacinamide，本研究得出的母體毒性 NOAEL 為 200 mg/kg bw/day (相當於 Niacinamide 198 mg/kg bw/day)，基於體重變化；生殖毒性和發育毒性的 NOAEL 為 200 mg/kg bw/day (相當於 Niacinamide 198 mg/kg bw/day) ，基於顯著降低的胎盤和雄性幼鼠體重。[1]
- 光毒性：在 UVA 和 UVB 光照射的完全封閉條件下使用含有 2% Niacinamide 的口紅或含有 5% Niacinamide 的粉底後，沒有證據顯示會產生光毒性。上述研究為 12 名成年志願者在封閉貼片條件下暴露 24 小時後，移除貼片並將一個貼片部位暴露於 UVA 為 20 J/cm^2，其他斑貼試驗部位作為未照射對照組，並於照射後 24 和 48 小時評估測試部位，得出結果為無光毒性。[2]
- 經皮吸收：Feldman 與 Maibach 在 1970 年發表的研究在人體前臂腹側施用 Niacinamide 5 天後，總施用劑量的 11.08%被吸收(大約每天吸收 2-3%)，將 ^{14}C 標記 Niacinamide 溶解在丙酮中塗抹在 13 cm^2 的皮膚區域即 4 μg/cm^2，該部位施用後 24 小時清洗並連續 4 天重複此過程，5 天收集尿液測定 ^{14}C 標記的 Niacinamide 的濃度，結果證明 Niacinamide 在局部施用後持續吸收長達 5 天，最高吸收率發

生在 48 小時和 72 小時之間。Franz 於 1975 年以切除的人體腹部皮膚體外測定 Niacinamide 吸收，在這項研究中，Niacinamide 溶解在丙酮中，用量為 4 μg/cm^2。Niacinamide 吸收到受體液中在 24 小時計算為起始劑量的 28.8%。[2]

- 毒理代謝動力學：有大量關於 Nicotinamide、Nicotinic acid 和 tryptophan 代謝的研究。Nicotinamide 及 Nicotinic acid 這兩種維生素可以通過不同的途徑摻入吡啶核苷酸輔酶 NAD(P)。外源性的 Nicotinamide 及 Nicotinic acid 使用有限，而主要的 NAD(P)前體是胺基酸 tryptophan 。Nicotinamide 以輔酶 NAD 的成分或游離形式存在於食物中，在腸黏膜中通過酶水解自 NAD 釋放出來。[3]
- 人體數據：三個單獨的 HRIPT 測試來調查含有 Niacinamide 的水包油乳液的效果，0, 1, 2.5 和 10 mg/cm^2 的半封閉和封閉斑貼條件，每項致敏研究有 100 位志願者，結果在任何志願者皆未發現能誘發遲發型致敏反應。[1]
- 其他安全資料：Niacinamide 為 GRAS 食品添加劑和營養和/或膳食補充劑，可用於臨床治療高膽固醇血症。[2] 關於 Niacinamide 對糖尿病患者或有糖尿病風險的患者的試驗中未有顯著的不良反應，這些患者已使用相當於每天 3 克的劑量持續時間長達 3 年，研究得出的 NOAEL 約為 25 mg/kg bw，為許多高質量試驗中報告的最低劑量，由於考慮到成年人消除 Niacinamide 的速度可能比實驗組(其中許多是兒童)更慢，而且兒童的數據不能反映全是老年受試者間的變異，以 2 作為不確定性係數，故 ESFA 根據此證據權重評估研究將 Niacinamide 的上限確定為 12.5 mg/kg/day 或成人約 900 mg/day。[4]
- 參考資料：

1. Registration Dossier. ECHA 網站: https://echa.europa.eu/registration-dossier/-/registered-dossier/14571/7/1
2. Final Report of the Safety Assessment of Niacinamide and Niacin. IJT 24(Suppl 5):1-31, 2005.
3. SIDS Initial Assessment Report For SIAM 15. 3-Pyridinecarboxamide (nicotinamide) (CAS No: 98-92-0),2002.
4. Tolerable Upper Intake Levels for Vitamins and Minerals. EFSA, 2006.

5. INCI name：Betaine

- 急性毒性：根據 OECD 401 和 GLP 進行的大鼠口服急性毒性研究，LD_{50} 為 11179 mg/kg bw。[1]
- 重複劑量毒性：Betaine 的大鼠口服亞急性(28 天)、亞慢性(90 天)、慢性毒性(52 週)和致癌性(104 週)依據 OECD 進行的研究結果，Betaine 在高達 5%的飼料不會引起任何不利影響、慢性毒性或致癌性。因此，NOAEL 設定為最高劑量即 5000 mg/kg bw/day。[1]
- 皮膚腐蝕性/刺激性：在非人類和人類刺激和抗刺激研究結果，均未發現 Betaine 具有刺激性或腐蝕性。在人類功效研究中對皮膚的 Betaine 具有抗刺激作用。[1]
- 眼刺激性：根據 OECD 405 進行體內眼睛刺激測試，Betaine(天然萃取溶於蒸餾水 10% w/v)的應用不會導致任何眼睛刺激。[1]
- 皮膚致敏性：根據 OECD 406 和 GLP 進行的天竺鼠皮膚致敏性測試以及人類致敏研究，Betaine 最高含量 50%對非人類和人類皮膚不會產生致敏性。[2]
- 致癌性：一項相當於 OECD 453 的研究中進行為期 104 週的致癌性研究中，未在大鼠中觀察到致癌性。[1]
- 致突變性/遺傳毒性：體外和體內遺傳毒性研究均顯示 Betaine 不具基因毒性。[2]
- 生殖毒性：根據遺傳毒性測試不具遺傳毒性且在重複劑量毒性測試中未顯示任何毒性特性，Betaine 被認為無任何致癌性或對生殖器官不利影響，還通過 QSAR 模型測試其與雌激素受體 Beta 結合的能力，雌激素受體 Beta 是內分泌干擾物的主要標靶。根據這個有效和適用的模型，Betaine 確定不會與這種受體結合。[1]
- 光毒性：無相關研究數據。
- 經皮吸收：使用類似於 OECD 428 方法，使用 Franz 測試經皮吸收。結果顯示 Betaine 具有極低的經皮滲透能力(無論配方如何均為初始劑量的 0.1%)。在本試驗條件下認為試驗物質無刺激性。[1]
- 毒理代謝動力學：Betaine 可以作為一種天然存在的物質存在於人體內，它是由膽鹼在體內氧化形成的。Betaine 作為滲透劑和防止體內不良現象的保護劑，並參與單碳代謝和甲基化過程。Betaine 的主要作用是提供同型半胱氨酸一個甲基，然後將其代謝為蛋氨酸。Betaine 本身首先代謝為二甲基甘氨酸，最終代謝為甘氨酸和肌氨

酸。[1]

- 人體數據：Betaine 的皮膚刺激性及皮膚致敏性已進行多項人體研究。[2]
- 其他安全資料：Betaine 代謝良好，並且是體內天然存在的物質，因此耐受性非常好，不會引起任何不良現象。[1]
- 參考資料：

1. Registration Dossier. ECHA 網站: https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15954/7/1
2. Safety Assessment of Alkyl Betaines as Used in Cosmetics. IJT 37(Suppl. 1):28-46, 2018.

6. INCI name：PEG-40 Hydrogenated Castor Oil

- 急性毒性：以固定劑量方法，5 隻雌性大鼠通過管飼法接受單劑量 2000 mg/kg bw，此後觀察大鼠 14 天，沒有發生死亡。一隻雌鼠在第一天有駝背姿勢、共濟失調、呼吸嘈雜、流涎增加和嗜睡情形，其他雌性在給藥後的 2 小時內表現出駝背姿勢，對體重沒有影響亦無宏觀病理學上症狀。基於上述其口服 LD_{50} > 2000 mg/kg bw。[1]
- 重複劑量毒性：根據 OECD 422 進行的研究中，Wistar 大鼠以通過管飼法口服劑量 100、300 和 1000 mg/kg/day，在交配前兩週至犧牲前日(包括雄性)或長達 13-15 天的哺乳期(雌性)的耐受性良好且沒有在研究期間與測試物質相關的死亡率，與臨床症狀、感覺反應、握力或運動活動相關的明顯毒性跡象，考慮到食物消耗和體重的輕微下降，雌鼠和雄鼠的重複給藥毒性 NOAEL 被認為是 1000 mg/kg/day。[1]
- 皮膚腐蝕性/刺激性：在 EpiDerm™人體皮膚模型中使用兩重複組織在 3 和 60 分鐘內進行測試。受試物質處理的組織的相對平均存活率對於 3 分鐘的暴露為 98.0%，對於 60 分鐘的暴露為 101.5%，顯示該物質對皮膚沒有腐蝕性。[1]
- 眼刺激性：以人類角膜細胞模型試驗評估，50 µL 的測試物質培養後未觀察到刺激作用，與陰性對照的值相比，對應於組織活力的相對平均吸收值沒有降低到低於 60% (92.1%)，表示該物質不具有任何刺激眼睛的可能性。[1]
- 皮膚致敏性：在誘導過程中觀察到刺激，但在使用高達 50% PEG-35 蓖麻油的天竺鼠研究中未發現致敏性，而此被發現是天竺鼠和小鼠的有效佐劑。儘管在使用 PEG-35 蓖麻油作為載體的靜脈注射藥物研究中發現一些致敏反應，但臨床數據通常對皮膚刺激和致敏是陰性的。在動物致敏中使用的最大濃度研究顯示 PEG 蓖麻油為 50%，PEG 氫化蓖麻油為 100%，得出結論為 PEG 蓖麻油可安全用於濃度高達 50%的化粧品配方中，所以 PEG 氫化蓖麻油在化粧品配方中使用是安全的。[2]
- 致癌性：，大鼠餵養研究作為載體對照組進行測試，沒有產生誘變或致癌作用 。[2]
- 致突變性/遺傳毒性：在 Ames 測試中，有和無代謝活化的情況下，在鼠傷寒沙門氏菌菌株 TA1535、TA1537、TA98、TA100 和大腸桿

菌菌株 WP2 uvrA 中的測試結果未發現突變頻率增加，在該測試條件下該物質被認為是非致突變性的。根據 OECD 490 在 L5178Y TK +/- Mouse Lymphoma Assay 中進行的測試，暴露時間 4 小時(有和無代謝活化)或 24 小時(無代謝活化)，沒有發現 TK +/- 基因座的突變頻率增加。故顯示該物質在此測定中是非致突變性的。以人類淋巴細胞測試四個劑量以及存在代謝活化的載體和陽性對照(4 小時)下評估染色體畸變並且在無代謝活化的情況下(4 和 24 小時) ，該物質無任何明顯的毒性，也沒有引起異常細胞頻率的任何統計學上顯著增加，並且被認為在體外對人類淋巴細胞無致染色體畸變性。[1]

- 生殖毒性：未發現發育毒性的證據。參照重複劑量毒性說明，生殖/發育毒性的 NOAEL 為 1000 mg/kg/day。[2]
- 光毒性：無相關研究數據。
- 經皮吸收：一般來說分子量低於 500 且 log Pow 值介於-1 和 4 之間有利於通過胃腸道(GI)吸收，前提是該物質具有足夠的水溶性(> 1 mg/L) ，親脂性化合物可能被膽汁鹽的膠束溶解吸收，這種機制對於高度親脂性化合物(log Pow > 4)可能特別重要，尤其那些難溶於水(≤ 1 mg/L)的化合物否則將很難被吸收。氫化、乙氧基化蓖麻油的分子量約為 1026。該物質為蠟狀固體，具有極高 logKow 和<0.5 mg/L 的水溶性，因此該物質的物理化學性質顯示吸收率低。[1]
- 毒理代謝動力學：對於蓖麻油(castor oil)，預計僅在脂肪分解後才能通過口服途徑進行氫化、乙氧基化吸收。預計皮膚吸收是最小的。如果被吸收，氫化的乙氧基化脂肪酸預計會通過類似於脂肪酸的機制進行分佈、代謝和排泄，預計氫化、乙氧基化蓖麻油的人體皮膚、口服和吸入吸收以及隨後的人體代謝、分佈和排泄曲線與哺乳動物衍生的膳食脂質相似，並利用相同的生化途徑和循環。[1]
- 參考資料：

1. Registration Dossier. ECHA 網站: https://echa.europa.eu/de/registration-dossier/-/registered-dossier/26320/7/1
2. Final report on the safety assessment of PEG-30, -35, -36, and -40 castor oil and PEG-30 and -40 hydrogenated castor oil. IJT 16(Suppl.3):269-306, 1997.
3. Safety Assessment of PEGylated Oils as Used in Cosmetics. IJT 33(Suppl 4):13-39, 2014.

7. INCI name：Olea Europaea (Olive) Leaf Extract

- 急性毒性：橄欖莖皮萃取物、水解橄欖果肉(果實)萃取物和橄欖葉萃取物的 LD_{50} 大於 2000 mg/kg，此為各成分測試的最大濃度。在大鼠研究中，橄欖葉萃取物的 LD_{50} 大於 2000 mg/kg。[1]
- 重複劑量毒性：已有多項對橄欖衍生成分的重複劑量口服毒性研究。在通過管飼法接受橄欖果實萃取物(高達 1381 mg/kg bw/d)或水解橄欖果肉萃取物(高達 2000 mg/kg/d) 90 天的大鼠中未觀察到與施用相關的死亡，橄欖果實萃取物的 LOAEL 為 1381 mg/kg bw/d 而 NOAEL 為 691 mg/kg bw/d，水解橄欖果肉萃取物的 NOAEL 為 2000 mg/kg/d。為期 14 天對大鼠專利橄欖葉萃取物(1000、1500 或 2000 mg/kg/d)的研究中，在 1000 和 2000 mg/kg 劑量組的雄性中觀察到劑量依賴性透明液滴腎病，但在較低劑量組中未觀察到。400 mg/kg 橄欖葉乙醇萃取物的 28 天研究中，未觀察到死亡、臨床毒性症狀或肝臟和腎臟異常，但與對照組相比，100 和 400 mg/kg 劑量組的雄性血液尿素氮濃度顯著增加。0.9%橄欖葉萃取物(水溶液)的 42 天研究中，肝臟含有脂肪各試驗組均觀察到變化和肝細胞壞死，但 0.7%和 0.9%劑量組效果更顯著，實驗組腎臟皮質區有條紋狀出血和充血，較高劑量出血較重。專利橄欖葉萃取物的 90 天大鼠管飼研究的 NOAEL 為 1000 mg/kg bw/day。[1]
- 皮膚腐蝕性/刺激性：無相關研究數據。
- 皮膚致敏性：無相關研究數據。
- 致癌性：無相關研究數據。
- 致突變性/遺傳毒性：專利橄欖葉萃取物在 V79 中國倉鼠肺細胞中的細菌回復突變分析(測試高達 5000 μg/plate)或哺乳動物染色體畸變測試(測試高達 1500 μg/ml)，結果不被認為具有遺傳毒性。[1]
- 生殖毒性：無橄欖葉萃取物的數據。參考水解橄欖果肉(果實)萃取物濃度高達 2000 mg/kg/d 在 F0 成熟大鼠或 F1 幼鼠中沒有產生與施用相關的死亡率，並且對生育力或生殖沒有產生不利影響。母鼠在懷孕第 6 天到第 20 天給藥的發育毒性 NOAEL 大於 2000 mg/kg/day。[1]
- 光毒性：無相關研究數據。
- 經皮吸收：無相關研究數據。
- 毒理代謝動力學：無相關研究數據。

- 人體數據：在一項關於補充橄欖葉萃取物的氧化作用的研究中，將 15 名年輕健康的成年男性和女性受試者隨機分成 3 組，兩組適用商業橄欖葉萃取物液體(5 毫升)或膠囊每天 3 次並持續 28 天，未說明商業補充劑中橄欖葉萃取物的濃度，完成評估的 36 人中未觀察到不良反應，與對照組相比亦沒有觀察到橄欖葉萃取物對氧化標誌物的顯著影響。[1]
- 參考資料：

1. Safety Assessment of Olea europaea (Olive)-Derived Ingredients as Used in Cosmetics. CIR Scientific Literature Review, 07/27/2022.

8. INCI name：Chlorphenesin

- 急性毒性：Sprague Dawley 大鼠急性經口毒性 LD_{50} 為 3000 mg/kg bw。[1]
- 重複劑量毒性：劑量 1000、100 和 10 mg/kg/day 通過口服管飼法在 28 天的給藥期間測試 Chlorphenesin 的重複口服毒性，結果大鼠重複經口毒性 28 天的 NOAEL 為 100 mg/kg bw/day。[1,2]
- 皮膚腐蝕性/刺激性：根據 OECD 439 以 EPISKIN™ 重建人類表皮模型進行的體外測試。結果 Chlorphenesin 被歸類為無刺激性。[1]
- 眼刺激性：兩項體外研究採 OECD 437- BCOP 方法及 OECD 492-EpiOcular™ 眼刺激測試，結果認為 Chlorphenesin 具有眼刺激性。[1]
- 皮膚致敏性：LLNA 測試結果為陰性，少數人反覆接觸含有 Chlorphenesin 作為防腐劑的化粧品後出現致敏的情況，該比率很低不足以將之分類為皮膚致敏劑。[1]
- 致癌性：無致癌性研究數據，但有研究顯示 Chlorphenesin 具有抗腫瘤活性。[2]
- 致突變性/遺傳毒性：AMES 試驗在鼠傷寒沙門氏菌和大腸桿菌試驗菌株(TA1535、TA1537、TA98、TA100 和 WP2 uvrA)中測試濃度為 5000 µg/plate 的誘導突變能力，無論是否有代謝激活均為陰性。在中國倉鼠卵巢 (CHO) 細胞中在存在和不存在外源性代謝激活的情況下至其毒性極限 (1500 µg/ml)結果為陰性。[1]
- 生殖毒性：評估 Chlorphenesin 對大鼠懷孕和子宮內發育，從交配後第 6 天到第 15 天每天單次通過口服管飼法將 0、10、50 和 100 mg/kg 的劑量給予每組 25 隻雌鼠，對於所有劑量顯示無母體毒性且無對胚胎胎兒存活、子宮內生長和發育的不利影響，對發育胎兒的 NOEL 被認為是 100 mg/kg/day。[1]
- 光毒性：11 名對 ketoprofen(一種非類固醇的抗發炎藥物)光敏感的患者以 Chlorphenesin 進行光斑貼測試，患者在第 2 天以 5 J/cm^2UVA 照射，在第 3 天和第 4 天結果無陽性反應。[2]
- 經皮吸收：涉及大鼠的體內經皮吸收研究中，高達 57%的施用劑量被吸收，所有吸收都在 96 小時內從尿液中排出。[2]
- 毒理代謝動力學：基於其低分子量(202.63)、在水中的溶解度 (5.471 g/l at T= 20°C) 和 log Kow (1.23)在-1 和 4 之間，Chlorphenesin 預計會被胃腸道和皮膚吸收且通過口服、腹腔注射和皮膚很容易吸收，

呼吸吸收不太可能。基於其水溶性及 Log Kow=1.23，無需擔心潛在生物蓄積性(生物蓄積臨界閾值為 4)。根據大鼠和狗體內代謝研究證實 QSAR 預測，主要轉化為氧化產物(即 3-p-chlorophenoxylactic acid 和 p-chlorophenoxyacetic acid)或其他氯酚和氯苯醚的共軛反應產物。由於在口服和皮膚吸收後具有高水溶性，Chlorphenesin 會迅速從尿液中排出。[1]

- 人體數據：使用人類重複損傷斑貼測試來評估含 5%至 9% Chlorphenesin 的測試材料的皮膚刺激和致敏性，55 名男性和女性患者評分結果無皮膚刺激或致敏反應。[2]
- 參考資料：

1. Registration Dossier. ECHA 網站: https://echa.europa.eu/de/registration-dossier/-/registered-dossier/22482/7/1
2. Safety Assessment of Chlorphenesin as Used in Cosmetics. IJT 33(Suppl. 2):5-15, 2014

9. INCI name：Mannitol

- 急性毒性：幾項急性口服毒性研究，當大鼠和小鼠給予高達 5 g/kg bw 的 Mannitol(甘露醇)時所有動物都存活，小鼠和大鼠的口服 LD_{50} 分別為 22 g/kg bw 和 17.3 g/kg bw。[1]
- 重複劑量毒性：每組 10 隻 B6C3F1/N 小鼠被餵食含有 0、0.3、0.6、1.2、2.5 或 5.0% Mannitol 的飲食，持續 13 週，除雄性給予 5.0%外，所有劑量實驗組的平均體重增加均高於對照組，未觀察到其他不良反應。在另一項研究每組 10 隻 F344 大鼠被給予含有 0、0.3、0.6、1.25 或 5%甘露醇(相當於 0、150、300、625 或 2500 mg/kg bw/day)的飲食 13 週，與對照組相比，高劑量組雄性平均體重增加少於 9.6%，所有其他組的平均體重增加與對照組相似，未觀察到與測試物質相關的臨床症狀。[1,2]
- 皮膚腐蝕性/刺激性：無 Mannitol 之相關研究數據。參考添加 Xylitol(木糖醇) 5%和 10%的添加凝膠和 60%乳膏製劑，將 0.5 g 給予置於 2 cm^2 紗布墊上塗抹於每個磨損及完好皮膚給藥部位，並用封閉膠帶固定 4 小時，貼片去除後根據 Draize 方法評估紅斑和水腫程度，所有測試的配方都被歸類為無刺激性。[1]
- 眼刺激性：將分離的牛角膜與 Mannitol 粉末(20%)或 imidazole(陽性對照)在 32°C 下培養 4 小時，以角膜的光透射測定不透明度，以分光光度計測量熒光素鈉穿過角膜的速率以測量滲透性。以不透明度和滲透性讀值得出綜合評分，低於 25 被認為是無刺激性的。結果 Mannitol 和 imidazole 的綜合得分分別為 0.2 和 142.4，所以 Mannitol 被認為非眼睛刺激物質。[1]
- 皮膚致敏性：以 Pirbright 白色天竺鼠進行 Magnusson-Kligman 天竺鼠最大化試驗，測試物質為由 15% Mannitol 和 15% disodium adenosine triphosphate 組成的商品，試驗物質的 0.5%水溶液稀釋液用於皮內誘導，試驗物質的 10%水溶液稀釋液用於表皮誘導和激發，在去除激發貼片後 24 小時和 48 小時後，沒有觀察到顯著免疫反應的刺激和皮膚反應跡象。[1]
- 致癌性：給 50 隻雄性和雌性 F344 大鼠組餵食含有 0、2.5 或 5%甘露醇 103 週(相當於 0、1250 或 2500 mg/kg bw/day)，實驗雄鼠與對照組相比體重相似而雌鼠則輕微低於對照組但不顯著，兩個劑量組的飼料消耗與對照組相似，沒有顯著對照組與實驗組之間的存

活率和腫瘤發生率的差異，測試物質被認為是非致癌物質。[1,2] 另一項研究 Wistar 通過飲食給予 10% Mannitol 持續 104 - 107 週。雌性的盆腔腎鈣質沉著症與盆腔增生有直接相關，但腫瘤發生率無顯著增加。[1]

- 致突變性/遺傳毒性：根據美國國家毒理學計劃 (NTP)進行的研究，Mannitol 在細菌回復突變試驗(鼠傷寒沙門氏菌 TA 98、TA 100、TA 1535 和 TA 1537；10 mg/plate)、小鼠淋巴瘤 TK+/-測試、或在中國倉鼠卵巢 (CHO) 細胞中的姐妹染色單體交換測定 (劑量未說明)中沒有致突變性。Mannitol 在使用鼠傷寒沙門氏菌 G46 和 TA1530 和釀酒酵母的宿主介導測定中是非致突變性的 D3 株，在大鼠骨髓或人 W1-38 細胞中的細胞發生試驗中，濃度為 2、20 和 200 µg/mL。在另一項研究中，甘露醇的致突變性(0.3 - 10,000 µg/plate) 在使用鼠傷寒沙門氏菌菌株 TA1535、TA1537、TA1538、TA98、TA 100 和大腸桿菌 WP2 (uvrA)進行的 Ames 試驗中進行了研究，有和無代謝活化，Mannitol 被認為是非致突變性的。[1]
- 生殖毒性：給懷孕的小鼠或大鼠口服 Mannitol1.6 g/kg/day 共 10 天，或倉鼠給予 1.2 g/kg/day 共 5 天，結果未觀察到母體或胎兒毒性症狀。[1]
- 光毒性：10 名志願者使用 15% Mannitol 和 15% disodium adenosine triphosphate 組成的商品進行光毒性研究。將商品 0.2 mL 10% 水溶液在封閉貼片下塗抹在兩個不同的區域前臂，一個照射另一則未照射，暴露 24 小時後用 UVA 光 (320 - 400 nm)照射一個部位 15 分鐘，在光照後立即以及 24 和 48 小時後對皮膚反應進行評分。在任何受試者的輻照或未輻照測試接觸部位均未發現反應。另一項以 34 名志願者進行的光敏感測試。三週內施用六個 24 小時誘導貼片，其中包含 2%的商品名混合物水溶液。隨後每個部位用紫外線(260 - 400 nm)照射 15 分鐘。2 週後在有和未照射的原始位置施用貼片。在照射或未照射部位均未出現皮膚反應。[1]
- 經皮吸收：以 Wistar-derived Alderley Park (AP)和 Sprague-Dawley (SD) 大鼠研究[^{14}C]-Mannitol 的皮膚滲透性，使用全皮膚和表皮膜。AP 大鼠全皮膜的總體平均滲透係數 (Kp)值為 3.23 (± 0.17) x 10^{-4} cm/h (n = 178)，SD 大鼠全皮膜為 2.89 (± 0.17)) x 10^{-4} cm/h (n = 150) 用於。而 AP 和 SD 大鼠的表皮膜平均 Kp 值分別為 2.30 (± 0.27) x 10^{-4} cm/h (n = 30)和 0.89 (± 0.15) x 10^{-4} cm/h (n = 22)。[1]

- 毒理代謝動力學：Mannitol 從人和動物的胃腸道吸收，預計不會蓄積。部分代謝後殘留物隨尿液排出。有證據顯示腸道菌群可以將 Mannitol 轉化為更容易利用的物質，這種轉化可能會影響肝臟吸收和代謝的甘露醇的實際量。10 名受試者禁食過夜，口服 28 至 100 g [U-^{14}C]- Mannitol 5% 水溶液。在此劑量範圍內，約 20%劑量以原形從尿中排出。在攝入後的前兩小時血液中的放射性增加，而放射性在 2 至 4 小時內保持穩定。攝入後 8 小時失效的 $^{14}CO_2$ 增加，口服 40 g 或更多劑量為會導致頻繁的排便、腹瀉和糞便排泄，佔劑量的百分比更高。攝入後 48 小時，尿液和糞便中僅出現極少量的放射性。[1]
- 人體數據：由 15% Mannitol 和 15% disodium adenosine triphosphate 組成的商品對 50 名志願者進行了人體重複斑貼試驗 (HRIPT)，將含 10% 商品之水稀釋液塗抹在受試者的背部，3 週內總共 9 次封閉測試程序，2 週的休息期後塗抹於先前未暴露的區域，在去除貼片後 24、48 和 96 小時觀察，結果在誘導或激發階段任何受試者均未發現皮膚反應。[1]
- 參考資料：

1. Safety Assessment of Mannitol, Sorbitol, and Xylitol as Used in Cosmetics. CIR Final Report, 12/10/2019.
2. World Health Organization (WHO). 616. Mannitol (WHO Food Additive Series 21). http://www.inchem.org/documents/jecfa/jecmono/v21je10.htm

10. INCI name：Ammonium Glycyrrhizate

- 急性毒性：Ammonium Glycyrrhizate(甘草酸銨)對小鼠的急性經口 LD_{50} 為 12.7 g/kg bw。甘草萃取物(53%甘草甜素，含甘草酸銨)的在雄性大鼠 LD_{50} 為 18 g/kg，雌性大鼠 LD_{50} 為 14.2 g/kg，而小鼠 LD_{50} 大於 7.5 g/kg。[1]
- 重複劑量毒性：0、18 或 90 mg/kg/day 的 Ammonium Glycyrrhizate 對雄性小鼠進行每週 6 天連續 16 週的口服管飼試驗(n = 10 隻小鼠)，所有小鼠都在給藥期間存活，並且沒有毒性的臨床跡象，施用組小鼠的體重增加與對照組小鼠相似，在屍檢檢查期間沒有明顯的觀察結果。[2] 一項為期 2 年的餵養研究在 Osborn-Mendel 大鼠 F0 代繁殖期間的粉狀飲食中添加 0%、0.5%、1.0%、2.0% 和 4.0% Ammonium Glycyrrhizate，F1 大鼠餵食與其各自父母組或對照飲食相同的劑量 102 週(n = 10 隻大鼠/組)。在本研究中餵養 Ammonium Glycyrrhizate 超過 2 年未產生任何損傷或解剖學改變。[2]
- 皮膚腐蝕性/刺激性：根據 OECD 439 及 GLP 研究的測試結果，Ammonium Glycyrrhizate 為非皮膚刺激物。[1]
- 眼刺激性：根據 OECD 492 及 GLP 研究的測試結果，Ammonium Glycyrrhizate 具眼刺激性，依 GHS 和 CLP 法規分類為第 2 類或第 1 類。[1]
- 皮膚致敏性：Glycyrrhizinate Monoammoniacal 分別根據 OECD 442C 和 442D 對進行 DPRA 測定和 Keratinsens 測定，兩種測試結果均為陰性。[1]
- 致癌性：無 Ammonium Glycyrrhizate 之研究數據。參考 Disodium Glycyrrhizinate(甘草酸二鈉) 於 B6C3F1 小鼠進行的致癌性研究，發現，濃度高達 0.15%(雄性)或 0.3%(雌性)的飲用水中給藥 96 週時，對任何腫瘤的發病率沒有影響。[2]
- 致突變性/遺傳毒性：甘草粉和 Ammonium Glycyrrhizate 在 TA97、TA98 和 TA100 沙門氏菌測試菌株中的濃度範圍為 0.01 至 0.5 mg/ml 時，無論是否有代謝活化，皆沒有遺傳毒性。[3]
- 生殖毒性： Mantovani 等人研究中懷孕大鼠在懷孕第 7-18 天以飲用水給予 Ammonium Glycyrrhizate，濃度為 0、100、1000 和 2500 mg/l (相當於 0、21、239 和 680 mg/kg bw/day)。在第 20 天分析血液、收集母體腎上腺用於組織學檢查、檢查子宮的胚胎和胎兒毒性

跡象，並研究後代的外部、骨骼和內臟畸形，除在高劑量下總骨骼變異在統計學上顯著增加外沒有觀察到顯著影響；組織檢查顯示低劑量組和高劑量組的異位腎臟發生率較高，而低劑量組其他腎臟變異發生率降低。作者指出骨骼變異應為可逆效應而異位腎是主觀的，根據此研究數據顯示 NOAEL 為 239 mg/kg bw/day。[3]

- 光毒性：在人體斑貼試驗中評估了 Glycyrrhizic Acid、Ammonium Glycyrrhizate 和 Disodium Glycyrrhizinate，將 5%測試物質施用於 21 名女性志願者的前臂 48 小時，觀察部位是否有刺激或炎症跡象，48 小時後將劑量部位暴露於 Dermaray Model 1(BLB; 15 cm, 3 min)的照射，並在 48 小時後再次評估。結果無論照射之前後，沒有任何暴露部位出現可觀察到的刺激反應。[2]
- 經皮吸收：無相關研究數據。
- 毒理代謝動力學：無 Ammonium Glycyrrhizate 之研究數據。甘草酸(Glycyrrhizinic Acid, GZ)在人類、大鼠、米格魯犬和天竺鼠的胃腸道中不易被吸收，在胃腸道被腸道細菌水解為甘草次酸(Glycyrrhetic Acid,GA)，而 Glycyrrhetic Acid 在腸道中被廣泛吸收，並且大部分在肝臟中被葡醣醛酸化為 3-單葡醣醛酸甘草次酸 (3-mono-glucuronyl-glycyrrhetinic acid, 3-MGA)，但被硫酸化的程度很小。在天竺鼠中，給予 Glycyrrhizinic Acid 100 mg/kg/day，連續 5 天會導致血漿中 3-MGA 的積累，但不會導致 GA 的累積。3-MGA 於膽汁排泄後在腸道菌群進一步水解導致 GA 的再次吸收。大鼠中 GA 與血清蛋白廣泛結合，並且其很少在組織中沉積，GA 主要通過糞便排泄掉，只有一小部分通過尿液排出。[4]
- 其他安全資料：Ammonium Glycyrrhizate 被 GRAS 認為是安全的且受到生命科學研究辦公室的審查支持(LSRO 1974)。[2]
- 參考資料：

1. Registration Dossier. ECHA 網站: https://echa.europa.eu/nl/registration-dossier/-/registered-dossier/23874/7/3/1
2. Final Report on the Safety Assessment of Glycyrrhetinic Acid, Potassium Glycyrrhetinate, Disodium Succinoyl Glycyrrhetinate, Glyceryl Glycyrrhetinate, Glycyrrhetinyl Stearate, Stearyl Glycyrrhetinate, Glycyrrhizic Acid,Ammonium Glycyrrhizate, Dipotassium Glycyrrhizate,Disodium Glycyrrhizate, Trisodium Glycyrrhizate, Methyl Glycyrrhizate, and Potassium Glycyrrhizinate.

IJT 26(Suppl. 2):79-112, 2007.

3. Opinion of the Scientific Committee on Food on Glycyrrhizinic Acid and its Ammonium Salt. SCF/CS/ADD/EDUL/225 Final 10 April 2003.
4. Scientific Opinion on the safety and efficacy of glycyrrhizic acid ammoniated (chemical group 30, miscellaneous substances) when used as a flavouring for all animal species. EFSA Journal 2015;13(1):3971.

11. INCI name：Butylene Glycol

- 急性毒性：基於幾個物種的口服 LD_{50} 值> 10000 mg/kg bw，且大鼠在飽和蒸氣濃度下暴露 8 小時沒有致死效應，皮膚 LD_{50} >20000 mg/kg bw 以及腸胃外施用後的低毒性，認為丁二醇(Butylene Glycol)的急性毒性低。[1] 丁二醇的急性口服 LD_{50} 在大鼠中為 23 g/kg bw，在天竺鼠中為 11 g/kg bw。含有 5.0%丁二醇的指甲油在大鼠體內的 LD_{50} 大於 5 g/kg，而含有 21.35%丁二醇的產品在以 15 g/kg bw 的劑量餵食大鼠時，不會導致死亡。[2]
- 重複劑量毒性：在一項為期 2 年的大鼠餵養研究(高達 5000 mg/kg bw/day)和對狗進行的餵養研究(攝入劑量最高為 750 mg/kg bw/day)。這兩項研究中，即使是最高劑量，也沒有觀察到與丁二醇相關的影響。在另一項狗的亞慢性 13 週餵養研究中，兩個丁二醇最高劑量組(9000 和 12000 mg/kg bw/day)的狗表現出毒性作用，例如行為變化(癲癇樣發作)、血液學、血液生化、器官重量和生長速度發生變化。但在 6000 mg/kg bw/day 時沒有發生與試驗物質相關的影響，推估 NOAEL 為 6000 mg/kg bw/day，LOAEL 為 9000 mg/kg bw/day。[1]
- 皮膚腐蝕性/刺激性：將含有 3%丁二醇的產品配方以 500 mg/kg bw/day 的劑量施用到 8 隻白化兔子剪毛後完整與磨損的皮膚上，持續 4 週。8 隻兔子的對照組保持未進行任何處理。所有動物都在研究期間存活，與丁二醇相關的重要性的臨床觀察僅限於皮膚，兔子皮膚有輕微的紅斑，乾燥和剝落。透過顯微鏡組織檢查證明沒有全身效應可歸因於丁二醇。當在兔子皮膚上封閉貼片 24 小時或每天連續 4 天進行測試時，未稀釋的丁二醇基本上不會產生皮膚刺激性。[2]
- 皮膚致敏性：丁二醇在 200 名受試者的其中 2 名產生了輕微的皮膚老化，但沒有皮膚致敏的證據。許多含有濃度高達 21.4%的乙二醇產品配方已在各種人體皮膚刺激和致敏試驗中進行了測試。產生的刺激程度取決於特定的劑型。刺激程度與製劑中存在的乙二醇濃度之間沒有相關性。在皮膚致敏試驗的 1087 名受試者中，沒有任何反應顯示皮膚對乙二醇致敏現象。在對產品配方進行的一些皮膚致敏試驗中，補充暴露於紫外線下沒有產生顯示有光毒性或光敏性的反應。[2]

- 生殖毒性：在一項採用嵌入式連續育種五代研究中，在 1~4 代中未觀察到對生育力的影響，直至第五代測試的最高濃度(飲食中的 24%；12000 mg/kg bw/day 丁二醇)，發現 F1A 大鼠的妊娠率在連續 5 個交配週期中下降。在丁二醇存在下未觀察到致畸作用。[1]
- 光毒性：在對產品配方進行的一些皮膚致敏試驗中，暴露於紫外線下沒有產生光毒性或光敏性的反應。[2]
- 其他安全資料：丁二醇和相關成分的安全性已經過化粧品成分審查(CIR)專家小組的評估。CIR 專家小組審查了科學數據並得出結論，丁二醇、己二醇(Hexylene Glycol)、乙氧基二甘醇(Ethoxydiglycol)和二丙二醇(Dipropylene Glycol)可安全用於化粧品和個人護理產品。2004 年，CIR 專家小組審議了有關丁二醇及相關成分的現有新數據，並重申了上述結論。CIR 專家小組指出，丁二醇可以被代謝並用作卡路里的來源。急性、亞慢性和慢性口服毒性研究的結果顯示這些乙二醇類物質(Glycol)的毒性較低。腸胃外注射、吸入以及急性和亞慢性皮膚毒性研究的結果同樣支持低毒性。丁二醇引起輕微至輕微的皮膚刺激，但沒有致敏跡象。在任何皮膚致敏試驗中，無顯示皮膚對這些乙二醇類物質有致敏現象，也沒有光毒性或光敏作用的跡象。[2]
- 參考資料：

1. ECHA 註冊檔案網站：https://echa.europa.eu/registration-dossier/-/registered-dossier/14962/7/1
2. Final Report on the Safety Assessment of Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol. CIR, 1985.

12. INCI name：Disodium EDTA

- 不純物：預計無重大雜質，但應監測重金屬。CIR 指出化粧品使用的 Disodium EDTA，重金屬含量一般應低於 10 ppm，甲醛含量低於 100 ppm。[1]
- 急性毒性：大鼠急性口服毒性 LD_{50} 為 2800 mg/kg bw，急性吸入毒性 LOAEL 為 30 mg/m³ air。[2]
- 腐蝕性和刺激性：對皮膚沒有刺激性，對眼睛沒有刺激性。[1]
- 皮膚致敏性：無相關研究數據。參考 Na_3EDTA 類似化合物不具致敏性。[1]
- 重複給藥毒性：在一項為期兩年的研究中，33 隻大鼠分 5 組給予了 0、0.5、1 和 5% Disodium EDTA。5%實驗組比其他組的大鼠表現出腹瀉和少食，沒有觀察到對體重增加的顯著影響，凝血時間、紅細胞計數或骨頭也沒有受到不利影響。動物的死亡率與 Disodium EDTA 量無關。死亡率最高的是對照組。各種器官的肉眼和顯微鏡檢查顯示兩組之間無顯著差異。[3] 在一項為期 13 週的重複給藥毒性研究中，餵食 Disodium EDTA (0%、1%、5%、10%) 的大鼠在最高劑量下顯示出死亡率，此外，在 5% (約 4206 mg/kg bw/day)及以上的劑量下，食物消耗減少(消瘦 10%)和腹瀉。Disodium EDTA NOAEL 為 1% (約 692 mg/kg bw/day)。[5]
- 致突變性/遺傳毒性：高劑量的體外和體內研究具弱致突變性，可能是由於次要機制[1]，測試顯示 Disodium EDTA 不具致突變性。[4]
- 致癌性：無相關研究數據。參考 Na_3EDTA 類似化合物以 7500 ppm 劑量餵食大鼠及小鼠達 103 週，結果無致癌性。[1]
- 生殖毒性：口服 EDTA 劑量高於 1000 mg/kg bw/day 可能導致鋅耗盡，使試驗動物產生生殖/發育毒性[1]。EDTA 使用濃度低和皮膚吸收差，皮膚給藥後不太可能產生生殖毒性。[4]
- 毒理代謝動力學：不太可能通過皮膚吸收，但可以用作滲透促進劑。[1] 口服的吸收率差，低於 20%劑量被胃腸吸收，吸收的物質隨著尿液迅速排出體外。[4]
- 光毒性：無相關研究數據。[1]
- 人體數據：四個正常血鈣受試者在 4 小時內靜脈滴注 4 g Sodium EDTA 或 Calcium EDTA，導致更多的鈣排泄率分別為 75%~88%和 57%~70%。服用 Sodium EDTA 4 小時內，約有 60%~80%的過量鈣排

泄出。當給三個人服用放射性劑量(未指定劑量)的 Calcium EDTA 時，24 小時之內就會排泄 100%。而口服的 Sodium EDTA 及 Calcium EDTA(6 g/day，共 6 天)在人體的胃腸道中吸收差。[1]

◆ 其他安全資料：CIR 專家小組評估科學數據並得出結論，Sodium EDTA 和相關成分用於化粧品和個人護理產品是安全的。化粧品和個人護理產品中使用濃度下的 EDTA 和相關成分不是皮膚刺激物或致敏劑。研究顯示，這些成分不是致癌物質。由於這些成分結合正常細胞分裂所需的金屬，一些研究顯示這些化合物具有弱致突變性。另研究資料顯示，口服暴露於大劑量金屬螯合劑後會對生殖和發育產生影響，這可能是正常生殖和發育所需的金屬結合的影響。CIR 專家小組審查了 EDTA 和相關成分，發現其不易透過皮膚吸收。因此，通過使用含有這些成分的化粧品和個人護理產品，皮膚接觸 EDTA 或 HEDTA 會導致非常少的皮膚滲透和全身暴露量，遠低於口服研究中顯示的產生不良影響的劑量。[6]

◆ 參考資料：

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

https://cosmeticsinfo.org/ingredient/disodium-edta

13. INCI name：Alpinia Galanga Extract

- 急性毒性：在小鼠中進行 Alpinia Galanga(高良薑)根乙醇萃取物的急性(24 小時)和慢性(90 天)口服毒性研究，急性劑量為 0.5、1.0 和 3 g/kg bw 而慢性劑量為 100 mg/kg/day，在研究期間與對照組相比沒有觀察到顯著的死亡率，實驗動物的體重增加與對照組一樣顯著，血液學研究顯示與對照組相比，實驗動物的紅血球顯著上升，雄性小鼠觀察到性器官重量的增加以及精子活力和精子數量的增加，未顯示出任何精子毒性作用。另一根據 OECD 進行 Alpinia Galanga 甲醇萃取物的 Wister 大鼠急性口服毒性研究測試劑量 2000-5000 mg/kg，即使在最高劑量測試下也沒有死亡，LD_{50} 估計超過 5000 mg/kg。[1]
- 重複劑量毒性：根據 OECD 408 進行 Sprague Dawley 大鼠的 90 天口服毒性試驗，給予劑量為 0、1000、2000 和 3000 mg/kg。試驗結果 NOAEL 為 3000 mg/kg/day。[2]
- 皮膚腐蝕性/刺激性：根據 OECD 404 以紐西蘭白兔進行 Alpinia Galang 根莖己烷萃取物，結果顯示未稀釋的萃取物對白兔未磨損皮膚的刺激性可忽略不計，主要刺激指數為 0.25，而對磨損皮膚則表現出刺激性。[3]
- 眼刺激性：以 HET-CAM 測試 Alpinia Galanga 根莖己烷萃取物之眼刺激性，結果濃度<20 mg/ml 的萃取物對 HET-CAM 無刺激性。[3]
- 皮膚致敏性：Alpinia galangal 可治療過敏，萃取的分離化合物可抑制小鼠被動皮膚致敏反應介導的抗 IgE 的釋放。[1]
- 致癌性：高良薑根莖中的 1,7-雙 (4-羥基苯基)-1,4,6-庚三烯-3-酮(BHPHTO)和雙去甲氧基薑黃(BDMC)以人類黑色素 A2058 進行細胞生長試驗中，顯示具有抑制黑色素瘤細胞增殖的活性。[1]
- 致突變性/遺傳毒性：Alpinia Galanga 甲醇萃取物以雄性小鼠進行微核試驗，口服給予萃取物劑量 300 和 600 mg/kg bw，口服 50 mg/kg bw 的 Na-CMC 作為陰性對照，腹腔注射 50 mg/kg bw 環磷酰胺(cyclophosphamide)作為陽性對照。結果 Alpinia Galanga 甲醇萃取物具有抗誘變活性。[4]
- 其他安全資料：Galanga 的根莖、萃取油和油樹脂被 GRAS 認為是安全的且受到生命科學研究辦公室的審查支持。[1]

◆ 參考資料：

1. A Review on Phytopharmacological Activity of Alpinia Galanga. Int J Pharm Pharm Sci ; 2019 Mar; 11(3): 6-11.
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4. Antimutagenic activity of methanol extracts of galangal rhizome (Alpinia galanga) on erytrocyte cell in mice bone marrow in vivo. Bioteknologi 11 (2): 36-43, November 2014.

14. INCI name：Caffeine

- 急性毒性：關於急性皮膚毒性，將溶於橄欖油中的咖啡因和茶鹼(Theophylline)在半封閉貼劑下施於大鼠 24 小時，兩種測試物質 LD_{50} > 2000 mg/kg bw。關於咖啡因的急性口服毒性研究，小鼠和大鼠發表最低的 LD_{50} 分別 127 mg/kg bw 和 192 mg/kg bw，豚鼠和倉鼠的 LD_{50} 為 230 mg/kg bw，兔子的 LD_{50} 為 224 mg/kg bw，狗的 LD_{50} 為 240 mg/kg bw。關於急性吸入毒性，將咖啡因與 2%的疏水性氣相二氧化矽混合於大鼠進行測試，結果 LC_{50} 為 4.94 mg/L。[1]
- 重複劑量毒性：在為期 90 天的研究，小鼠和大鼠在飲用水中加入咖啡因，雄性和雌性小鼠的 NOAEL 分別為 167 和 179 mg/kg bw/day，而雄性和雌性大鼠的 NOAEL 分別為 151 和 174 mg/kg bw/day。[2]
- 皮膚腐蝕性/刺激性：將 500 mg 含有 50%咖啡因的測試物質以半封閉貼劑的形式塗抹在三隻維也納白兔的皮膚上 4 小時，主要刺激指數為 0。[1]
- 眼刺激性：將 0.1 mL 未稀釋的咖啡因滴入三隻兔子的眼睛，平均刺激指數為 0.9 (角膜混濁)、0(虹膜炎)、1.6(結膜紅斑)和 0.6(結膜水腫)。在前 24 小時內所有三隻兔子都觀察到些微刺激反應，到 8 天只有一隻表現出微小的角膜和結膜刺激，測試物質被認為是無刺激性。[1]
- 皮膚致敏性：根據 OECD429 進行局部淋巴結試驗(LLNA)，濃度 0、0.5、2 和 5%的咖啡因以乙醇：水(70:30)作為載體，沒有觀察到不良反應。[1]
- 致癌性：在一項致癌性研究，雄性和雌性 Sprague-Dawley 大鼠在飲水中以 0、200、430、930、2000 ppm 的劑量給予食品級咖啡因(純度未知)104 週，與對照組相比腫瘤發病率未增加。在 Sprague-Dawley 大鼠中，接觸咖啡因 2 年並沒有增強或誘導腫瘤形成。[2]
- 致突變性/遺傳毒性：關於咖啡因的遺傳毒性，大多數細菌體外試驗產生陽性結果，但大多數哺乳動物細胞體外遺傳毒性試驗產生陰性結果。細菌研究在沒有代謝活化的情況下大多為陽性而在代謝活化情況下大多是陰性的，而體內基因毒性試驗則主要為陰性結果。IARC 得出結論，咖啡因對實驗動物和人類的致癌性證據不足，國際癌症研究中心(International Agency for Research on Cancer, IARC) 總體評估後認為咖啡因對人類致癌性不能分類。[1]

- 生殖毒性：大鼠已進行多項生殖毒性研究，一項研究在 61 隻 Osborne-Mendel 大鼠妊娠第 0 至 19 天管飼攝入高達 125 mg/kg 的咖啡因，6/61 的雌鼠在最高劑量下死亡，在 80 mg/kg 劑量下 2 胎被再吸收，在 125 mg/kg 劑量下 4 胎被再吸收。另在一項 61 隻雌性大鼠的不同研究中，在 1500 和 2000 ppm 的濃度下也發現了胎兒再吸收，這些大鼠在妊娠第 0-2 天在飲用水中給予咖啡因。在這些劑量下也注意到胚胎植入效率降低和存活胎兒數量減少。發育和生殖研究的陽性結果，但考慮到這些影響僅在遠遠超過報告的化粧品使用濃度的致死濃度下可見，因此被認為可以忽略。[1]
- 光毒性：無相關研究數據。
- 經皮吸收：大鼠皮膚的最大吸收率(6.82 μg/cm²/h)明顯高於人類皮膚的平均值(2.24 ± 1.43 μg/cm²/h)，24 小時後受體液中的量分別為人體和大鼠皮膚所用劑量的 24.5 ± 11.6% 和 53.7%。大鼠皮膚的總滲透(劑量百分比)為 61.3±4.0 %也高於人體皮膚的平均值 26.75± 10.9 %，皮膚厚度僅輕微影響咖啡因的吸收。總結人體皮膚的總吸收量約為 25%。[2]
- 毒理代謝動力學：咖啡因很容易通過細胞膜吸收，口服後，咖啡因在人體中的典型半衰期為 2.5 - 4.5 小時，但在妊娠晚期和服用口服避孕藥的女半衰期會延長。咖啡因廣泛分佈於全身組織，並僅通過肝酶系統被代謝。70 - 80%咖啡通過肝臟 CYP1A 酶進行的 3-N-去甲基化代謝為副黃嘌呤(paraxanthine)，大約 7 - 8%的咖啡因通過 1-N-去甲基化代謝為可可鹼(Theobromine)，而 7-N-去甲基化為茶鹼(Theophylline)也約佔咖啡因代謝產物的 7 - 8%，剩餘的咖啡因通過 C-8 羥基化代謝，導致形成 1,3,7-三甲基尿酸。在肝臟之其他器官中沒有發生明顯的咖啡因代謝。大部分咖啡因通過尿液排出(人體> 95%)。[1]
- 人體數據：對 105 名受測者進行人體重複斑貼測試(HRIPT)， 將 20 μL 含 6%咖啡因的產品以封閉方式施用於受測者背部，在誘導階段的 3 週內施用程序 9 次。在 2 週的休息後將測試物質施用於原始測試部位和先前未處理的測試部位，結果在誘導或激發階段未發現致敏反應。[1]
- 參考資料：

1. Safety Assessment of Methylxanthines as Used in Cosmetics. CIR Final Report 12/04/2018.
2. Registration Dossier. ECHA 網站:

https://echa.europa.eu/de/registration-dossier/-/registered-dossier/10085/7/1

15. INCI name：Zinc Gluconate

- 急性毒性：以 WISW 品系大鼠研究葡萄糖酸鋅(Zinc Gluconate)的急性經口毒性，結果在測試劑量測試物質沒有引起任何臨床毒理學症狀，經口 LD_{50} 為> 5g/kg。在 Sprague-Dawley 雌性大鼠中進行氯化鋅(zinc chloride)的急性吸入毒性研究，動物暴露於濃度 600、940、1220 和 1950 mg Zn/m^3(Zn: $ZnCl_2$ 的摩爾比 1:2.1)的測試物質 10 分鐘，動物表現出呼吸窘迫，肺部臨床檢查顯示變化、不同程度的充血、斑片狀變色、水腫和間質性肺氣腫、肺不擴張、充血和出血。根據結果，大鼠急性吸入 zinc chloride 的 LD_{50} 約為 2000 mg $ZnCl_2$/m^3；將 $ZnCl_2$ 的 LC_{50} 交叉參照至 Zinc Gluconate，$ZnCl_2$ 分子量為 136.296 而 Zinc Gluconate 分子量為 455.682。因此推得 Zinc Gluconate 的 LD_{50} 為 6686.65 mg ZnGlc /m^3。[1]
- 重複劑量毒性：大鼠和小鼠(雄性和雌性)在 90 天亞慢性口服毒性研究中觀察到 NOAEL 為 234 mg/kg/day。[1]
- 皮膚腐蝕性/刺激性：以兔子研究葡萄糖酸鋅顆粒的原發性皮膚刺激程度，測試物質暴露時間 4 小時後，在 72 小時的觀察期間記錄任何紅斑、焦痂和水腫形成的跡象，在貼片去除後 24h、48h 和 72h 判讀皮膚改變情況，在 72 小時的觀察期內，樣品沒有引起任何皮膚刺激，主要刺激指數為 0.0，所有動物都表現出正常的食物消耗和正常的體重增加，測試物質被認為在所述條件下沒有刺激性。[1]
- 眼刺激性：以紐西蘭白兔進行的體內眼睛刺激試驗。在施用後 1、2、8 小時和 1、2、3、4、5、6 和 7 天對眼睛進行評分，沒有觀察到角膜混濁，最大虹膜評分為 1，最大結膜評分為 3，最大結膜水腫評分為 3，觀察到的所有影響都是完全可逆的(最多在四天內)，測試結果被認為具有輕微刺激性。以紐西蘭白兔進行的第二次體內研究，測試的物質被認為對眼睛有刺激性並有嚴重損傷的風險，考慮到在研究期間觀察到的不可逆影響，該物質應根據 GHS 標準被視為第 1 類。[1]
- 皮膚致敏性：無 Zinc Gluconate 數據。交叉參照硫酸鋅 ($ZnSO_4.7H_2O$) 的致敏性研究，根據指令 96/54/EC B.6 和 OECD 406 進行在雌性 Dunkin Hartley 天竺鼠進行的最大化測試。實驗結果得出結論硫酸鋅不會引起實驗動物的致敏反應。[1]
- 致癌性：無 Zinc Gluconate 數據。交叉參照硫酸鋅於 Chester Beatty

小鼠在其飲用水添加硫酸鋅(七水合物；1000 ppm 和 5000 ppm，或游離鋅分別為 227 ppm 和 1135 ppm)，持續 45~53 週，有對照組但部分因病毒感染死亡而更換其他對照動物(未有進一步細節)。結果任何腫瘤發生率都沒有增加。[2]

- 致突變性/遺傳毒性：無 Zinc Gluconate 相關研究數據。交叉參照氯化鋅(Zinc chloride) 以小鼠淋巴瘤 5L5178Y 細胞株進行的研究，細胞以測試物質濃度 1.21 - 12.13 µg/mL 處理 3 小時，48 小時後用 4 µg/mL 三氟胸苷 (TFT)處理細胞 7 天，計數在三氟胸苷(TFT 抗性)存在下生長的菌落，TFT 抗性菌落被記為突變體。測試結果在測試條件下是非致突變性的。[1]
- 生殖毒性：無 Zinc Gluconate 相關研究數據。交叉參照氯化鋅(Zinc Chloride)在大鼠中進行的兩代生殖毒性研究，對成年雄性和雌性大鼠在成熟、交配、妊娠和早期泌乳期間給予試驗物質 30 和 15 mg/kg/day 會對成年和後代產生顯著影響(一般毒性)，儘管在 7.5 mg/kg/day 時觀察到影響但被認為在毒理學上不顯著，因此被認為是 NOAEL，考慮到可能的生殖影響，NOAEL 訂為 15 mg $ZnCl_2$/kg bw/day，此相當於 50.15 mg ZnGlc/kg bw/day (對於葡萄糖酸鋅)。僅在引起顯著全身毒性的劑量觀察到對生殖性能的可能不良影響。[1]
- 光毒性：無相關研究數據。
- 經皮吸收：無 Zinc Gluconate 數據。交叉參照硫酸鋅(Zinc Sulfate)的體外研究，將硫酸鋅塗在豬皮膚上 8 小時而未封閉，鋅的吸收可能達到 1.6%，因為保留在皮膚中的量應該被視為被吸收，受體液中回收 0.3%的鋅，角質層中回收 1.3%的鋅。餵食缺鋅飲食的懷孕 Sprague-Dawley 大鼠局部施用飽和氯化鋅油 24 小時將導致血漿接近或高於餵食足夠鋅飲食的大鼠的血漿鋅量。在天竺鼠中< 1%到 3.9% 的 0.005 - 45.87M [^{65}Zn]-氯化鋅在 5 小時內被吸收。在兔子中，標記的硫酸鋅和十一烯酸鋅的施用顯示[^{65}Zn]在皮膚中吸收的主要方式是通過毛囊擴散，施用不同化合物的皮膚中[^{65}Zn]的量或位置沒有顯著差異。[2]
- 毒理代謝動力學：在皮膚研究中，各種氯化鋅溶液中[^{65}Zn]滲透到大鼠完整皮膚中，導致[^{65}Zn]在血液和其他組織中迅速出現，血清中的最大量[^{65}Zn]是在施用後的第一小時內或前後，並且幾乎完全與施用的鋅濃度 pH 值無關。在口服研究中，隨著醋酸鋅(Zinc Acetate)劑量的增加，狗的血漿、尿液和血液中的鋅水平會增加。飲食中給

予碳酸鋅(Zinc Carbonate)的 Sprague-Dawley 大鼠，研究者認為鋅的吸收能力是具適應性的，就是在鋅缺乏或輕微缺乏的個體中鋅的吸收會更大。餵食放射性標記的碳酸鋅(Zinc Carbonate)、氯化鋅(Zinc Chloride)和氫氧化氯化鋅(Zinc Chloride Hydroxide)的大鼠中，三種物質的 [^{65}Zn]吸收百分比相似，範圍為 40-48%。大鼠單次口服氯化鋅(Zinc Chloride)後，鋅對不同器官的影響，確定鋅主要在小腸、肝臟、腎臟和大腸中積累。[2]

- 人體數據：一項臨床試驗中，11 位受試者將含 0.05% Zinc Gluconate 臉頸霜以封閉貼片單次施用 25 µl 於肩胛背部 48 小時，貼片去除後 30 分鐘和 24 小時檢查皮膚，結果不具刺激性。[2]
- 其他安全資料：鋅鹽成分中的幾種如氯化鋅(Zinc Chloride)、葡萄糖酸鋅(Zinc Gluconate)、硬脂酸鋅(Zinc Stearate)和硫酸鋅(Zinc Sulfate)，當符合優良製造規範作為人類食用營養素時通常被認為是安全的(GRAS)(21CFR182.8985、21CFR182.8988、21CFR182.8994, 21CFR182.8997)，預計該食品使用的每日暴露量會導致比化粧品使用產生的全身劑量大得多。對於 GRAS 成分，CIR 報告主要為局部影響(皮膚暴露、刺激和致敏)而非口服毒性和生物利用度。[2]
- 參考資料：

1. Registration Dossier. ECHA 網站: https://echa.europa.eu/de/registration-dossier/-/registered-dossier/24253/7/1
2. Safety Assessment of Zinc Salts as Used in Cosmetics. CIR Final Report 03/06/2018.

16. INCI name：Aesculus Hippocastanum (Horse Chestnut) Seed Extract

- 急性毒性：七葉樹種子萃取物(horse-chestnut seed extract, HCSE)在小鼠、大鼠、天竺鼠和兔子進行的單劑量毒性研究(商品 Venostatin delay ®製劑，標準為 240-290 mg 萃取物中含 50 mg 七葉皂苷)發現靜脈內和腹腔內給藥時的毒性(LD_{50} 6.8–465 mg/kg bw)大於口服給藥(LD_{50}910–2600 mg/kg bw)，實驗動物靜脈內和腹腔內施用七葉皂苷後，LD_{50} 為 3 至 17 mg/kg bw。[1]
- 重複劑量毒性：HCSE 的慢性經口毒性研究在狗(20、40、80 mg/kg bw；5 天/週/3 個月)和大鼠(100、200、400 mg/kg bw；5 天/週/ 3 個月)的結果證明施用萃取物沒有毒性。亞急性靜脈毒性研究中，HCSE 以 9、30、90 mg/kg/day 的劑量給予大鼠 60 天，研究第一天 90 mg/kg/day 劑量就導致 30 隻動物中有 8 隻死亡，而 30 和 9 mg/kg/day 劑量不會導致任何明顯的疾病並且對動物是安全的。[2]
- 致突變性/遺傳毒性：以鼠傷寒沙門氏菌 TA 98 菌株進行的 Ames 試驗中測試商業乾萃取物和七葉樹種子萃取液結果具弱基因毒性活性。[1]
- 生殖毒性：HCSE 在大鼠和兔子(100 和 300mg/kg bw)的研究顯示沒有致畸作用，僅在高劑量觀察到胎兒平均體重下降。[1]
- 毒理代謝動力學：已發表部分關於七葉皂苷(aescin)的藥代動力學和藥物利用度的文獻，比較七葉皂苷(50 mg 於 240-290 mg 的 HCSE 中)在口服給藥後緩釋製劑及其他藥物製劑中的生物利用度。在單劑量實驗中 C max 為 3.2–9.8 ng/ml，而在重複劑量實驗中 C max 為 6.5–16.7 ng/ml。此外，口服七葉皂苷溶液後絕對生物利用度僅 1.5%，可能是由於首渡效應(代謝和膽汁排泄)。七葉皂苷在靜脈內給藥後的藥代動力學與開放式三室模型相對應，5 mg 七葉皂苷(輸注速率：718 μg/min)的消除半衰期為 $t_{0.5}\alpha$ – 6.6 min、$t_{0.5}\beta$ – 1.74h 和 $t_{0.5}\gamma$ – 14.36h。此外，分佈容積為 100.91，與血漿蛋白的結合率為 84%，總血漿和腎臟清除率分別為 21.8 ml/min 和 1.7 ml/min，給藥 120 小時後七葉皂苷從尿中排出。[1]
- 其他安全資料：七葉樹種子(Aesculus hippocastanum L.，無患子科)中萃取的七葉皂苷含量標準化，用於治療慢性靜脈功能不全，具有抗炎和抗水腫特性，對靜脈張力、流變特性和血液凝固性有正面作

用，在體外和體內研究已有七葉樹籽萃取物和七葉皂苷活性的機制，也有大量隨機臨床試驗證明其有效性。[1]

◆ 參考資料：

1. Horse chestnut – efficacy and safety in chronic venous insufficiency: an overview. Revista Brasileira de Farmacognosia 25 (2015) 533–541.

17. INCI name：Sodium Hyaluronate

- 急性毒性：透明質酸(Hyaluronic Acid) 的急性經口毒性試驗中，給予 ICR 小鼠> 1200 mg/kg 未觀察到死亡。透明質酸鈉(Sodium Hyaluronate)對小鼠(高達 15,000 mg/kg bw)和大鼠(高達 5280 mg/kg bw)進行的急性經口毒性試驗，在任何這些試驗中均未報告毒性或死亡跡象。[1]
- 重複劑量毒性：一項 30 天試驗中 Wistar 大鼠(10 隻/性別/組)通過飼料給予高達 1500 mg/kg bw 的透明質酸鈉，一項 90 天試驗中 Sprague-Dawley 大鼠(5~ 10 隻/性別/組)通過管飼法給予 48 mg/kg bw/d 的 1%透明質酸鈉滴眼液。一項 90 天試驗中 Wistar 大鼠(10 隻/性別/組)通過飼料給予高達 1000 mg/kg bw/d 的透明質酸鈉，透明質酸鈉的短期和亞慢性口服毒性試驗中均未觀察到毒性跡象。[2]
- 皮膚腐蝕性/刺激性：以日本兔和天竺鼠進行的單次刺激皮膚試驗中，透明質酸沒有刺激性。對 9 名受試者進行了皮膚點刺試驗，用透明質酸鈉 (10 mg/ml) 對每個受試者的前臂進行穿刺，並在穿刺後 15 分鐘、2、6 和 24 小時進行評估，未觀察到皮膚反應。[1]
- 皮膚致敏性：無相關研究數據。
- 致癌性：無相關研究數據。
- 致突變性/遺傳毒性：當以高達 5 mg 的劑量進行 Ames 突變測試時，無論是否有代謝活化(鼠傷寒沙門氏菌鏈 TA97a、TA98、TA100、TA102 和 TA1535 中進行試驗)，透明質酸鈉被確定為無遺傳毒性。此外，在使用 KS 小鼠(5 隻/性別/組)的小鼠微核試驗中，透明質酸鈉(高達 5000 mg/kg bw)是非致突變性的。[1]
- 生殖毒性：在大鼠和兔身上進行幾項關於皮下注射透明質酸(高達 60 mg/kg/d)和透明質酸鈉(高達 50 mg/kg/d)的生殖和發育研究，測試物質對死亡率、分娩後的屍檢觀察、食物或水的消耗或親代的生育力沒有影響。然而在一項試驗中，大鼠通過皮下注射給予高達 60 mg/kg bw 的 1%透明質酸生理鹽水溶液，在處理動物的腎上腺中出現網狀帶細胞的結節性增生，在大鼠或兔中未觀察到嚴重的胎兒異常。[1]
- 經皮吸收：無 Sodium Hyaluronatevu 相關研究數據。交叉參照透明質酸在 SKh/1 無毛小鼠進行的皮膚滲透試驗，每 12 小時施用一次共 3 或 12 次，最後一次施用後 12 至 16 小時檢查動物，放射

性主要存在於真皮中，從最外層到淋巴管和血管。以 Sprague-Dawley 大鼠進行的皮膚滲透試驗中，每天兩次皮膚應用透明質酸(分子量 1350 – 4500 Da)持續 5 天，透明質酸滲透到表皮下方最大深度 136 µm。另一項將放射性標記透明質酸放置於 Sprague-Dawley 大鼠背部，在 4 小時的吸收期後發現測試物質穿透大鼠皮膚的最大深度約為 800 µm。[1]

- 毒理代謝動力學：無 Sodium Hyaluronate 相關研究數據。交叉參照透明質酸的吸收測定，雄性 Sprague-Dawley 大鼠(n = 3)通過管飼法給予 25 mg/kg [^{14}C]透明質酸 (MW = 920,000 Da) ，峰值血漿放射性為 7.6 µg eq/ml 8 h 給藥後，給藥後 8 小時在腸內容物中觀察到最高量的放射性，到給藥 168 小時後，尿液、糞便和呼出氣中的總排泄率為給藥劑量的 91.3%。[1]
- 參考資料：

1. Safety Assessment of Hyaluronates as Used in Cosmetics. CIR Scientific Literature Review for Public Comment. 10/05/2022.
2. Final Report of the Safety Assessment of Hyaluronic Acid, Potassium Hyaluronate, and Sodium Hyaluronate .IJT 28(Suppl. 1):5-67, 2009.
3. Bloomage Biotechnology Corp Ltd. Conclusion of GRAS Status of Sodium Hyaluronate. GRAS Associates, LLC;2020. https://www.fda.gov/media/152869/download

18. INCI name：Xanthan Gum

- 急性毒性：Xanthan Gum 的急性口服毒性研究在小鼠、大鼠和狗沒有觀察到明顯的毒性，LD_{50} 依序為>1 g/kg、>5 g/kg 和>20 g/kg。Xanthan Gum 在急性吸入研究顯示兔子的 LC_{50} >21 mg/L。[1]
- 重複劑量毒性:3 隻雄性和 3 隻雌性米格魯犬餵食加有 Xanthan Gum 0、0.25 或 0.5 g/kg bw/day 的飼料，持續 12 週。高劑量組的動物大便較正常軟，但沒有腹瀉，高劑量組雄性的生長略有減緩，血清膽固醇水平降低，未見其他不良反應。此測試的 NOAEL 被認為是 0.25 g/kg bw/day。[1,2]
- 皮膚腐蝕性/刺激性：1% Xanthan Gum 對兔子皮膚沒有刺激性；一項含 5% Xanthan Gum 的水溶液施用於剃毛兔皮膚上產生局部刺激，沒有提供研究細節。[1]
- 皮膚致敏性：在天竺鼠皮內激發試驗，將 0.1% Xanthan Gum 以皮內注射 3 次/週共注射 10 次，在 10 天非處理期後進行激發，結果顯示致敏性。[1]
- 致癌性:在大鼠中進行的兩年研究未能顯示任何的致癌或其他毒性作用。[2]
- 致突變性/遺傳毒性：無 Xanthan Gum 相關研究數據。交叉參照 20 mg/mL 結冷膠(gellan gum)、25 mg/plate 葡聚醣硫酸鈉(sodium dextran sulfate)、5,000 mg/plate β-葡聚醣(beta-glucan)、50,000 mg/plate 羧甲基 β-葡聚醣鈉(sodium carboxymethyl beta-glucan)和 12 mg/mL 支鏈澱粉(pullulan)等之 Ames 測試、染色體畸變測定或 DNA 修復測試進行的評估結果，無論有無代謝活化結果是陰性的，唯一非陰性結果是在使用枯草芽孢桿菌進行的 rec 測定中，20 mg/plate 支鏈澱粉的弱陽性結果。另 5,000 mg/kg β-葡聚醣和 1,800 mg/kg 支鏈澱粉的體內小鼠微核試驗結果亦為陰性。[1]
- 生殖毒性：一項 3 代生殖毒性研究於白化大鼠的飲食添加 Xanthan Gum 0、0.25 和 0.5 g/kg bw/day。第一代使用 10 隻雄鼠和 20 隻雌鼠，後續兩代則為 20 隻雄鼠和 20 隻雌鼠，交配後每代產 2 窩，從第二胎的斷奶仔鼠中選出後續代數。測試組及對照組親代的生存和生殖參數相似，測試組的親代大鼠體重與每一代的對照相比略有下降，發育沒有顯著差異，測試和對照窩之間的發育參數沒有顯著差異，並且在任何後代中都沒有觀察到畸形。[1]

- 光毒性：無 Xanthan Gum 相關研究數據。交叉參照含 2%羧甲基β-葡聚醣鈉(sodium carboxymethyl beta-glucan)的水溶液在臨床研究的結果中無光敏性。[1]
- 毒理代謝動力學：熱量利用率和消化率研究顯示 Xanthan Gum 不被人體利用，研究數據顯示在 7 天內餵食的所有 Xanthan Gum 都可以在糞便中發現。[1]
- 其他安全資料：在人體中進行的幾項研究顯示每日攝入量高達 10-13 g 不會產生不良影響。[2]
- 參考資料：

1. Safety Assessment of Microbial Polysaccharide Gums as Used in Cosmetics. IJT 35(Suppl. 1):5-49, 2016.
2. Inchem 網站: Xanthan Gum. Web site. http://www.inchem.org/documents/jecfa/jecmono/v21je13.htm. 2010.

19. INCI name：Caprylic/Capric Triglyceride

- 急性毒性：辛酸/癸酸甘油三酯(Caprylic/Capric Triglyceride)的急性經口 LD_{50} 在小鼠為 >25 ml/kg 而在大鼠為>5 g/kg。雄性大鼠和天竺鼠每組 10 隻在裝有 40L 辛酸/癸酸甘油三酯氣溶膠的室中暴露 6 小時，標稱濃度為 28.1 µl/l 空氣，具有足以被吸入肺部的顆粒的氣溶膠部分即直徑為 5 µm 或更小，表示為 1.97 µl/l 的測試物質，研究結果未觀察到不良反應。[1]
- 重複劑量毒性：在 Wistar 大鼠中進行癸酰和辛酰甘油酯(CAS No. 73398-61-5)的 90 天口服餵養研究，將測試物質以 10,000 和 50,000 ppm 的濃度混合到飲食中，在臨床症狀、體重增加、食物消耗、血液學、臨床化學、尿液分析和大體病理學方面未觀察到與施用相關的異常，假設食物中的 1 ppm 相當於幼鼠每天的 0.1 mg/kg bw，則 NOAEL 為 5000 mg/kg bw/day。在雄性 Wistar 大鼠進行癸酰和辛酰甘油酯(CAS No. 73398-61-5)的 30 天的口服管飼研究，每組 10 隻動物接受 10 g/kg bw/ day，在任何劑量下均未觀察到與受測物相關的異常，根據研究結發現雄性 Wistar 大鼠的亞急性 NOAEL 為 10000 mg/kg bw/day。[2] 另一項研究使用含有 22%辛酸/癸酸甘油三酯的鞣製黃油配方，以 2000 mg/kg 的劑量對三隻雄性和三隻雌性紐西蘭白化兔進行研究，每週 5 次持續 28 天，在測試過程中沒有對體重、身體外觀和行為的影響，測試結束時，沒有觀察到相關的系統性、總體或組織病理學變化，在皮膚受測區域無論皮膚是否磨損或完好無損，都會出現輕微至中度的紅斑以及輕微的脫皮和開裂。根據研究結果，發現雄性和雌性兔的亞急性(28 天)皮膚暴露 NOAEL 為 2000 mg/kg bw/day。[2]
- 皮膚腐蝕性/刺激性：以 2 ml/kg 5 天/週的劑量將含有 4%辛酸/癸酸甘油三酯的芳香皮膚軟化配方施用於雌性大鼠的剃毛皮膚上，持續 13 週不會導致任何局部皮膚影響。含有 95.51%辛酸/癸酸甘油三酯的臉部油類產品不是刺激物。[1]
- 皮膚致敏性：辛酸/癸酸甘油三酯不是天竺鼠的致敏劑。在 17 名人類受試者中進行的 24 小時單次封閉斑貼試驗，以及在 26 名受試者進行的人類改良最大化斑貼試驗中，結果不是致敏劑。[1]
- 致癌性：無 Caprylic/Capric Triglyceride 相關研究數據。交叉參照三辛精(Tricaprylin)的致腫瘤性研究，30 隻雌性小鼠腹腔注射 0.25 ml

後，37% 的動物出現肺腫瘤。在 30 隻未經施用的對照組中，肺腫瘤發生率為 23%。國家毒理學計劃 (NTP) 的一項口服致癌性研究結果顯示，三辛精在大鼠胰腺腺泡細胞增生和腺瘤的發生率上引起統計學上顯著的劑量相關增加，三辛精不誘導腺泡細胞癌。此外，與對照組相比，最高劑量組(10 ml/kg 三辛精)大鼠胃鱗狀細胞乳頭狀瘤的發病率顯著增加。

- 致突變性/遺傳毒性：根據歐盟方法 B.13，鼠傷寒沙門氏菌菌株 TA 1535、TA 1537、TA 1538、TA 98 和 TA 100 用丙酮稀釋的癸酰和辛酰甘油酯(CAS No. 73398-61-5)處理，在添加和無添加大鼠肝臟勻漿代謝系統(S9)的情況下測試濃度 0、8、40、200、1000、5000 µg/plate 5000 µg/plate 觀察到沉澱，但最高沉澱劑量下沒有引起細胞毒性，對於任何細菌菌株，無論有或無代謝活化，任何劑都沒有記錄到回復菌落的顯著增加。[2]
- 生殖毒性：無 Caprylic/Capric Triglyceride 相關研究數據。交叉參照甘油酯、C8-18 和 C18-unsatd 單乙酸雙乙酸(CAS No. 91052-13 -0)可以確定大鼠的親代生育能力 NOAEL 為 1000 mg/kg bw/day，對於蓖麻油(CAS No.8001-79-4) 可以確定大鼠的親本生育能力 NOAEL 為 5000 mg/kg bw/day 而小鼠 NOAEL 為 15000 mg/kg bw/day。[2]
- 光毒性：在 27 名受試者中完成 RIPT 光接觸致敏性試驗，為進行誘導將 40 mg 測試材料組成的封閉貼片均勻塗抹在 2 x 2 cm (10 mg/cm^2) 棉布上，用於每位受試者的下背部，持續時間為 24 小時；貼片移除後，測試部位立即受到來自氙弧太陽模擬器照射兩次最小紅斑劑量(MED)。該程序重複 2 次/週，持續 3 週，總共 6 次誘導應用。在 10 天的非測試期後，將挑戰貼片應用到背部另一側先前未施用的部位 24 小時，然後暴露於 ½ MED 的太陽模擬照射加上 4 J/cm^2 UVA，結果顯示含有 95.51% 辛酸/癸酸甘油三酯的面部油在人體皮膚中不具有可檢測的光敏感性。[1]
- 毒理代謝動力學：辛酸/癸酸甘油三酯(Caprylic/Capric Triglyceride 和含有長鏈甘油三酯(LCT)混合物(烷基鍊長度大於 12, C > 12)的食物口服吸收和代謝不同。C>12 被唾液、腸道和胰脂肪酶降解成兩個脂肪酸和一個單酰基甘油，而辛酸/癸酸甘油三酯被相同的酶降解成三個脂肪酸和簡單的甘油，辛酸/癸酸甘油三酯很容易從小腸直接吸收到血液中並轉運到肝臟進行肝臟代謝，而 C>12 則被納入乳糜微粒並進入淋巴系統，辛酸/癸酸甘油三酯很容易分解為二氧化

碳和雙碳碎片，而 C > 12 則被重新酯化為三酰基甘油並代謝為能量或儲存在脂肪組織中。[1]

- 人體數據：在 128 名受試者的 Draize 重複損傷貼片測試，結果顯示辛酸/癸酸甘油三酯非刺激物或致敏劑。在一項人體安慰劑對照雙盲研究中，健康受試者每天攝入 42 克的中鏈和長鏈甘油三酯(medium- and long-chain triacylglycerol, MLCT)，未觀察到不良反應。[1]
- 其他安全資料：根據 21 CFR § 170.3，中長鏈甘油三酯(MLCT)-油已被科學程序確定為安全(GRAS)，適用於其預期使用條件。MLCT-Oil 的安全性得到了臨床前和臨床研究的支持，中鏈甘油三酯已用於吸收不良綜合徵患者，添加到嬰兒配方中，並從天然來源的飲食中攝取，而含有長鏈甘油三酯的植物油通常在人類飲食中食用。
- 參考資料：

1. Amended Safety Assessment of Triglycerides as Used in Cosmetics. CIR Final Amended Report 12/05/2017.
2. Registration Dossier. ECHA 網站: https://echa.europa.eu/de/registration-dossier/-/registered-dossier/16019/7/1

(11) 產品安定性試驗報告

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

產品名稱	柔柔化粧水			
包裝材質	玻璃、PE			
試驗時間 / 試驗項目	第 0 個月 40 ℃ 75 %RH	第 1 個月 40 ℃ 75 %RH	第 3 個月 40 ℃ 75 %RH	第 6 個月 40 ℃ 75 %RH
外觀	流動液體	流動液體	流動液體	流動液體
顏色	淡黃色澄清透明	淡黃色澄清透明	淡黃色澄清透明	淡黃色澄清透明
氣味	海洋清香	海洋清香	海洋清香	海洋清香
pH (at 25 °C)	5.8	5.6	5.7	5.6
黏度(at 25 °C)	9.8 mPa·s	9.5 mPa·s	10.2 mPa·s	9.9 mPa·s
密度(at 25 °C)	1.00 g/cm^3	1.01 g/cm^3	1.03 g/cm^3	1.00 g/cm^3
微生物檢測結果	未檢出	未檢出	未檢出	未檢出
包材外觀	無膨脹、變色、腐蝕及脆裂之現象	無膨脹、變色、腐蝕及脆裂之現象	無膨脹、變色、腐蝕及脆裂之現象	無膨脹、變色、腐蝕及脆裂之現象
結果判定	■合格 □不合格	■合格 □不合格	■合格 □不合格	■合格 □不合格
參考試驗方法	ISO/TR 18811 Cosmetics-Guidelines on the stability testing of cosmetics products,2018. 參考 5.3.2 建議之溫度及濕度進行加速安定性試驗			
檢測人員/日期	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)
複核人員/日期	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)

(12)微生物檢測報告

產品名稱	柔柔化粧水		
產品批號	IT22080H		
產品製造日期	111.08.10		
包裝材質		試驗日期	111.08.15
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)	柔柔化粧水
測試日期(Date Tested): 111.05.03~06.15	
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	9.8×10^5	1.0×10^6	8.6×10^6	8.5×10^4	8.8×10^4
第 7 天	<10	<10	<10	4.2×10^2	5.3×10^2
第 14 天	<10	<10	<10	<10	<10
第 28 天	<10	<10	<10	<10	<10

檢測人員/日期	(請簽名並加上日期)
複核人員/日期	(請簽名並加上日期)

(14) 功能評估佐證資料

相關功能性測定，依產品宣稱之功能提供相關佐證資料。

(15) 與產品接觸之包裝材質資料

產品容量 ：200 ml

包裝材料	包裝材質
瓶身	玻璃
內塞	PE
瓶蓋泡沫墊片	PE

III. 安全評估資料

(16) 產品安全資料

柔柔化粧水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
使用表面積(cm^2)	565
駐留因子	1.00

每日皮膚暴露量($E_{product}$)

對於此柔柔化粧水，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)*
Skin care					
Body lotion	7.82	123.20	1.00	**7.82**	**123.20**
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。

柔柔化粧水各成分 MoS 值計算

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

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

MoS = POD_{sys}/SED

SED (mg /kg bw/day)為全身暴露劑量；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 DA_P(%)	NOAEL (mg /kg bw/day)	SED (mg /kg bw/day)	MoS
Aqua	89.408	100	-	21.58309	-
Pentylene Glycol	3.508	100	1000.0	0.84683	1181
Dipropylene Glycol	2.000	100	470.0	0.48280	973
PPG-12-Buteth-16	2.000	100	75.0	0.48280	155
Niacinamide	1.000	100	33.1	0.24140	137
Betaine	1.000	100	777.8	0.24140	3222
PEG-40 Hydrogenated Castor Oil	0.400	100	500.0	0.09656	5178
Olea Europaea (Olive) Leaf Extract	0.325	100	500.0	0.07966	6277
Chlorphenesin	0.200	100	15.6	0.04828	323
Mannitol	0.075	100	312.5	0.01811	17256
Ammonium Glycyrrhizate	0.020	100	47.5	0.00483	9834
Butylene Glycol	0.020	100	3000.0	0.00483	621118
Sodium Hyaluronate	0.010	100	500.0	0.00241	207469
Disodium EDTA	0.010	10	346.0	0.00024	1441667
Fragrance	0.010	100	-	0.00241	附 IFRA 符合性聲明

Alpinia Galanga Extract	0.008	100	1500.0	0.00193	777202
Caffeine	0.002	100	75.5	0.00048	157292
Zinc Gluconate	0.002	100	117.0	0.00048	243750
Aesculus Hippocastanum (Horse Chestnut) Seed Extract	0.001	100	28.6	0.00024	119167
Xanthan Gum	0.0008	100	115.4	0.000193	597927
Caprylic/Capric Triglyceride	0.0002	100	444.4	0.000048	9258333

INCI name	**NOAEL 校正說明**
Pentylene Glycol	交叉參照 1,2 己二醇的 90 天皮膚毒性研究得知 NOAEL 為 1000 mg/kg bw/day。
Dipropylene Glycol	大鼠 2 年的口服重複毒性研究得知最低 NOAEL 為 470 mg/kg bw/day，此為更保守值故未以不確定因子進行校正。
PPG-12-Buteth-16	交叉參照 PPG-33-Buteth-45 的大鼠 90 天口服亞慢性研究，得知 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。
Niacinamide	由大鼠 4 週亞急性口服毒性研究得知 NOAEL 為 215 mg/kg/day，考慮口服生物可用率 50%及試驗天數等不確定因子，將 215*50%*4/13=33.1 mg/kg bw/day。
Betaine	由大鼠 28 天口服亞急性毒性研究得知 NOAEL 為 5000 mg/kg bw/day，考慮口服生物可用率 50%及試驗天數等不確定因子，將 5000*50%*28/90=777.8 mg/kg bw/day。
PEG-40 Hydrogenated Castor Oil	大鼠合併重複劑量毒性與生殖/發育毒性篩選試驗得知 NOAEL 為 1000 mg/kg/day，考慮口服生物可用率 50%將 1000*50%=500 mg/kg bw/day。
Olea Europaea (Olive) Leaf Extract	90 天大鼠管飼研究得知 NOAEL 為 1000 mg/kg bw/day，考慮口服生物可用率 50%之不確定因子，將 1000*50%

	=500 mg/kg bw/day。
Chlorphenesin	28 天大鼠重複經口毒性研究得知 NOAEL 為 100 mg/kg bw/day，考慮口服生物可用率 50%及試驗天數等不確定因子，將 100*50%*28/90=15.6 mg/kg bw/day。
Mannitol	13 週餵食大鼠試驗中於 625 mg/kg bw/day 實驗組未觀察到與測試物質相關的臨床症狀，考慮口服生物可用率 50%之不確定因子，將 625*50% =312.5 mg/kg bw/day。
Ammonium Glycyrrhizate	0、18 或 90 mg/kg/day 的 Ammonium Glycyrrhizate 小鼠每週 6 天 16 週的口服管飼試驗得知 NOAEL 為 90 mg/kg bw/day，考慮口服生物可用率 50%及試驗天數等不確定因子，將 90*50%*6/7*16/13=47.47 mg/kg bw/day。
Butylene Glycol	狗的亞慢性 13 週餵養試驗得知 NOAEL 為 6000 mg/kg bw/day，考慮口服生物可用率 50%之不確定因子，將 6000*50%*=3000 mg/kg bw/day。
Disodium EDTA	為期 13 週餵食大鼠試驗中得知 NOAEL 為 692 mg/kg bw/day，考慮口服生物可用率 50%之不確定因子，692*50% =346 mg/kg bw/day。
Alpinia Galanga Extract	大鼠 90 天口服毒性試驗得知 NOAEL 為 3000 mg/kg/day，考慮口服生物可用率 50%之不確定因子，將 3000*50%*=1500 mg/kg bw/day。
Caffeine	小鼠和大鼠的 90 天口服研究得知最低 NOAEL 為 151 mg/kg bw/day，考慮口服生物可用率 50%之不確定因子，將 151*50%*=75.5 mg/kg bw/day。
Zinc Gluconate	大鼠和小鼠的 90 天口服毒性研究得知最低 NOAEL 為 234 mg/kg/day，考慮口服生物可用率 50%之不確定因子，將 234*50%*=117 mg/kg bw/day。
Aesculus Hippocastanum (Horse Chestnut) Seed Extract	狗的亞慢性經口毒性研究(5 天/週，3 個月) 得知 NOAEL 為 80 mg/kg/day，考慮口服生物可用率 50%及試驗天數等不確定因子，將 80*50%*5/7=28.57 mg/kg bw/day。
Sodium Hyaluronate	大鼠的 90 天口服毒性研究得知 NOAEL 為 1000 mg/kg bw/day，考慮口服生物可用率 50%之不確定因子，將 1000*50%*=500 mg/kg bw/day。

Xanthan Gum	狗的 12 週口服毒性研究得知 NOAEL 為 0.25 g/kg bw/day，考慮口服生物可用率 50%及試驗天數等不確定因子，將 250*50%*12/13=115.38 mg/kg bw/day。
Caprylic/Capric Triglyceride	兔子的 28 天(每週 5 次)亞急性皮膚毒性研究得知 NOAEL 為 2000 mg/kg bw/day，考慮試驗天數之不確定因子，將 2000*5/7*28/90=444.44 mg/kg bw/day。

柔柔化粧水安全評估結論

安全評估結論簡述

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

標籤警語和使用說明

柔柔化粧水的包裝材料/標籤上提到了以下警告和使用說明：

使用方式：早晚清潔肌膚後，取適量於手心或化妝棉上均勻塗抹於臉部肌膚。

使用注意事項：使用時若有不適請立即停止使用，並以清水沖洗。

安全評估理由

柔柔化粧水的安全性評估基於每種成分的毒理學特徵並評估所收集之產品數據。

1. 該產品在符合化粧品優良製造規範之場所和生產設施中生產，並進行微生物品質管理以及倉儲管理作業。
2. 本產品添加 0.2% Chlorphenesin(限量 0.3%)及 0.002% Zinc Gluconate(限量 1%)符合我國化粧品防腐劑成分名稱及使用限制表及化粧品成分使用限制表之規定。
3. 根據本產品「柔柔化粧水」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「柔柔化粧水」產品配方具有足夠安定性及微生物安全性。由六個月之加速安定性試驗推測本產品於架儲期間品質穩定，上市後將同時進行長期安定性試驗確認之。
4. 微生物檢測報告結果符合我國化粧品微生物容許量基準之要求。防腐效能試驗報告顯示符合衛福部食藥署 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. 本產品使用之包裝材質為玻璃及 PE，根據過去類似配方及此包材之使用經驗，評估此包裝材料合適且安全。
6. 根據 SCCS 化粧品成分測試及其安全性評估指引第 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，採用國際間常用 SCCS 用於面部產品之標準暴露值以計算安全邊際值(MoS)。

7. 使用之香精符合國際香料協會標準(IFRA 50th Amendment)，應用於柔柔化粧水之最大濃度為 6.86%，此柔柔化粧水添加 0.01%香精，推測不具致敏性。
8. 此柔柔化粧水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，可支持此產品的安全性。
9. 目前此產品尚未出現不良反應和嚴重不良反應，如有不良反應和嚴重不良反應的相關資料時，會及時提供給安全資料簽署人員重新評估此產品之安全性，並更新於本產品資訊檔案。

（請簽名並加上日期）

_____

安全資料簽署人員簽名及日期

*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：Chlorphenesin

MATERIAL SAFETY DATA SHEET

According to Regulation(EC) N° 1272/2008 REACH

Date Updated: January 15, 2021

Section 1 - Product and Company Information

Product Name PROCARE CP-DEO

Use of the Substance Product for cosmetic use

REACH Registration Status and Number

Status Registered

Registration Number 01-2120758358-42-XXXX

Details of Supplier

Company Name

Address

Email

Section 2 - Hazards Identification

Classification of the Substance or Mixture

Physical Hazards

Based on available data, the classification criteria are not met

Health Hazards

Skin Corrosion/Irritation	Category 2
Serious Eye Damage/Eye Irritation	Category 2

Specific Target Organ Toxity - (Single Exposure) Category 3

Encironmental Hazards

Based on available data, the classification criteria are not met

Label Elements

Signal Word **Warning**

Hazard Statements

H315	Causes skin irritation
H319	Causes serious eye irritation
H335	May cause respiratory irritation

Precautionary Statements

Prevention

P261	Avoid breathing dust/fume/gas/mist/vapors/spray
P264	Wash face, hands and any exposed skin thoroughly after handling
P271	Use only outdoors or in a well-ventilated area
P280	Wear protective gloves/protective clothing/eye protection/face protection

Response

P302 + P352	IF ON SKIN: Wash with plenty of soap and water
P304 + P340	IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing
P305 + P351 + P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing
P312	Call a POISON CENTER or doctor/physician if you feel unwell
P362 + P364	Take off all contaminated clothing and wash it before reuse
P321	Specific treatment (see supplemental first aid instructions on this label)
P332 + P313	If skin irritation occurs: Get medical advice/attention
P337 + P313	If eye irritation persists: Get medical advice/attention

Storage

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

Disposal

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

Other Hazards

NFPA

Health	Flammability	Instability	Physical hazards
2	1	0	-

Section 3 – Composition / Information on Ingredient

Single or Mixture Single

Composition / Information

INCI Name	CAS No.	EC Number
Chlorphenesin (3-(p-Chlorophenoxy)-Propane-1,2-diol)	104-29-0	203-192-6

Chemical Formula $C_9H_{11}ClO_3$

Section 4 - First Aid Measures

Description of First Aid Measures

General Advice If symptoms persist, call a physician

Eye Contact Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Get medical attention

Skin Contact Wash off immediately with plenty of water for at least 15 minutes. If skin irritation persists, call a physician

Ingestion Clean mouth with water and drink afterwards plenty of water. Get medical attention if symptoms occur

Inhalation Remove to fresh air. If not breathing, give artificial respiration. Get medical attention if symptoms occur

Self-Protection of the First Aider Ensure that medical personnel are aware of the material(s) involved, take precautions to protect themselves and prevent spread of contamination

Most Important Symptoms and Effects, both Acute and Delayed

None reasonably foreseeable

Indication of any Immediate Medical Attention and Special Treatment Needed

Notes to Physician Treat symptomatically

Section 5 - Fire Fighting Measures

Extinguishing Media

Suitable Extinguish Media

Carbon dioxide(CO_2), Powder, Water spray. In case of major fire and large quantities: Evacuate area. Fight fire remotely due to the risk of explosion.

Extinguishing media which must not be used for safety reasons

No information available.

Special hazards arising from the substance or mixture

Thermal decomposition can lead to release of irritating gases and vapors.

Hazardous Combustion Products

Carbon monoxide(CO), Carbon dioxide(CO_2), Hydrogen chloride

Advice for fire-fighters

As in any fire, wear self-contained breathing apparatus pressure-demand, MSHA/NIOSH (approved or equivalent) and full protective gear.

Section 6 - Accidental Release Measures

Personal Precautions, Protective Equipment and Emergency Procedures

Ensure adequate ventilation. Use personal protective equipment as required.
Avoid dust formation.

Environmental precautions

Should not be released into the environment. See section 12 for additional Ecological Information.

Methods and material for containment and Cleaning Up

Sweep up and shovel into suitable containers for disposal. Keep in suitable, closed containers for disposal.

Reference to Other Sections

Refer to protective measures listed in Sections 8 and 13.

Section 7 - Handling and Storage

Precautions for Safe Handling

Wear personal protective equipment/face protection. Ensure adequate ventilation.
Do not get in eyes, on skin, or on clothing. Avoid ingestion and inhalation. Avoid dust formation.

Conditions for Safe Storage, Including any Incompatibilities
Keep container tightly closed in a dry and well-ventilated place.

Specific End Uses
Product for cosmetic use.

Section 8 - Exposure Controls / Personal Protection

Control Parameters

Component	Cas No.	Korea	ACGIH TLV	OSHA PEL
Chlorphenesin	104-29-0	Not listed	Not listed	Not listed

Component	Cas No.	European Union	The United Kingdom	Germany
Chlorphenesin	104-29-0	Not listed	Not listed	Not listed

Biological Exposure Indices

Component	Cas No.	Biological Exposure Indices
Chlorphenesin	104-29-0	Not listed

Exposure Controls

Engineering Measures
Ensure that eyewash stations and safety showers are close to the workstation location.
Wherever possible, engineering control measures such as the isolation or enclosure of the process, the introduction of process or equipment changes to minimise release or contact, and the use of properly designed ventilation systems, should be adopted to control hazardous materials at source

Personal protective equipment

Eye Protection Goggles
Hand Protection Protective Gloves
Skin and Body Protection Long Sleeved Clothing

Inspect gloves before use.
Please observe the instructions regarding permeability and breakthrough time which are provided by the supplier of the gloves. (Refer to manufacturer/supplier for information) Ensure gloves are suitable for the task: Chemical compatibility, Dexterity, Operational conditions, User

susceptibility, e.g. sensitization effects, also take into consideration the specific local conditions under which the product is used, such as the danger of cuts, abrasion.
Remove gloves with care avoiding skin contamination.

Personal Protective Equipment
Use only those certified by the Korea Occupational Safety and Health Administration.
Respiratory Protection
When workers are facing concentrations above the exposure limit they must use appropriate certified respirators
Recommended Filter Type
Particle filter Particulates filter conforming to EN 143
To protect the wearer, respiratory protective equipment must be the correct fit and be used and maintained properly When RPE is used a face piece Fit Test should be conducted

Hygiene Measures
Handle in accordance with good industrial hygiene and safety practice

Environmental Exposure Controls
No information available

Section 9 – Physical / Chemical Properties

Information on Basic Physical and Chemical Properties

Appearance	White Solid Crystalline Powder
Odor	Characteristic Odor
Odor Threshold	N/A
Molecular Weight	202.64
pH	N/A
BP/BP Range	N/A
MP/MP Range	78.0 ~ 82.0℃ / 172.4 ~ 179.6℉
Freezing Point	N/A
Vapor Pressure	N/A
Vapor Density	N/A
Saturated Vapor Conc.	N/A
SG/Density	N/A
Bulk Density	N/A
Volatile%	N/A
VOC Content	N/A
Water Content	N/A
Solvent Content	N/A
Evaporation Rate	N/A
Viscosity	N/A
Surface Tension	N/A

Partition Coefficient	N/A
Decomposition Temp.	N/A
Flash Point	N/A
Explosion Limits	N/A
Flammability	N/A
Auto Ignition Temp	N/A
Refractive Index	N/A
Optical Rotation	N/A
Miscellaneous Data	N/A
Solubility	Water Insoluble, Alcohol Soluble
Molecular Formula	$C_9H_{11}ClO_3$
Molecular Weight	202.64

(N/A = not available)

Section 10 - Stability and Reactivity

Reactivity

None known, based on information available

Chemical Stability

Stable under normal conditions.

Possibility of Hazardous Reactions

Hazardous Polymerization No information available.

Hazardous Reactions None under normal processing.

Conditions to Avoid

None known.

Incompatible Materials

Oxidizing agent.

Hazardous Decomposition Products

Carbon monoxide (CO). Carbon dioxide (CO_2). Hydrogen chloride.

Section 11 - Toxicological Information

Information on toxicological effects

Product Information

Information on expected route of exposure

Inhalation Not an expected route of exposure
Ingestion May be harmful if swallowed.
Eyes Irritating to eyes. Avoid contact with eyes.
Skin Avoid contact with skin. May cause irritation.

Information on Health Hazards

(a) acute toxicity

Oral No data available
Dermal No data available
Inhalation No data available

Component	Cas No.	LD50 Oral	LD50 Dermal	LD50 Inhalation
Chlorphenesin	104-29-0	No data available	No data available	No data available

(b) Skin Corrosion/Irritation Category 2

(c) Serious Eye Damage/Irritation Category 2

(d) Respiratory or Skin Sensitization

Respiratory No data available
Skin No data available

Component	Cas No.	Test Method	Test Species	Study Result
Chlorphenesin	104-29-0	No data available	No data available	No data available

(e) Germ Cell Mutagenicity No data available

Component	Cas No.	Test Method	Test Species	Study Result
Chlorphenesin	104-29-0	No data available	No data available	No data available

(f) Carcinogenicity No data available

Component	Cas No.	Test Method	Test Species / Duration	Study Result
Chlorphenesin	104-29-0	No data available	No data available	No data available

There are no known carcinogenic chemicals in this product

Component	Cas No.	IARC	NTP	ACGIH	OSHA	UK
Chlorphenesin	104-29-0	Not Listed	Not Listed	Not Listed	Not Listed	Not Listed

(g) Reproductive Toxicity No data available

Component	Cas No.	Test Method	Test Species / Duration	Study Result
Chlorphenesin	104-29-0	No data available	No data available	No data available

(h) STOT-Single Exposure Category 3
Result / Target Organs Respiratory System
(i) STOT-Repeated Exposure No data available
Target Organs No information available

(j) Aspiration Hazard Not applicable
Solid

Other Adverse Effects

No information available.

Component	Cas No.	EU - Endocrine Disrupters Candidate List	EU - Endocrine Disruptors - Evaluated Substances	Japan - Endocrine Disruptor Information
Chlorphenesin	104-29-0	Not applicable	Not applicable	Not applicable

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Section 12 - Ecological Information

Ecotoxicity effects

Contains no substances known to be hazardous to the environment or that are not degradable in waste water treatment plants.

Component	Cas No.	Freshwater Fish	Water Flea	Freshwater Algae	Microtox
Chlorphenesin	104-29-0	Not data available	Not data available	Not data available	Not data available

Persistence and Degradability

Persistence Insoluble in water.

Bioaccumulative Potential

May have some potential to bioaccumulate

Mobility in Soil

Spillage unlikely to penetrate soil is not likely mobile in the environment due its low water solubility.

Ozone Depletion Potential

Component	Cas No.	Ozone Depletion Potential
Chlorphenesin	104-29-0	Not Listed

Other Adverse Effects

No Information available

Section 13 - Disposal Considerations

Waste Treatment Methods

Waste from Residues/Unused Products

Waste is classified as hazardous. Dispose in accordance with the Wastes Control Act.

Contaminated Packaging

Dispose of this container to hazardous or special waste collection point.

Other Information

Waste codes should be assigned by the user based on the application for which the product was used. Do not empty into drains.

Section 14 - Transport Information

Road and Rail Transport	Not Regulated
IATA	Not Regulated
IMDG/IMO	Not Regulated
Marine Pollutant	No Hazards Identified
Special Precautions for User	No Special Precautions Required

Section 15 – Regulatory Information

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

Legend: X - Listed '-' - Not Listed

International Inventories

Component	CAS No.	KECL	TSCA	EINECS	IECSC	DSL	NDSL	PICCS	ENCS	AICS
Chlorphenesin	104-29-0	-	-	203-192-6	X	X	-	-	-	X

Component	CAS No.	Seveso III Directive (2012/18/EC) Qualifying Quantities for Major Accident Notification	Seveso III Directive (2012/18/EC) Qualifying Quantities for Safety Report Requirements	Rotterdam Convention (PIC)	Basel Convention (Hazardous Waste)
Chlorphenesin	104-29-0	Not applicable	Not applicable	Not applicable	Not applicable

Component	CAS No.	OECD HPV	Persistent Organic Pollutant	Ozone Depletion Potential
Chlorphenesin	104-29-0	Not applicable	Not applicable	Not applicable

Korean National Regulations

Component	CAS No.	Act on Registration and Evaluation of Chemical Substances (K-REACH)	Authorised Chemicals	Existing Substances Subject to Registration
Chlorphenesin	104-29-0	Not applicable	Not applicable	Not applicable

Component	CAS No.	Chemical Control Act Toxic Chemicals	Chemical Control Act Prohibited Chemicals	Chemical Control Act Use Restricted Chemicals
Chlorphenesin	104-29-0	Not applicable	Not applicable	Not applicable

Component	CAS No.	Chemical Control Act Accident Precaution Chemicals (% in mixtures)	Chemical Control Act Accident Precaution Chemicals - Quantity limits Storage (% in mixtures)	Chemical Control Act Accident Precaution Chemicals - Quantity limits Manufacture/Use (% in mixtures)
Chlorphenesin	104-29-0	Not applicable	Not applicable	Not applicable

Component	CAS No.	Waste Control Law	Ministry of Environment - CMR risk	Ministry of Environment - Critically Controlled Substance
Chlorphenesin	104-29-0	Not applicable	Not applicable	Not applicable

Component	CAS No.	ISHA - Harmful Agents Subject to Work Environment Monitoring	ISHA - Prohibited substances	ISHA - Substances requiring permission
Chlorphenesin	104-29-0	Not applicable	Not applicable	Not applicable

Component	CAS No.	ISHA - Substances subject to control	ISHA - Harmful Agents Requiring Health Examination	ISHA - Permissible Exposure Limits
Chlorphenesin	104-29-0	Not applicable	Not applicable	Not applicable

Component	CAS No.	ISHA - Subject to Process Safety Reports (minimum quantity)	ISHA - Threshold Limit Values (TLVs) Chemicals	ISHA - Special management materials
Chlorphenesin	104-29-0	Not applicable	Not applicable	Not applicable

National Fire Association - Dangerous Substances Minimum quantity requiring a permit

Component	CAS No.	Class 1 - Oxidising solids	Class 2 - Flammable solid	Class 3 - Spontaneously Combustible Substances and Dangerous Substances When Wet	Class 4 - Flammable liquids	Class 5 - Self-reactive substances	Class 6 - Oxidising liquids
Chlorphenesin	104-29-0	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

Control Parameters

Component	CAS No.	Korea	Biological Exposure Indices
Chlorphenesin	104-29-0	Not listed	Not listed

US Management Information

OSHA - Occupational Safety and Health Administration

Not applicable

Component	CAS No.	Specifically Regulated Chemicals	Highly Hazardous Chemicals
Chlorphenesin	104-29-0	Not applicable	Not applicable

CERCLA Not applicable

Component	CAS No.	CERCLA EHS RQs	Hazardous Substances RQs	SARA 313 - Threshold Values %
Chlorphenesin	104-29-0	Not applicable	Not applicable	Not applicable

CLP Classification - Regulation (EC) No 1272/2008

Warning.

H315 - Causes skin irritation.

H319 - Causes serious eye irritation.

H335 - May cause respiratory irritation.

P302 + P352 - IF ON SKIN: Wash with plenty of soap and water.

P337 + P313 - If eye irritation persists: Get medical advice/attention.

P304 + P340 - IF INHALED: Remove victim to fresh air and keep at rest in a position

comfortable for breathing.
P312 - Call a POISON CENTER or doctor/physician if you feel unwell.
P280 - Wear protective gloves/protective clothing/eye protection/face protection.
P332 + P313 - If skin irritation occurs: Get medical advice/attention.

Section 16 - Other Information

Legend

CAS - Chemical Abstracts Service
EINECS/ELINCS - European Inventory of Existing Commercial Chemical Substances/EU List of Notified Chemical Substances
PICCS - Philippines Inventory of Chemicals and Chemical Substances
IECSC - Chinese Inventory of Existing Chemical Substances
KECL - Korean Existing and Evaluated Chemical Substances
WEL - Workplace Exposure Limit
ACGIH - American Conference of Governmental Industrial Hygienists
RPE - Respiratory Protective Equipment
LC50 - Lethal Concentration 50%
POW - Partition coefficient Octanol:Water
ADR - European Agreement Concerning the International Carriage of Dangerous Goods by Road
IMO/IMDG - International Maritime Organization/International Maritime Dangerous Goods Code
OECD - Organisation for Economic Co-operation and Development
BCF - Bioconcentration factor
TSCA - United States Toxic Substances Control Act Section 8(b) Inventory
DSL/NDSL - Canadian Domestic Substances List/Non-Domestic Substances List
ENCS - Japanese Existing and New Chemical Substances
AICS - Australian Inventory of Chemical Substances
NZIoC - New Zealand Inventory of Chemicals
TWA - Time Weighted Average
IARC - International Agency for Research on Cancer
LD50 - Lethal Dose 50%
EC50 - Effective Concentration 50%
ICAO/IATA - International Civil Aviation Organization/International Air Transport Association
MARPOL - International Convention for the Prevention of Pollution from Ships
ATE - Acute Toxicity Estimate
VOC - volatile organic compound

Key literature references and sources for data
Suppliers safety data sheet, Chemadvisor - LOLI, Merck index, RTECS,

ThermoFisher Scientific

Disclaimer

For industrial use only. Not appropriate for drug, food or other uses.

Warranty

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. shall not be held liable for any damage resulting from handling or contact with the above product.

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：Chlorphenesin

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Article

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Safety Assessment of Chlorphenesin as Used in Cosmetics

Wilbur Johnson Jr[1], Wilma F. Bergfeld[2], Donald V. Belsito[2], Ronald A. Hill[2], Curtis D. Klaassen[2], Daniel C. Liebler[2], James G. Marks Jr[2], Ronald C. Shank[2], Thomas J. Slaga[2], Paul W. Snyder[2], and F. Alan Andersen[3]

Abstract

Chlorphenesin functions as a biocide in cosmetics and is used at concentrations up to 0.32% in rinse-off products and up to 0.3% in leave-on products. The Cosmetic Ingredient Review Expert Panel (Panel) noted that chlorphenesin was well absorbed when applied to the skin of rats; however, any safety concern was minimized because available data demonstrated an absence of toxicity. The Panel concluded that chlorphenesin is safe in the present practices of use and concentration.

Keywords

chlorphenesin, safety, cosmetics

Introduction

As stated in the *International Cosmetic Ingredient Dictionary and Handbook*,[1] chlorphenesin functions as a biocide (preservative) in cosmetic products. The Expert Panel (Panel) noted that chlorphenesin (CAS No. 104-29-0) may be confused with the muscle relaxant drug, chlorphenesin carbamate (CAS No. 886-74-8), which has also been known as chlorphenesin. Chlorphenesin carbamate is not a cosmetic ingredient and is not reviewed in this safety assessment.

Chemistry

Definition and Structure

As given in the *International Cosmetic Ingredient Dictionary and Handbook*, chlorphenesin (CAS No. 104-29-0) is a chlorophenol derivative defined as the organic compound that conforms to the formula shown[1] in Figure 1. Other names for this chemical include 3-(4-chlorophenoxy)-1,2-propanediol; 1,2-propanediol,3-(4-chlorophenoxy)-; and *p*-chlorophenyl glyceryl ether.[1]

Chemical and Physical Properties

An ultraviolet (UV) spectrum of 0.01% aqueous chlorphenesin solution exhibited an absorption maximum at 279 nm.[2] Additional properties of chlorphenesin are given in Table 1.

Methods of Production

Chlorphenesin is prepared by condensing equimolar amounts of *p*-chlorophenol and glycidol in the presence of a tertiary amine or a quaternary ammonium salt as a catalyst.[3]

Use

Cosmetic

Chlorphenesin reportedly functions as a biocide in cosmetic products.[1] Reportedly, chlorphenesin (ELESTAB CPN; concentration of use = 0.10%-0.30%) has bactericidal activity against gram-positive and gram-negative bacteria, fungicidal activity against *Aspergillus niger* IMI 149007, and *Penicillium pinophilum* IMI 87160 (fungi), and is also active against *Candida albicans* NCPF 3179 and *Saccharomyces cerevisiae* NCPF 3275 (yeasts).[4]

According to information supplied to the US Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2011, chlorphenesin is used in 1386 cosmetic products.[5] These data are

[1] Cosmetic Ingredient Review Senior Scientific Analyst, Washington, DC, USA
[2] Cosmetic Ingredient Review Expert Panel Member, Washington, DC, USA
[3] Former Director, Cosmetic Ingredient Review, Washington, DC, USA

Corresponding Author:
Lillian J. Gill, Director, Cosmetic Ingredient Review, 1620 L St., NW, Suite 1200 Washington, DC 20036, USA.
Email: cirinfo@cir-safety.org

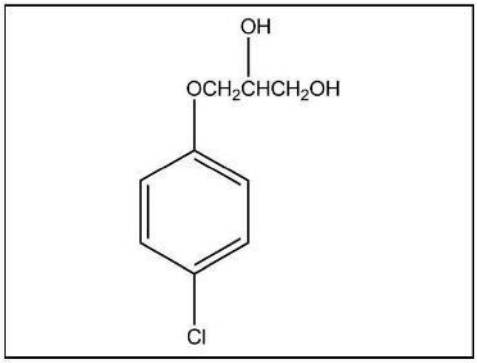

Figure 1. Chlorphenesin.

Table 1. Properties of Chlorphenesin.[a]

Form	White powder with bitter taste. Almost odorless[4]
Molecular weight[3]	202.63
Density[4]	0.70-0.75
Solubility[3,4]	Soluble in 200 parts water and in 5 parts alcohol (95%); soluble in ether; slightly soluble in fixed oils; solubility in water < 1%
Melting range[4]	78°C to 81°C
Flash point[4]	100°C
Assay (dried basis)[4]	Contains not less than 99.0% $C_9H_{11}ClO_3$
Loss on drying[4]	Not more than 1.0%
Sulfated ash[4]	Not more than 0.10%

[a] Complies with British Pharmacopoeia specifications for chlorophenol as a component.[4]

summarized in Table 2. Results from a survey of ingredient use concentrations provided by the Personal Care Products Council (also included in Table 2) in 2011 indicate that chlorphenesin is used at similar concentrations in rinse-off and leave-on cosmetic products—up to 0.32% in rinse-off products and up to 0.3% in leave-on products.[6]

Cosmetic products containing chlorphenesin may be applied to the skin and hair or, incidentally, may come in contact with the eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Chlorphenesin is used in hair, foot, and suntan sprays and could possibly be inhaled. In practice, 95% to 99% of the particles released from cosmetic sprays have aerodynamic equivalent diameters in the 10 to 110 µm range, with propellant sprays yielding a greater fraction of droplets/particles below this range when compared to pump sprays.[7,8] Therefore, most aerosols incidentally inhaled from these sprays are deposited in

Table 2. Current Frequency and Concentration of Use According to Duration and Type of Exposure Provided in 2011and 2012.[a,5,6]

	Chlorphenesin	
	# of Uses	Conc (%)
Exposure type		
Eye area	246	0.02-0.3
Incidental ingestion	3	0.2-0.3
Incidental inhalation—sprays	25	0.2-0.3
Incidental inhalation—powders	57	0.2-0.3
Dermal contact	1280	0.00004-0.32
Deodorant (underarm)	NR	NR
Hair—noncoloring	48	0.0003-0.3
Hair—coloring	NR	0.000008-0.003
Nail	2	0.0003-0.2
Mucous membrane	24	0.00004-0.3
Baby products	NR	NR
Duration of use		
Leave on	1224	0.0003-0.3
Rinse off	159	0.000008-0.32
Diluted for (bath) use	3	0.0006-0.3
Totals/conc range	1386	0.000008-0.32

Abbreviations: NR, not reported; Conc, maximum (max) use concentration or range of max use concentration values; totals, rinse-off + leave-on product uses.
[a] Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not be equal to sum total uses.

the nasopharyngeal region and are not respirable to any appreciable level.[9,10] Thus, toxicological concerns could arise from direct effects on nasopharyngeal tissues or from swallowing of the resulting minute amounts. Based on further toxicological assessments contained herein, such exposures would pose no identifiable risks.

According to the European Union Cosmetics Directive, chlorphenesin is listed among the preservatives that may be contained in cosmetic products marketed in the European Union (EU). The maximum authorized use concentration for this ingredient is 0.3%.[11]

Noncosmetic

Chlorphenesin (0.10%) is one of the ingredients in an antimicrobial product identified as Miol cream. The reason for adding chlorphenesin as an ingredient was not stated.[12]

Toxicokinetics

Absorption, Distribution, Metabolism, and Excretion

The absorption, distribution, and metabolic fate of chlorphenesin was evaluated using male Sprague-Dawley rats and Beagle dogs.[13] In the first experiment (4 rats), a 16.7 mg oral dose of chlorphenesin-1,3-^{14}C (in physiological saline) was administered via oral gavage, after which concentrations in the blood were determined. In a second experiment, chlorphenesin-1,3-^{14}C (15.2 mg) was administered intraperitonelly (ip) to 1 rat and the distribution of administered radioactivity was

determined. A third experiment was performed to isolate chlorphenesin metabolites from the urine. Nonradioactive chlorphenesin (500 mg/kg) was administered orally to 2 Beagle dogs and urine was collected for 24 hours. Urine from 2 Beagle dogs was also collected after the animals received 2 ip injections of nonradioactive chlorphenesin (250 mg/kg, 6 hours apart). In a fourth experiment to identify conjugated metabolites, 4 male rats were injected ip with chlorphenesin UL-ring-^{14}C (30 mg) and urine was collected for 24 hours.

Following oral ingestion, chlorphenesin-^{14}C was absorbed rapidly in the rat. Radioactivity reached a peak blood concentration in 30 minutes, and the half-life of serum radioactivity was approximately 140 minutes.

Results of the distribution experiment indicated that over half of the administered ip dose of chlorphenesin-1,3-^{14}C in the single rat studied was excreted in the urine after 4 hours. The remainder was found primarily in the gastrointestinal tract and carcass. A small portion of the radioactivity was recovered as exhaled CO_2.

The urinary end products (expressed as % of urinary radioactivity) identified after administration of the compound to rats and dogs were 3-*p*-chlorophenoxylactic acid (57.3% in dogs; 41.8% in rats), *p*-chlorophenoxyacetic acid (12% in dogs; 22.8% in rats), and unchanged chlorphenesin (30.4% in dogs; 35.5% in rats). Additional urinary end products identified as a conjugate of chlorophenol and a conjugate of chlorphenesin were observed after rats were injected ip with chlorphenesin UL-ring-^{14}C.[13]

Percutaneous Absorption

The percutaneous absorption of ^{14}C-chlorphenesin was evaluated using 16 male rats of the Sprague-Dawley CD strain (~6 weeks old). ^{14}C-chlorphenesin (in 0.05% weight/weight cold cream; mean dose = 1.14 mg/kg [~ 14 μCi]) was applied topically to shaved skin on the back (9 cm^2). Application sites were occluded with aluminum foil until the animals were killed.[14] After test substance application, the animals were placed in individual metabolism cages for the collection of urine and feces. Pairs of animals were killed at various intervals, beginning at 1 hour and ending at 96 hours. The mean total recovery of radioactivity (application site, excreta, selected tissues, and residual carcass) was 92.35% dose ± 3.11 (standard deviation) for the 0 to 96 hours time period. The proportion of administered ^{14}C-chlorphenesin dose that remained at the application site (in and on the skin) decreased from ~89% at 1 hour to ~43% at 96 hours. During the 0 to 96 hours time period, ~48% (mean value) of the applied dose was excreted in the urine. Approximately 0.5% was excreted in the feces and ~0.7% was recovered in cage washings. Thus, practically all of the absorbed dose was excreted in the urine over a period of 96 hours.

Not more than 1% of the applied dose was present in any tissues during the 1 to 96 hours time frame although up to 57% of the dose was absorbed. At 96 hours, ~7% to 8% of the administered dose remained. Apparently, the radioactivity was absorbed biphasically, with initial and terminal half-lives for absorption ≈4 hours and 126 hours, respectively. The urinary excretion rate was proportional to plasma radioactivity concentrations during 0 to 96 hours, suggesting that the renal clearance of radioactivity was concentration independent. The terminal excretion half-life (~22 hours) was considerably shorter than the terminal absorption half-life (~126 hours). Thus, the excretion of radioactivity was absorption rate limited, causing plasma concentrations to remain quite low.[14]

Toxicology

Acute Oral Toxicity

The acute oral toxicity of chlorphenesin (in 0.5% carboxymethylcellulose aqueous gel) was evaluated using 5 groups of 10 (5 males, 5 females/group; ~6 weeks old) Sprague Dawley rats.[15] The 5 groups received single oral doses of 1200, 1620, 2187, 2952, and 3985 mg/kg, respectively. Dosing was followed by a 14-day observation period, after which all surviving animals were killed. The following signs were observed after test substance administration of each dose: dyspnea, decrease in spontaneous activity, hypotonia, piloerection, and loss of reflex. Necropsy findings for animals that died were mainly an intestinal meteorism and lung congestion. A mean lethal dose, 50% (LD_{50}) of 3000 mg/kg (95% confidence interval = 2830-3180 mg/kg) was reported.

Repeated Dose Toxicity

A repeated dose oral toxicity study on chlorphenesin was performed using 4 groups of 16 rats of the Charles River Crl: CD(SD) BR strain (8 males, 8 females/group; 47 days old).[16] Chlorphenesin (suspension in 1% aqueous methylcellulose) was administered by gavage to 3 groups at doses of 10, 100, and 1000 mg/kg/d (dose volume = 10 mL/kg/day), respectively, for 28 consecutive days. Control rats were dosed similarly with 1% aqueous methylcellulose. Except for 1 animal killed during week 4, the animals were killed on day 29. Microscopic examination of the rat (high-dose male) killed during week 4 revealed renal tubular dilatation and necrosis of the papillary tip, both treatment related. No microscopic changes were observed in high-dose female rats or the remaining high-dose male rats. Clinical findings in the highest dose group included hunched posture, abnormal gait, pallor, lethargy, ptosis, a badly groomed appearance, noisy respiration, and piloerection. A badly groomed appearance was also observed in rats of the low-dose (according to the authors, not toxicologically significant) and intermediate-dose groups, and increased salivation was also observed in the intermediate-dose group. Compared to controls, a statistically significant reduction ($P < 0.01$) in body weight gain was noted for male and female rats of the highest dose group. The decreased body weight gain correlated with the decreased food intake. Significantly lower hemoglobin levels were reported for high-dose males and females and intermediate-dose males.

Statistically significant increases ($P < 0.01$) in glutamic pyruvic transaminase were reported for high-dose males and females. Alkaline phosphatase levels in high-dose males were slightly higher when compared to controls, but the difference was not statistically significant. Potassium and calcium ion concentrations were significantly lower ($P < 0.05$) in high-dose females. Immunoglobulin (Ig) G and IgM serum levels in high-dose females, when adjusted for predose levels, were significantly higher than control values at the end of dosing. The authors considered these changes as a reflection of hematological and biochemical changes due to treatment with chlorphenesin and not a specific effect on the immune system. Absolute spleen weights (high-dose males and females) and thymus weights (high-dose males) were significantly lower ($P < 0.05$ or $P < 0.01$) when compared to controls. At macroscopic examination, general brown staining of the fur was observed in all 5 high-dose female rats examined, compared to the absence of this finding in controls. The only microscopic finding (in kidney) is mentioned in the preceding paragraph. The reported changes in the high- and intermediate-dose groups were considered treatment related. A dose of 10 mg/kg/d was considered the no adverse effect level in this study.[16]

Ocular Irritation

The ocular irritation potential of chlorphenesin (1% [weight/volume, w/v] in distilled water) was evaluated using 3 New Zealand albino rabbits (ages not stated).[17] The test substance (0.1 mL) was instilled into the right eye of each animal and the lids were held together for approximately 10 seconds. Untreated left eyes served as controls. The eyes were examined for ocular reactions at 1 hour and then at days 1, 2, 3, 4, and 7 postinstillation. Slight conjunctival irritation (enanthema, chemosis, and lacrimation) was reported for each rabbit and these reactions had cleared by 24 hours postinstillation. Chlorphenesin was classified as a weak ocular irritant (maximum ocular irritation index = 6 [at 1 hour postinstillation]).

Skin Irritation

Nonhuman. The skin irritation potential of chlorphenesin was evaluated using 6 male New Zealand albino rabbits (age not stated).[17] A 2.5 × 2.5 cm occlusive patch containing chlorphenesin (1% [w/v] in distilled water, 0.5 mL) was applied to the shaved flanks of each animal. The right flank was abraded and the left remained intact. Patches were secured with fastening tape and the trunk was wrapped with an elastic bandage secured with adhesive tape. At 24 hours, the patches were removed. Slight, reversible erythema was observed in 2 rabbits and there was no evidence of structural modification. Chlorphenesin was classified as a nonirritant (primary irritation index = 0.1).

Human. A study was performed to investigate the side effects of cosmetic preservatives by evaluating objective and subjective skin irritants.[18] In a 24-hour occlusive patch test involving 30 patients (20 females, 10 males; mean age = 33.7 years), 2% chlorphenesin (20 µL) was applied to filter paper discs on IQ test chambers and patches remained in contact with the forearm for 24 hours. Reactions were evaluated at 30 minutes and 1 day after patch removal. A mean irritation score of 0.17 ± 0.38 was reported. A cumulative skin irritation test was performed using 15 healthy patients (8 females, 7 males; mean age = 29.7 years). The formulations tested were an emulsion base with a preservative mixture consisting of 0.2% methylparaben, 0.1% propylparaben, and 0.25% chlorphenesin and an emulsion base containing 0.2% methylparaben, 0.1% propylparaben, 0.25% chlorphenesin, and 0.3% phenoxyethanol. Each formulation (20 µL) was applied according to the preceding method 3 times per week over a 21-day period. Each patient received 9 applications (same site) of the test substance. For type 1 formulations tested, the highest reported total cumulative irritation mean score was 0.40 ± 0.91. For type 2 formulations, a mean score of 0.87 ± 1.19 was the highest reported.

A facial sensory irritation test was performed using 16 healthy participants (6 females, 10 males; mean age = 28.3 years). A cotton swab soaked with 0.4% chlorphenesin (in 0.5% carbopol solution, 0.5 mL volume) was rubbed briskly and applied (under occlusion) to each side of the nasolabial fold and cheek. Any evidence of a stinging/burning reaction was recorded over a period of 9 minutes. Carbopol (0.5%) solution served as the vehicle control. The sensory irritation potential of 0.4% chlorphenesin (mean score = 0.54) was greater than the control (mean score = 0.22). Emulsion bases (with or without chlorphenesin in preservatives mixture) were tested according to the same procedure. Facial sensory irritation induced by the formula containing methylparaben, propylparaben, and chlorphenesin was greater when compared to the same formula without chlorphenesin.[18]

Facial sensory irritation testing was initially proposed by Frosch and Kligman.[19] In a previous Cosmetic Ingredient Review (CIR) safety assessment of α-hydroxy acids (AHAs),[20] for example, it was concluded that the sensitivity of tissue around the area of the eye to sensory irritation was such that AHA-containing products intended for use near the eye be formulated in such a way as to reduce stinging and burning reactions. The AHAs were also used as dermal irritants.

The acute dose skin irritation potential of 0.3% chlorphenesin (in water) was evaluated using 25 patients (20 females, 5 males; 19 to 62 years old).[21] An occlusive patch containing the test substance (0.1 mL) was applied to the back of each patient for 48 hours. Reactions were scored 20 minutes after patch removal. Faint, minimal erythema was observed in 2 patients and erythema (score = 1) was observed in a third patient. Chlorphenesin was classified as having negligible dermal irritation potential.

Skin Irritation and Sensitization

Nonhuman. Prior to initiation of the sensitization study subsequently, a range-finding test was performed to determine the maximal nonirritant concentration of chlorphenesin.[22] The test involved 3 male albino Dunkin Hartley guinea pigs (ages not

stated). A dorsal surface area of ~60 cm^2 was clipped free of hair, and, on both sides of the spinal column, 3 symmetrical intradermal injections (0.1 mL) of the following preparations were made: (1) 50% Freund Complete Adjuvant (FCA) in distilled water, (2) distilled water, and (3) a 50/50 mixture of 1 and 2. Sites were clipped free of hair 7 days later, and the following concentrations of chlorphenesin (0.5 mL volume) were applied under an occlusive patch for 24 hours: 0.1%, 0.25%, 0.5%, and 1.0% in distilled water. Irritation reactions were scored at 24 hours and 48 hours after patch removal. Irritation was not induced by any of the concentrations tested. Test concentrations of 0.5% and 1.0% were designated for use during the challenge phase of the sensitization study.

The skin sensitization potential of chlorphenesin was evaluated in a modified guinea pig maximization test using 30 female albino Dunkin-Hartley guinea pigs (ages not stated). Test and control groups consisted of 20 and 10 guinea pigs, respectively. Dorsal skin was clipped free of hair, and 3 symmetrical intradermal injections (0.1 mL) of 1% chlorphenesin (in distilled water), 1% chlorphenesin (in a mixture of FCA and distilled water), and a mixture of FCA and distilled water, respectively, were made on both sides of the spinal column (scapular level) during induction of test animals. During induction, control animals were injected with FCA/distilled water mixtures and distilled water. Induction injections were followed by a single 48-hour application of an occlusive patch (2 × 4 cm) moistened with 1% chlorphenesin in distilled water (0.5 mL, test animals) or distilled water (0.5 mL, controls). During the challenge phase, chlorphenesin (1% or 0.5% in distilled water, 0.5 mL) was applied, under occlusive patch (2 × 2 cm), to a new test site for 24 hours. Reactions were evaluated at 24 and 48 hours after patch removal. Chlorphenesin did not induce sensitization in guinea pigs at a concentration of 1%, followed by challenge with 0.5% or 1.0%.[22]

Human. A human repeated insult patch test was used to evaluate the skin irritation and sensitization potential of a test material containing 5% to 9% chlorphenesin.[23] Fifty-five male and female patients (between 27 and 67 years of age) completed the study. Of the original 58 patients, 3 withdrew for reasons unrelated to test material application. During induction, a 1 × 1 in semiocclusive patch containing the test material (0.2 mg/cm^2) was applied to the back, between the scapulae, of each patient. Patches were removed at 24 hours and any irritation reaction was scored 24 hours after patch removal. The scoring of reactions was followed by application of a new patch that remained for 24 hours. This cycle was repeated for a total of 9 consecutive patch applications (ie, 3-week induction phase). The 4-day challenge phase was initiated after a 10- to 14-day nontreatment period. A new patch containing 0.2 mL or 0.2 g of the test material was applied (24 hours) to a new test site on the back. Reactions were scored at 48 and 72 hours postapplication. Neither irritation reactions nor sensitization reactions were observed during the study, and it was concluded that the test material did not have dermal irritation or allergic contact sensitization potential.

The skin irritation and sensitization potential of a different test material containing 12% to 17% chlorphenesin was evaluated using 53 male and female patients (between 18 and 66 years of age).[24] Of the original 56 patients, 3 withdrew from the study and it was stated that 1 of the patients withdrew for reasons unrelated to test material application. The test material (0.2 mL or 0.2 g) was applied using a semiocclusive patch according to the test procedure mentioned earlier. In 1 patient, barely perceptible erythema (score = 0.5) was observed on day 19 of induction and mild erythema (score = 1) was observed on day 22. The mild erythema observed was classified as a transitory, weak response that could be considered clinically insignificant skin irritation. There was no evidence of skin sensitization in any of the patients tested.

In a multicenter study, the prevalence of preservative allergy in 584 patients (from 111 hospital dermatology departments in Korea) with cosmetic contact dermatitis symptoms was investigated.[25] From January 2010 to March 2011, the patients were patch tested to identify preservative allergens. An irritancy patch test (30 normal control participants) involving allergens at various test concentrations was also performed. Study results indicated preservative hypersensitivity in 41.1% of the patients and the allergens with the highest rates were as follows: benzalkonium chloride (12.1%), thimerosal (9.9%), and methylchloroisothiazolinone/methylisothiazolinone (5.5%). Results of the irritancy patch tests identified benzalkonium chloride and chlorphenesin as having the highest irritancy rate. At 4 days, 7 of the 30 normal patients had a positive irritant patch test reading to 0.1% benzalkonium chloride and 8 of 30 had the same reaction to 0.5% chlorphenesin in petrolatum. The authors noted that the maximum concentration of chlorphenesin for avoiding skin reactions is less than 0.5%.

Case Reports

A 38-year-old woman developed widespread acute dermatitis after using a proprietary antifungal powder and cream, both containing chlorphenesin.[26] Signs included severe maceration of the toe webs, with severe eczema of the foot. A generalized rash on the legs, forearms, and hands was also observed. Patch testing of individual constituents of the products used revealed a positive response only to 1% chlorphenesin in petrolatum. No reaction to this test concentration was observed in 3 control participants.

A 60-year-old atopic woman developed facial eczema within several hours after applying a foundation (cosmetic) containing chlorphenesin.[27] Patch testing revealed an allergic response (++ reaction) to 1% chlorphenesin in petrolatum. The patient was not patch tested with the foundation. In a second report, a 33-year-old woman who used a proprietary moisturizing cream containing chlorphenesin had a 1-month history of facial eczema. The eczema eventually involved the entire face and spread to the neck, upper chest, and upper arms. The patient had no personal or family history of atopy. Patch test results indicated a + reaction to 1% chlorphenesin

in petrolatum and a ++++ reaction to the undiluted moisturizer. Both reactions were observed by day 2 and persisted to day 4.

In another case report, a 24-year-old man applied an ointment containing 0.5% chlorphenesin to his feet twice daily to relieve itching.[28] Following 3 days of treatment, a symmetrical vesiculo-bullous eruption was observed on the dorsa of the feet. This reaction extended to the ankles and was accompanied by extensive eczema on the trunk and arms within 24 hours. Patch testing resulted in a ++++ reaction to 0.5% chlorphenesin in white soft paraffin and to the ointment.

Chronic dermatitis of the axillae was reported for a 29-year-old woman who used a deodorant that contained chlorphenesin.[29] She also had a past history of allergy to metallic jewelry. Patch results for the deodorant were positive at 48 hours (+ reaction) and 96 hours (+ reaction) and patch test results for 1% chlorphenesin in petrolatum were positive at 48 hours (+ reaction) and 96 hours (++ reaction). Positive reactions were not observed in 5 control participants patch tested with 1% chlorphenesin in petrolatum.

A 43-year-old woman experienced burning discomfort and developed a florid eczema after applying a facial moisturizer containing chlorphenesin.[30] The patient had a history of hay fever but no history of medicament or cosmetic intolerance. Patch test reactions were positive (++) for chlorphenesin on days 2 and 4. Positive patch test reactions were also reported for the product on day 2 (++) and day 4 (+).

Photoallergenicity

Eleven patients photoallergic to ketoprofen (a nonsteroidal anti-inflammatory drug) were photo patch tested with chlorphenesin.[31] Testing was initiated on day 0 and the patients were irradiated with UVA light (5 J/cm^2) at day 2. Readings were obtained on days 3 and 4. There were no positive reactions in patients photo patch tested with chlorphenesin.

Immunosuppression

The immunosuppressive activity of chlorphenesin was evaluated using groups of 3 to 4 albino rabbits.[32] The groups were immunized with 1 mL of antigen (gram-positive bacteria [CA+] alone or antigen + chlorphenesin). A total of 3 intravenous (iv) injections (1 mL) of each was made on days 0, 3, and 7 according to the following procedure: group 1 (control) received the mixture of 1 part of CA(+) antigen (final dilution of 1:100) and 9 parts of buffer. Group 2 received a mixture of 1 part of antigen and 9 parts of chlorphenesin at concentrations of 0.01, 0.1, 1, or 10 mg/mL. Prior to injection, these mixtures were incubated (37°C) for 30 minutes. Group 3 received the same antigen–chlorphenesin mixtures without prior incubation. The fourth group received antigen and chlorphenesin, albeit separate injections. When tested at a concentration of 1 or 10 mg/mL, but not 0.01 or 0.1 mg/mL, chlorphenesin markedly inhibited the CA (−) hemagglutinin response. It was also noted that injection of the nonincubated mixture and separate administration of the 2 materials into separate ear veins caused an undiminished immune response. The results of additional experiments indicated that chlorphenesin suppressed antibody formation less effectively when larger amounts of antigen were used. With smaller amounts of antigen, chlorphenesin partially inhibited the antibody response, even at a concentration of 0.1 mg/mL.

The immunosuppressive activity of chlorphenesin was studied using a wide variety of in vitro assays for cellular immunity in both humans (25-40 years old) and mice (6-11 months old) of the following strains: BALB/c, C57Bl/6, and BDF$_1$ (C57Bl × DBA) F$_1$ mice.[33] At concentrations of 20 to 50 µg/mL, chlorphenesin inhibited mitogenic responses of B and T cells from mice and humans. Exposure to these doses for 72 hours did not result in death of B or T cells. Mixed lymphocyte reactions in cells from inbred strains of mice and unrelated humans were also inhibited at concentrations of approximately 50 µg/mL. In light of these results, the generation of cytotoxic T cells in cell-mediated lympholysis assays was not inhibited to the same extent as proliferation in mixed lymphocyte reactions. Also, the cytotoxic potential of presensitized mouse T cells for allogeneic targets was totally unaffected. The results of these studies suggest that chlorphenesin may have a broad spectrum of suppressive effects on both B and T lymphocytes and that the predominant inhibition of proliferative responses in these lymphocytes may reduce the expansion of clones of immunocompetent cells in vivo.

The effect of chlorphenesin on the immune response in mice, rabbits, and guinea pigs was studied.[34] Male Swiss Webster mice were injected with chlorphenesin mixed with sheep red blood cells or chicken red blood cells or penicillin conjugated with keyhole limpet hemocyanin, iv (volume = 0.1 mL). An assay for localized hemolysis was then performed, in which the degree of hemolysis was determined after 2 hours. Groups of 4 to 8 New Zealand White rabbits were used to determine the presence of circulating antibodies. The antigens were injected into the hind footpads and subcutaneously over each shoulder. The rabbits were bled and tested for antibody titers for up to 21 days postimmunization. Male albino guinea pigs were sensitized with BCG vaccine intradermally and challenged intradermally with tuberculin at 5 weeks postsensitization. In the localized hemolysis assay, partial hemolysis was noted at a chlorphenesin concentration of 10 mg/mL. The joint administration of an antigen with chlorphenesin (50 mg/kg dose) greatly reduced the number of antibody-forming cells in the spleen. The simultaneous administration of antigen with chlorphenesin also resulted in suppression of formation of humoral antibodies in mice and rabbits. Chlorphenesin was effective as an immunosuppressive agent only when administered jointly with an antigen, did not affect existing antibody levels or the secondary response, and did not increase the susceptibility of the animals to infections. If administered at the time of challenge, chlorphenesin (100 and 200 mg/kg doses) affected the bacillus Calmette-Guérin reaction (ie, significantly decreased the reaction to tuberculin) in guinea pigs.

Reproductive and Developmental Toxicity

The effect of chlorphenesin (suspension in 1% methylcellulose) on pregnancy and in utero development of the rat was evaluated using 4 groups of 25 sexually mature, specific pathogen-free female rats of the Crl: CD BR VAF/Plus strain (8 to 10 weeks old).[35] Three groups received oral doses (gavage; 10 mL/kg body weight) of 10, 50, and 100 mg/kg, respectively, once daily on days 6 to 15 postcoitum. The control group was dosed with the vehicle (1% methylcellulose) according to the same procedure. The animals were killed on day 20 and necropsy was carried out to identify any congenital abnormalities or macroscopic pathological changes in maternal organs. Tissues were preserved for microscopic examination. There was no evidence of maternal toxicity at any of the 3 administered doses, and neither maternal body weight gain nor food intake was affected by treatment. Increased fur loss and transient postdosing salivation were observed in the highest dose (100 mg/kg/d) group. Based on necropsy results, it was considered unlikely that fur loss was test substance related. At all doses administered, chlorphenesin had no adverse effect on embryo–fetal survival, growth, or development in utero. The no observed effect level for selective toxicity to the developing fetus was considered to be 100 mg/kg/d.

Genotoxicity

The genotoxicity of chlorphenesin was evaluated in the Ames test (bacterial reverse gene mutation assay) using the following *Salmonella typhimurium* strains: TA98, TA100, TA1535, TA1537, and TA1538.[36] Test concentrations up to 5000 µg/plate were evaluated with and without metabolic activation . 2-Aminoanthracene served as the positive control for metabolic activation cultures and 2-nitrofluorene, 9-aminoacridine, and *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine served as positive controls for nonactivation cultures. Chlorphenesin was not genotoxic with or without metabolic activation over the range of concentrations tested. The positive controls were genotoxic. The same conclusion was reached in another Ames test evaluating the genotoxicity of chlorphenesin in *Salmonella typhimurium* strain TA102 and *Escherichia coli* strain WP2 uvrA over the same test concentration range (with and without metabolic activation).[37] Both positive controls (2-aminoanthracene and methyl methane sulfonate [nonactivation]) were genotoxic to both strains.

Chlorphenesin was also evaluated in a forward gene mutation assay using Chinese hamster ovary cells.[38] The test substance was evaluated at concentrations up to 1500 µg/mL with and without metabolic activation. In this assay, forward mutation at the functionally hemizygous hypoxanthine-guanine phosphoribosyl transferase locus is detected by the ability of the cells that have had genetic damage at this locus to form colonies in the presence of 6-thioguanine. Dimethyl sulfoxide served as the vehicle control and ethyl methanesulfonate (without metabolic activation) and 20-methylcholanthrene (20-Mc, with metabolic activation) served as positive controls. Without and with metabolic activation, dose-related cytotoxicity was noted at concentrations >850 µg/mL and >550 µg/mL, respectively. No significant correlation between mutant frequency and increasing dose levels was induced by chlorphenesin either with or without metabolic activation. Neither chlorphenesin nor the vehicle control was genotoxic with or without metabolic activation, whereas the positive controls exhibited the expected genotoxicity.

Carcinogenicity

Antitumorigenicity

In a study involving groups of Strain A (inbred strain) female mice, immune competence during initiation–promotion carcinogenesis was determined by the length of time required to reject allografts of tail skin and by the incorporation of [^{3}H]thymidine by lymphocytes in culture stimulated with the mitogens phytohemoagglutinin (PHA) and pokeweed mitogen (PWM).[39]

During initiation–promotion carcinogenesis, mice were also treated with chlorphenesin, predicated on its reported effects to increase immunological reactivity, particularly cellular immunity. The skin grafting experiment for determining immune competency involved 5 groups of mice. The animals were not dosed with chlorphenesin. Initially, 2.5% croton oil (20 µL) was applied to the intrascapular area twice per week for 30 weeks and mice were then treated with a single application of 7,12-dimethylbenzanthracene (DMBA, 100 µg) 10 days later. The mice were then separated into 2 groups, those with and without tumors. In order to study the effect of the initiating and promoting agents, DMBA (100 µg) was applied to the interscapular area of each animal in the third group at 10 days before grafting. The fourth group was treated only with 2.5% croton oil (20 µL) according to the same procedure, and the fifth group served as the untreated control group. The allografts of the DMBA plus croton oil-treated, tumor-bearing mice were retained significantly longer ($P < 0.02$) than were the grafts on either the control mice or the DMBA plus croton oil-treated mice that had not developed tumors. The mice that received 1 application of DMBA 10 days before grafting were also inhibited ($P < 0.02$) from rejecting their skin grafts.

The experiment using lymphocyte cultures also involved 5 groups of mice. Groups 1 and 2 were treated with DMBA and croton oil, respectively (same doses), and group 3 received two 2.5-mg doses of chlorphenesin ip (same day). Group 4 received a dermal application of croton oil and 2 ip doses of chlorphenesin and group 5 served as the untreated control group. The mitogenic response of lymphocytes to PHA and PWM was determined using whole blood lymphocyte cultures. Chlorphenesin inhibited the stimulation of PWM mitogenesis observed in lymphocytes from croton oil-treated mice.

The tumor initiation–promotion experiment involved 2 groups of 30 Swiss mice. In the first group, DMBA (100 µg) was applied to the interscapular area of each animal,

and, after 3 weeks, 2.5% croton oil was applied to the skin twice weekly for 20 weeks. Group 2 animals received applications of DMBA and croton oil plus two 2.5-mg injections of chlorphenesin ip (same day) at the same time that croton oil was applied. The animals were necropsied at 20 weeks. The carcinogen DMBA inhibited the cellular immune competence of mice, and lymphocytes from mice treated with croton oil had enhanced PWM response. Chlorphenesin inhibited tumorigenesis in initiation–promotion skin carcinogenesis when injected during promotion.[39]

Female Swiss mice were injected ip (day 0) with 0.2 mL of Rauscher murine leukemia virus (RMLV) or Friend murine leukemia virus (FMLV) suspension and distributed randomly into paired groups of 18 to 20 mice each.[40] Chlorphenesin in warm Hank balanced salt solution (HBSS) was then injected ip (dose = 100 mg/kg in 0.5 mL) in the morning and late afternoon on each day of treatment. Chlorphenesin was injected into the RMLV mice on days 1, 2, 3, 4, 7, and 8 and FMLV mice received injections on days 1, 2, 6, 7, 9, 12, and 13. Control mice were injected with HBSS only after virus injection according to the same schedules. Injected virus routinely resulted in 80% mortality in leukemic control groups within 50 to 60 days. Chlorphenesin caused a pronounced sparing effect on mortality due to leukemia after infection with RMLV. Delayed onset of early death in chlorphenesin-treated mice was observed, but the most characteristic finding was the marked sparing effect in later stages of the disease. Mortality in mice dosed with chlorphenesin leveled off at 40%; however, controls continued to die at a nearly constant rate.

Additional experiments evaluating antiviral activity suggested that chlorphenesin was probably acting on malignant cells rather than against the transforming virus. In an effort to confirm this, Leukemia L-1210 in ascites form was implanted sc into B6DF1 mice and results indicated that chlorphenesin had little effect against conventional massive ip doses of this highly malignant cell line. However, when the system was modified using reduced numbers of cells implanted sc, the sparing effect was readily demonstrable. Although all control mice survived the 50-day study period, more than 40% of the treated mice survived until the experiment was terminated at 50 days, at which time there was no visible evidence of residual tumor.

Clinical trials involving patients with cancer were conducted by the Clinical Screening Group of the European organization for Research on Treatment of Cancer. Patients (31) with a wide range of neoplasms had been treated with chlorphenesin for periods ranging from 1 to 6 weeks. Oral doses ranged from 1 to 6 g daily, with a usual dose of 4 g/day. Treatment with chlorphenesin was ineffective in 16 cases of carcinoma (cervix, uterus, tonsil, esophagus, and lung) and in 4 cases of sarcoma. However, in 9 cases of squamous cell carcinoma of the skin, complete remission was achieved in 1 patient and substantial, though incomplete, remission was achieved in 4 other patients. Also, for 2 patients with basal cell carcinoma, no benefit was observed.[40]

Summary

Chlorphenesin, a biocide, is produced by condensing equimolar amounts of *p*-chlorophenol and glycidol in the presence of a tertiary amine or a quaternary ammonium salt as a catalyst. According to information supplied to the FDA by industry as part of the VCRP in 2012, chlorphenesin was being used in 1386 cosmetic products. Furthermore, results from a survey of ingredient use concentrations provided by the Personal Care Products Council in 2011 indicate that chlorphenesin was being used at concentrations up to 0.32% (rinse-off products) and up to 0.3% (leave-on products). Similarly, the maximum authorized use of this ingredient as a preservative in cosmetic products marketed in the EU is 0.3%.

Some confusion in terminology may result because the drug chlorphenesin carbamate (CAS No. 886-74-8) has also been referred to as chlorphenesin. Chlorphenesin carbamate is a muscle relaxant whereas the cosmetic ingredient chlorphenesin (CAS No. 104-29-0) is not.

The results of a toxicokinetic study (oral dosing) involving rats and dogs indicated that chlorphenesin was rapidly absorbed and excreted mainly in the urine. Urinary end products identified included 3-*p*-chlorophenoxylactic acid, *p*-chlorophenoxyacetic acid, and unchanged chlorphenesin. In an *in-vivo* percutaneous absorption study involving rats, up to 57% of the applied dose was absorbed and practically all of the absorbed dose was excreted in urine over a period of 96 hours.

In an acute oral toxicity study (rats), a mean oral LD_{50} of 3,000 mg/kg was reported for chlorphenesin. Repeated oral dosing of rats with chlorphenesin for 28 days caused a significant decrease in body weight gain and significantly lower hemoglobin levels in the highest dose group (1,000 mg/kg/day) when compared to controls. Significantly decreased spleen and thymus weights were also reported for this group. The only treatment-related microscopic finding in the study, renal tubular dilatation/necrosis, occurred in one male rat from the highest dose group. A badly groomed appearance and increased salivation were observed in the 100 mg/kg/day dose group. A dose of 10 mg/kg/day was considered the no adverse effect level in this study.

Chlorphenesin was classified as a weak ocular irritant when instilled into the eyes of rabbits at a concentration of 1%. The same test concentration did not induce skin irritation when applied, under an occlusive patch, to rabbits for 24 hours. Negligible dermal irritation was observed in 3 of 25 patients tested with 0.3% chlorphenesin in a 48-hour occlusive patch test. In a facial sensory irritation test involving 16 healthy patients, irritation induced by a formula containing methylparaben, propylparaben, and chlorphenesin (0.4%, in 0.5% aqueous carbopol vehicle) was greater when compared to the same formula without chlorphenesin. In the guinea pig maximization test, chlorphenesin did not induce sensitization at a concentration of 0.5% or 1%. These 2 concentrations were classified as nonirritating in a preliminary test to determine the maximal irritant concentration.

In a human repeated insult patch test (HRIPT) involving 55 patients, a test material containing 5% to 9% chlorphenesin did not exhibit skin irritation or allergic contact sensitization potential. A test material containing 12% to 17% chlorphenesin induced clinically insignificant erythema in 1 of 53 patients in another HRIPT; skin sensitization was not observed in any of the patients. When 11 patients photoallergic to ketoprofen were photo patch tested with chlorphenesin, results were negative. In case reports, positive patch test reactions to 0.5% and 1% chlorphenesin were reported.

In a study evaluating the immunosuppressive activity of chlorphenesin in albino rabbits, marked inhibition of the CA (+) hemagglutinin response was observed at test concentrations of 1 or 10 mg/mL but not 0.01 or 0.1 mg/mL. In other animal studies, the simultaneous administration of antigen with chlorphenesin resulted in suppression of formation of antibodies in mice and rabbits. When the immunosuppressive activity of chlorphenesin was studied using a wide variety of in vitro assays for cellular immunity in both human and mouse test systems, the results suggested that it may have a broad spectrum of suppressive effects on both B and T lymphocytes. However, dosing with chlorphenesin did not increase the susceptibility of animals to infections in vivo.

Chlorphenesin had no adverse effect on embryo fetal survival, growth, or development in utero when administered orally to rats at doses up to 100 mg/kg/d on days 6 to 15 postcoitum. In the Ames test, chlorphenesin was not genotoxic to the following bacterial strains when tested at concentrations up to 5000 µg/plate, with or without metabolic activation: *S typhimurium* strains TA98, TA100, TA102, TA1535, TA1537, and TA1538 and *E coli* strain WP2 uvrA. Chlorphenesin was also not genotoxic, with or without metabolic activation, in a forward mutation assay using Chinese hamster ovary cells.

In an initiation–promotion experiment designed to assess the antitumorigenic activity of chlorphenesin, DMBA (100 µg) was applied to the interscapular area of each of 30 mice and, after 3 weeks, 2.5% croton oil was applied to the skin twice weekly for 20 weeks. A second group of 30 mice received applications of DMBA and croton oil plus two 2.5 mg injections of chlorphenesin ip (same day) at the same time that croton oil was applied. Chlorphenesin inhibited tumorigenesis when injected during promotion. In another study, mice previously injected with murine leukemia virus (RMLV or FMLV) were injected ip with 100 mg/kg chlorphenesin for up to 7 days. Chlorphenesin caused a pronounced sparing effect on mortality due to leukemia after infection with RMLV. Thirty-one patients with cancer received chlorphenesin orally at a usual daily dose of 4 g/day for 1 to 6 weeks. Treatment was ineffective in 16 cases of carcinoma (cervix, uterus, tonsil, esophagus, and lung) and in 4 cases of sarcoma. However, in 9 cases of squamous cell carcinoma of the skin, complete remission was achieved in 1 patient and substantial, though incomplete, remission was achieved in 4 other patients.

Discussion

The CIR Panel noted that the drug chlorphenesin carbamate (CAS No. 886-74-8), sometimes referred to as chlorphenesin, has muscle relaxant effects not expected for the cosmetic ingredient, chlorphenesin (CAS No. 104-29-0).

Chlorphenesin induced low acute oral toxicity in rats, exhibited a no observable adverse effect level of 10 mg/kg/d in a 28-day repeated oral toxicity study involving rats, and elicited minimal ocular irritation potential in rabbits. Chlorphenesin was not a dermal irritant, sensitizer, or photosensitizer in animals or humans, except in a very small number of case reports. Chlorphenesin is not genotoxic in bacterial or mammalian assays. Oral and other carcinogenicity studies suggested antitumor activity. The ingredient was not an oral reproductive or developmental toxicant. When applied to the skin, chlorphenesin was well absorbed.

The Panel acknowledged the potential immunosuppressive activity of chlorphenesin, based on in vitro assay results. However, after considering that dosing with chlorphenesin did not increase the susceptibility of animals to infections or act as a tumor promoter in in vivo studies, it was agreed that there would be very little to no safety concern relating to the immunosuppressive activity of chlorphenesin as an ingredient under current conditions of use in cosmetic products.

The Panel considered the study in which chlorphenesin was reported to increase the sensory irritation potential of some creams, especially when used concomitantly with parabens + phenoxyethanol. The Panel had evaluated such sensory irritation potential when it considered AHA ingredients and determined that the sensitivity of tissue around the area of the eye to sensory irritation was such that AHA-containing products intended for use near the eye be formulated in such a way to reduce stinging and burning reactions. The AHA ingredients, however, were also known dermal irritants, whereas chlorphenesin is not. Concerns about sensory irritation may be more relevant for baby products, for example, diaper creams. Chlorphenesin, however, is not reported to be used in baby products.

Conclusion

The CIR Expert Panel concluded that chlorphenesin is safe in the present practices of use and concentration described in this safety assessment.

Authors' Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1620 L St. NW Suite 1200 Washington, DC 20036, USA.

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