化粧品產品資訊檔案(範例)

<玩色染髮-瞬時棕>

＜PIF **無特定之格式**，本範例**僅提供參考用**＞

中華民國 111 年 7 月

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I. 產品敘述

(1) 產品基本資料

項目	內容描述
產品名稱(中文/英文)	玩色染髮-瞬時棕 (第一劑、第二劑) Hair dye Brown (First dose、Second dose)
產品類別	頭髮用化粧品類
產品劑型	第一劑-乳劑、第二劑-液劑
用途	染髮
製造作業場所資訊	製造廠名稱：XX 化粧品股份有限公司 廠址：○○市○○區○○路○○號 國別：台灣
包裝作業場所資訊	包裝廠名稱：YY 股份有限公司 廠址：○○市○○區○○路○○號 國別：台灣
產品製造業者資訊	製造業者：AJP 化粧品股份有限公司 地址：oo 市 oo 路 oo 段 XX 號 公司負責人：李○基 聯絡電話：02-2xxx-xxxx 統一編號：0123XXXX

(2) 完成產品登錄之證明文件

登錄號碼：0123XXXXTEST1000000000

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

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

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

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

(3) 全成分名稱及其各別含量

第一劑

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

第二劑

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

*供應商：ABC Company

(4) 產品標籤、仿單、外包裝或容器

項目	資 料
內包裝/容器 第一劑(正反面)	 
內包裝/容器 第二劑 (正反面)	 

外盒	
標籤/仿單	內容物：玩色染髮-瞬時棕染髮劑(第一劑、第二劑)、拋棄式手套、梳子。 品名：玩色染髮-瞬時棕(第一劑、第二劑) 用途：染髮 用法： (1)染髮前：請先將頭髮洗淨擦拭，濕度呈半乾燥狀態。 (2)戴上拋棄式手套，將第一劑及第二劑等比例混合攪拌均勻。 (3)使用梳子沾取混合後玩色染髮-瞬時棕染髮劑均勻塗抹於髮絲上，直到玩色染髮-瞬時棕染髮劑覆蓋所有頭髮。 (4)等待 30~40 分鐘，建議不超過 60 分鐘。(靜置時間越久可能導致髮色呈深黑色)將剩餘玩色染髮-瞬時棕染髮劑建議丟棄，混合後染髮劑放置過久會失去染髮作用。 (5)靜置時間完成後，請徹底將頭髮上玩色染髮-瞬時棕染髮劑沖洗乾淨，並將髮絲吹整至乾燥。 (6)染髮後髮色會因為個人髮色與髮質有所不同。 保存方法：避免高溫及日光直射，置於孩童伸手不及之場所。 使用注意事項：染髮劑使用前、染髮操作、避免使用染髮劑對象、儲放注意事項請詳見外盒標示，並依據使用方法正確使用。 製造業者名稱/地址/電話號碼： AJP 化粧品股份有限公司 / oo 市 oo 路 oo 段 XX 號 / 02-2xxx-xxxx 製造日期及保存期限： 製造日期：2021.07.05、保存期限：2024.07.04。 批號：P018AUG 容量： 第一劑 40 mL / 第二劑 40 mL 全成分-第一劑： 特定用途成分：

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

(5) 製造場所符合化粧品優良製造準則之證明文件或聲明書

衛 生 福 利 部

化 粧 品 優 良 製 造 證 明 書

證號：(C)GMPOOOO-OOO

製造廠（場所）名稱：

製造廠（場所）地址：

核定劑型及作業項目：

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

衛生福利部

發 證 日 期：　　年　　月　　日
有 效 日 期：　　年　　月　　日

XXXX(流水號)

符合化粧品優良製造準則聲明書(範例)

符合化粧品優良製造準則聲明書

Declaration of Conformity

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

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

一、製造廠名稱：

Manufacturer's Name

二、製造廠地址：

Manufacturer's Address

三、產品劑型：

Product forms

四、作業項目：

The process of operations

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

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

立聲明書人：　　(Signature)

Applicant

負責人/代表人：　　(Signature)

Person in charge

統一編號或身分證字號：

Company Tax ID No. / ID Number

地址：

Address:

申請廠商蓋公司章

負責人或代表人章

中 華 民 國　　年　　月　　日

Date　　year　　month　　day

(6) 製造方法、流程

第一劑

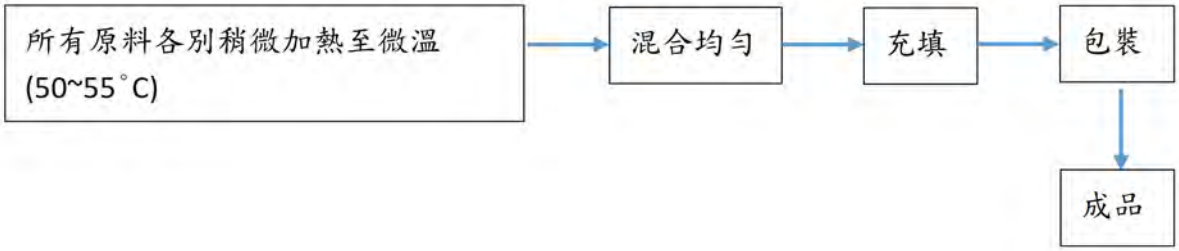
INCI Name	w/w%
Aqua	55.0
Alcohol	30.0
Polysorbate 80	5.0
Dimethicone	3.0
Ammonia (28% Solution)	2.0
p-Phenylenediamine	2.0
Resorcinol	1.0
Ammonium Laureth Sulfate	1.0
Sodium Bisulfite	0.5
m-Aminophenol	0.3
Disodium EDTA	0.1
Fragrance	0.1

製程簡述：

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

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

製程流程圖：



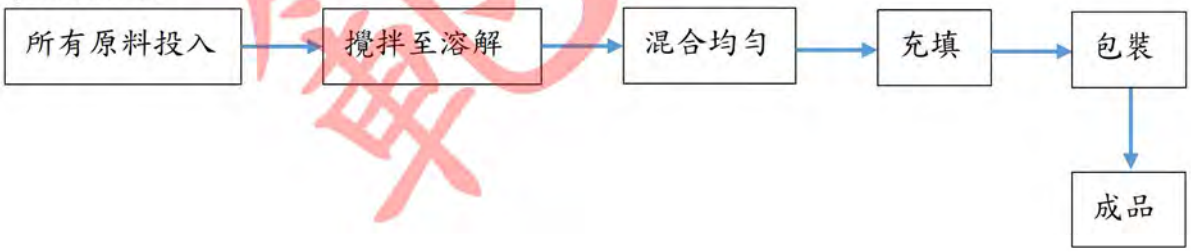
第二劑

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

製程簡述：

1. 將所有原料投入料桶，攪拌至完全溶解。
2. 確認混合均勻即可。

製程流程圖：



(7) 使用方法、部位、用量、頻率及族群

使用方法：

(1)染髮前：請先將頭髮洗淨擦拭，濕度呈半乾燥狀態。

(2)戴上拋棄式手套，將第一劑及第二劑等比例混合攪拌均勻。

(3)使用梳子沾取混合後染髮劑均勻塗抹於髮絲上，直到染髮劑覆蓋所有頭髮。

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

(5)靜置時間完成後，請徹底將頭髮上染髮劑沖洗乾淨，並將髮絲吹整至乾燥。

(6)染髮後髮色會因為個人髮色與髮質有所不同。

使用部位：頭髮。

用量：每次染髮使用第一劑 40 mL、使用第二劑 40 mL。

使用族群：適用於頭髮及頭皮無受損之成年人。

使用頻率：每 3 個月 1 次 (每次染髮至少間隔 3 個月) 。

(8) 產品使用不良反應資料

目前本產品尚未有任何不良反應事件報告。如有不良影響和嚴重不良影響的資料時會立即更新於本產品資訊檔案，並及時提供給安全資料簽署人員。

II. 品質資料

(9) 產品及各別成分之物理及化學特性

成品規格檢驗報告

第一劑

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

第二劑

第二劑 成品 CoA			
檢測項目	規格	實際檢驗結果	檢驗方法
外觀	流動液體	流動液體	目視
顏色	白色不透明	白色不透明	目視
氣味	添加香精	具香氣	嗅覺
pH	4.0 ± 0.5	3.85	使用已校正之 pH meter 依 pH meter 檢測方法測定
密度	1.05 ± 0.05 g/cm^3	1.02 g/cm^3	定量瓶
微生物規格	生菌數< 1000 cfu/g 不得檢出： 大腸桿菌 金黃色葡萄球菌 綠膿桿菌 白色念珠菌	生菌數 未檢出 (<10 cfu /g)； 大腸桿菌 陰性； 綠膿桿菌 陰性； 金黃色葡萄球菌 陰性； 白色念珠菌 陰性；	參考衛生福利部食品藥物管理署 109.07.28 及 111.04.21 公布建議檢驗方法-化粧品中微生物檢驗方法及化粧品中白色念珠菌之檢驗方法。
檢測人員/日期		(請簽名並加上日期)	
複核人員/日期		(請簽名並加上日期)	

各成分物理化學特性

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

Aqua CoA			
檢測項目	規格	實際檢驗結果	檢驗方法
pH	6.0~8.5	7.15	使用已校正之線上(on line) pH meter 測定
導電度	<20 µS/cm	16.9 µS/cm	使用已校正之線上(on line)導電度計測定
微生物規格	生菌數< 100 CFU/mL	生菌數 未檢出 (<10 cfu /mL)；	參考環境保護署環境檢驗所公告之水中總菌落數檢測方法測定
檢測人員/日期		(請簽名並加上日期)	
複核人員/日期		(請簽名並加上日期)	

INCI name：Alcohol

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

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

INCI name：Polysorbate 80

Certificate of Analysis

Product Name:

TWEEN® 80

CAS Number:

9005-65-6

TEST

SPECIFICATION

hydroxyl value

74.7

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

INCI name：Dimethicone

Certificate of Analysis

(Representative Sample Certificate)

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

Expiration Date: 24 months from production date

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

INCI name：Ammonia (28% Solution)

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

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

Description

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

Properties

Chemical Formula:

Molecular Weight: 35.05

General Information:

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

Product Code: AA005

CAS No.: 1336-21-6

Hazard and Safety Data

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

Quality Specification

Typical Assay: 28.0 - 30.0 % w/w

Specific Properties and Impurities [Typical levels]:

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

INCI name：p-Phenylenediamine

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

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

p-Phenylenediamine 為強皮膚致敏劑，純度相關 COA

10.5 Impurities

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

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

▸ Hazardous Substances Data Bank (HSDB)

10.6 Formulations/Preparations

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

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

▸ Hazardous Substances Data Bank (HSDB)

INCI name：Resorcinol

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

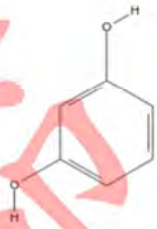
1. PHYSICAL AND CHEMICAL PROPERTIES

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

2. ANALYTICAL DATA

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

3. CHEMICAL STRUCTURE

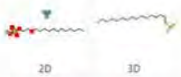


4. USAGE GUIDE

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

INCI name：Ammonium Laureth Sulfate

Ammonium lauryl ether sulfate

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

3.1 Computed Properties

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

INCI name：Sodium Bisulfite

Product Specification

Product Name:
Sodium bisulfite - ACS reagent

$NaHSO_3$

Formula:	NaHSO3
Formula Weight:	104.06 g/mol

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

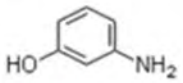
INCI name：m-Aminophenol

TECHNICAL DATA SHEET

Product: ***m-Aminophenol***

CAS No.: 591-27-5

Molecular structure:



Molecular formula: C6H7NO

Molecular weight: 109.13

Specifications:

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

Application:

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

Storage:

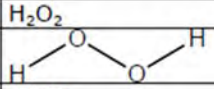
Keep container tightly closed in a dry, cool and well-ventilated place.

INCI name：Disodium EDTA

Product name: **Disodium edetate**

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

INCI name：Hydrogen Peroxide (28% Solution)

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

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

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

INCI name：Glycerin

Certificate of Analysis

GLYCERIN

Glycerin 99.7% USP / Kosher Grade

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

INCI name：Urea

CERTIFICATE OF ANALYSIS

Name of Product : Urea AR

CAS No. : 57-13-6

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

(10) 成分之毒理資料

- 由 AJP 化粧品股份有限公司及安全資料簽署人員查詢蒐集之各個成分毒理資料，另存放於玩色染髮-瞬時棕成分毒理資料檔案夾(附錄 2)。
- 安全資料簽署人員依據上述資料內容摘錄各成分相關毒理資料如下：

1. INCI name：Alcohol

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

每天≥3600 mg/kg bw/day 濃度下觀察到不利的肝臟作用。[1]

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

- 參考資料：

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

2. INCI name：Polysorbate 80

- 暴露途徑：經皮膚吸收、眼睛接觸吸收、吸入。[2]
- 不純物：製造過程中，需將聚山梨酯(Polysorbate)進行蒸餾以去除不需要的水溶性副產物，例如：1,4-二噁烷(1,4-Dioxane)。由於聚乙二醇 (Polyethylene glycol, PEG)是環氧乙烷(ethylene oxide)與水的縮合產物，其鍊長取決於聚合的環氧乙烷之摩爾數，因此它們可能含有 1,4-Dioxane 不純物（乙氧基化的副產物）。1,4-Dioxane 是已知的

動物致癌物，美國食品藥物管理局(U.S. Food and Drug Administration, FDA) 一直在定期監測化粧品中 1,4-Dioxane 的含量，根據化粧品行業報告顯示已知 1,4-Dioxane 可能是 PEG 中的製程中生成之不純物，因此，在摻入化粧品配方前須另進行純化步驟以降低其殘留量。[1]

- 重複劑量毒性：90 天以狗為試驗對象對於 Polysorbate 80 最高口服 NOAEL 為 5 mL/kg bw/day，大鼠 4 週試驗中對於 Polysorbate 80 的最高口服 NOAEL 為 5 mL/kg bw/day。鼻腔給藥方式給予小鼠 0.2% Polysorbate 80 的 NOAEL 為 10 µL /鼻腔/day。在對 Sprague-Dawley 大鼠(n = 6 /性別)高脂餵食 28 天後，口服 28 天的 Polysorbate 80 (148、740 或 3700 mg/kg bw/day)，無不良反應或致命的報導，但尚不清楚大鼠在施用 Polysorbate 80 期間是否繼續高脂飲食。對大鼠使用 Polysorbate 80 進行的亞慢性研究(NTP, 1992a)顯示，NOAEL 相當於 4500mg/kg bw/day。在大鼠膳食亞慢性研究(BIBRA, 1981)中，確定的 NOAEL 相當於 1460 mg/kg bw/day。[1]
- 生殖毒性：在一項生殖和發育研究中，在妊娠第 6 天，透過管飼法對 25 隻 Crl：CD BR VAF/Plus TM 大鼠餵食 Polysorbate80（在蒸餾水中濃度為 500 和 5000 mg/kg bw/day；5 mL），對照組接受 5 mL/kg 蒸餾水。據實驗結果顯示母親和發育中胎兒的 NOAEL >5000 mg/kg bw/day。未觀察到產婦死亡或與治療有關的毒性中毒臨床症狀，對體重增加、器官重量(非不利的相對肝臟重量增加)以及飼料和水的消耗沒有影響，在實驗組和對照組之間沒有觀察到畸形的差異。[1]
- 致癌性：在已發表的文獻中未發現有關聚山梨酯的致癌性數據。[1]
- 細胞/遺傳毒性：Polysorbate 80 對鼠傷寒沙門氏菌(菌株 TA1535、TA1537、TA98 和 TA100)和大腸桿菌(菌株 WP2 uvr A)遺傳毒性試驗，濃度高達 5000 µg/plate（在 Alcohol 中），無論在有或沒有代謝活化的情況下，均無遺傳毒性，對照均達到預期的結果。[1]
- 皮膚刺激性：在人體刺激性研究中，乙氧基化的聚山梨酯 60 (100%)，Polysorbate 80 (100%)和脫水山梨糖醇單硬脂酸酯(25%)對皮膚無刺激性。[1]
- 毒理代謝動力學：使用 Franz 體外穿透試驗發現 Polysorbate 80 增強硫酸鹽穿過大鼠皮膚，提高皮膚滲透率。[1]
- 其他安全資料：Polysorbate 20、Polysorbate 21、Polysorbate 40、Polysorbate 60、Polysorbate 61、Polysorbate 65、Polysorbate 80、Polysorbate 81 和 Polysorbate 85 的安全性，經 CIR 專家小組評估科學數據並得出結論，Polysorbate 20、21、40、60、61、65、80、

81 和 85 作為化粧品成分是安全的。Polysorbate 80 已獲得 FDA 批准作為眼科緩和劑，可用於非處方藥(Over The Counter, OTC)眼科藥物產品。Polysorbate 是一系列聚氧乙烯化脫水山梨糖醇酯，它們的不同之處在於聚合氧乙烯亞單元的數量以及存在的脂肪酸基團的數量和類型。CIR 專家小組表示 Polysorbate 不是誘變劑或完全致癌物。現有數據顯示，這些成分被用於許多製劑中，但沒有出現明顯不良反應的臨床報告。[3,4]

◆ 參考資料：

1. Safety Assessment of Polysorbates as Used in Cosmetics. CIR, March 31, 2015.
2. Scientific Opinion on the re-evaluation of polyoxyethylene sorbitan monolaurate (E432), polyoxyethylene sorbitan monooleate (E433), polyoxyethylene sorbitan monopalmitate (E 434), polyoxyethylene sorbitan monostearate (E435) and polyoxyethylene sorbitan tristearate (E436) as food additives. EFSA Journal 2015;13(7):4152.
3. Food Safety Commission, Evaluation report of food Additives. Polysorbates (Polysorbates 20, 60, 65 and 80), 2007. Original: Japanese- Available. from: https://www.fsc.go.jp/english/evaluationreports/foodadditive/polysorbate_report.pdf
4. Cosmetics Info 網站：https://cosmeticsinfo.org/ingredient/polysorbate-80

3. INCI name：Dimethicone

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

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

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

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

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

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

- 參考資料：

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

4. INCI name：Ammonia

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

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

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

◆ 參考資料：

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

5. INCI name：p-Phenylenediamine

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

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

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

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

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

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

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

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

- 參考資料：

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

6. INCI name：Resorcinol

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

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

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

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

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

7. INCI name：Ammonium Laureth Sulfate

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

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

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

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

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

8. INCI name：Sodium Bisulfite

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

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

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

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

9. INCI name：m-Aminophenol

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

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

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

出有關致癌性的結論。[1]

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

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

10. INCI name：Disodium EDTA

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

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

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

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

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

11. INCI name：Hydrogen Peroxide

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

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

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

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

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

- 參考資料：

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

12. INCI name：Glycerin

- 不純物：美國藥典國民處方集(USP-NF)標準規定甘油中任何單體雜質的含量不得超過 0.1%，所有雜質（包括二甘醇 Diethylene Glycol 和乙二醇 Ethylene Glycol）的總量不得超過 1%。[1]
- 急性毒性：大鼠口服 LD_{50} 2530~58400 mg/kg。大鼠皮膚 LD_{50}>21900 mg/kg bw。據研究顯示，針對人類甘油的口服 LD_{50} 為 1428 mg/kg。當人類口服 30 ml 甘油時，沒有毒性跡象。當作為藥物口服給藥時，對人類的不良反應包括輕度頭痛、頭暈、噁心、嘔吐、口渴和腹瀉。[1]
- 腐蝕性和刺激性：刺激眼睛和皮膚的可能性極小。[1]
- 皮膚致敏性：非皮膚致敏物。[1]
- 重複給藥毒性：當雜種犬口服給藥 3 天時的 NOAEL 為 950 mg/kg

bw/day，在劑量 3800 mg/kg bw/day 時，胃粘膜嚴重充血並伴有點狀出血。當雜種狗在飼料中加入 35%甘油時，在 36 週後體重減輕。天竺鼠口服 6300 mg/kg bw/day 甘油 30 至 40 天未見病理變化。當人類患者口服大約 1300 至 2200 mg/kg bw/day 甘油 50 天時，沒有出現毒性或對血液或尿液產生影響的跡象，NOAEL 為 2200 mg/kg bw/day。當 100%甘油每天局部施用於兔子 30%的體表 45 週時，沒有任何效應。[1]

- 致突變性/遺傳毒性：既沒有致突變性也沒有遺傳毒性。[1]
- 致癌性：非致癌性。[1]
- 生殖毒性：非生殖毒性物質。[1]
- 毒理代謝動力學：來自人類和動物研究的數據顯示，甘油在腸道和胃中迅速被吸收，並分佈在細胞外。由於甘油的 Log Pow(-2.66 至-1.76)較低且缺乏其他研究數據，甘油的皮膚吸收率設定為 80%。[2]
- 人體案例報導：一名 29 歲女性因眼瞼、面部、頸部、頭皮和腋窩出現斑片狀濕疹 7 個月就診。根據歐洲化粧品和美髮系列標準，對她自己的化粧品和洗漱用品進行了 Patch Test，她在第 4 天對二甲氨基丙胺（1%水溶液）和她自己的手部保濕霜有 a+陽性反應。對該保濕霜成分的進一步測試在第 4 天對甘油（1%水溶液）有 a+陽性反應，當她避免使用含甘油的化粧品時，她的濕疹得到了緩解。[1]
- 其他安全性資料：2014 年化粧品成分審查專家小組對支持用於化粧品和個人護理產品的甘油安全性科學數據進行了徹底審查，並根據現有文獻和數據，專家小組得出結論： 甘油在目前的使用和濃度實驗中是安全的（即在免沖洗類產品中高達 79%，在沖洗類產品中高達 99%）。美國食品和藥物管理局承認甘油在食品包裝中的使用是一般公認安全的(GRAS)，並且在按照優良製造規範使用時，它是一種多用途的 GRAS 食品物質。此外，甘油已獲得美國食品和藥物管理局批准用於 OTC 藥物，例如肛門直腸藥物產品、皮膚保護劑、眼科藥物和口腔保健產品。可用的甘油科學數據顯示，單次和重複劑量使用後，口服和皮膚不良反應較低。此外，數據顯示在人體臨床研究中沒有報告過敏性皮膚反應。在多項實驗室繁殖和發育安全性研究中，甘油不會對親代繁殖能力或其後代的生長發育、生育力或繁殖性能產生任何不利影響。在對製造合成甘油的男性員工進行的一項人類生育研究中，與使用化粧品的消費者相比，他們預

期會接觸到更高暴露量，與使用化粧品的組別相比，在精子數量或正常形狀精子的百分比方面沒有觀察到差異。此外，多項實驗室研究顯示，在口服天然和合成甘油長達兩年的情況下，甘油不會導致基因突變，也沒有證據顯示腫瘤發生率會增加（即甘油不會導致癌症）。[3]

- 參考資料：

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

13. INCI name：Urea

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

劑量毒性較低。[2]

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

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

(11) 產品安定性試驗報告

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

產品名稱	玩色染髮-瞬時棕染髮劑第一劑			
包裝材質	鋁管			
試驗時間 / 試驗項目	第 0 個月	第 1 個月	第 3 個月	第 6 個月
	40 ℃ 75 %RH	40 ℃ 75 %RH	40 ℃ 75 %RH	40 ℃ 75 %RH
外觀	乳霜狀	乳霜狀	乳霜狀	乳霜狀
顏色	淡黃色~黃色	淡黃色~黃色	淡黃色~黃色	淡黃色~黃色
氣味	具香氣	具香氣	具香氣	具香氣
pH	9.72	9.41	9.63	9.30
黏度	8100 mPas	8250 mPas	8078 mPas	8630 mPas
密度	1.1 3g/cm^3	1.1 8g/cm^3	1.13 g/cm^3	1.17 g/cm^3
結果判定	■合格 □不合格	■合格 □不合格	■合格 □不合格	■合格 □不合格
參考試驗方法	ISO/TR 18811 Cosmetics-Guidelines on the stability testing of cosmetics products, 2018. 參考 5.3.2 建議之溫度及濕度進行加速安定性試驗			
檢測人員/日期	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)
複核人員/日期	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)

產品名稱	玩色染髮-瞬時棕染髮劑第二劑			
包裝材質	HDPE			
試驗時間 / 試驗項目	第 0 個月	第 1 個月	第 3 個月	第 6 個月
	40 ℃ 75 %RH	40 ℃ 75 %RH	40 ℃ 75 %RH	40 ℃ 75 %RH
外觀	流動液體	流動液體	流動液體	流動液體
顏色	白色不透明	白色不透明	白色不透明	白色不透明
氣味	具香氣	具香氣	具香氣	具香氣
pH	3.85	3.72	4.17	3.94
密度	1.02 g/cm^3	1.05 g/cm^3	1.07 g/cm^3	1.04 g/cm^3
微生物檢測結果	未檢出	未檢出	未檢出	未檢出
結果判定	■合格 □不合格	■合格 □不合格	■合格 □不合格	■合格 □不合格
參考試驗方法	ISO/TR 18811 Cosmetics-Guidelines on the stability testing of cosmetics products, 2018. 參考 5.3.2 建議之溫度及濕度進行加速安定性試驗			
檢測人員/日期	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)
複核人員/日期	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)

(12) 微生物檢測報告

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

產品名稱	玩色染髮-瞬時棕染髮劑-第二劑		
產品批號	P018AUG		
產品製造日期	110.07.05		
包裝材質	HDPE	試驗日期	110.07.08
檢測項目	規 格	檢測結果	參考測試方法
生菌數	<1000 CFU/g	未檢出 (<10 CFU/g)	參考衛生福利部食品藥物管理署 109.07.28 及 111.04.21 公布建議檢驗方法-化粧品中微生物檢驗方法及化粧品中白色念珠菌之檢驗方法。
大腸桿菌	不得檢出	未檢出	
綠膿桿菌	不得檢出	未檢出	
金黃色葡萄球菌	不得檢出	未檢出	
白色念珠菌	不得檢出	未檢出	
結果判定	■合格	□不合格	
檢測人員/日期	(請簽名並加上日期)		
複核人員/日期	(請簽名並加上日期)		

(13) 防腐效能試驗報告

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

樣品名稱 (Sample Name)	玩色染髮-瞬時棕染髮劑第二劑				
測試日期(Date Tested): 110/06/01~110/06/30					
試驗參考方法(Method Code): ISO 11930:2019					
測試菌種 (Organism)					
分析時間點 (Assay Time)	大腸桿菌 *Escherichia coli* (ATCC 8739) (CFU/g or ml)	金黃色葡萄球菌 *Staphylococcus aureus* (ATCC 6538) (CFU/g or ml)	綠膿桿菌 *Pseudomonas aeruginosa* (ATCC 9027) (CFU/g or ml)	白色念珠菌 *Candida albicans* (ATCC 10231) (CFU/g or ml)	黑麴菌 *Aspergillus* brasiliensis (ATCC 16404) (CFU/g or ml)
第 0 天	9.8×10^5	8.2×10^5	9.4×10^5	8.6×10^4	7.7×10^4
第 7 天	<10	<10	<10	$1.4X10^2$	$3.3X10^2$
第 14 天	<10	<10	<10	<10	<10
第 28 天	<10	<10	<10	<10	<10
檢測人員/日期	(請簽名並加上日期)				
複核人員/日期	(請簽名並加上日期)				

(14) 功能評估佐證資料

染髮劑相關功能性測定，如染髮色度測試驗等。

(15) 與產品接觸之包裝材質資料

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

III. 安全評估資料

(16) 產品安全資料

玩色染髮-瞬時棕染髮劑每日皮膚暴露量計算

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

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

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

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

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

SSA (cm^2)：預計使用化粧品產品的皮膚表面積

f (day^{-1})：產品的使用頻率

bw (kg bw)：人體體重（默認值：60 公斤）

玩色染髮-瞬時棕染髮劑各個成分 MoS 值計算

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

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

MoS= PODsys/SED

SED (mg /kg bw/day)為全身暴露劑量；Eproduct (mg /kg bw/day)為每日皮膚暴露量；C(%)為配方百分比；DAp(%)為皮膚吸收率；PODsys 一般常用 NOAEL 估算。或者是 BMDL、LOAEL 。

p-Phenylenediamine、Resorcinol 及 m-Aminophenol 採用文獻之皮膚吸收量。SCCS 化粧品成分測試及其安全性評估指引第 11 版 (SCCS/1628/21) 提及 90 天口服毒性試驗是化粧品成分最常用的重複劑量毒性試驗，當有科學合理的 90 天研究確認明確的 PoD 時，SCCS 會考慮以該研究計算 MoS，當對亞慢性毒性研究的品質存疑或缺乏支持 90 天研究的 PoD 時，則建議應用不確定性因子來推估，為了保守嚴謹評估，故亦將各成分之 NOAEL 在考慮各別的毒理試驗條件後將不確定因子進行校正。以校正後之 NOAEL 值計算結果如下:

第一劑

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

第二劑

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

INCI name	NOAEL 校正說明
Alcohol	對大鼠每日飲食研究報告的最低NOAEL為約2400 mg /kg bw/day (未說明天數)，考慮口服生物可用率50%等不確定因子， 將2400*50% =1200 mg/kg bw/day。
Polysorbate 80	大鼠膳食亞慢性研究(BIBRA, 1981)中，確定的NOAEL相當於1460 mg/kg bw/day(未說明天數)，考慮口服生物可用率50%之不確定因子，將1460*50% =730 mg/kg bw/day。
Dimethicone	通過封閉貼劑經皮給藥4週(28天)，家兔皮膚施用二甲基矽油的NOAEL被認為是1000 mg/kg bw/day，考慮試驗天數之不確定因子，將1000*28/90 =311.1 mg/kg bw/day。
Ammonia (28% Solution)	參照在飲用水中添加0.01%氨水大鼠試驗8週中，磷酸二銨NOAEL為250 mg/kg bw/day，考慮口服生物可用率50%及試驗天數之不確定因子，將250*50%*56/90=77.8 mg/kg bw/day。
p-Phenylenediamine	參照SCCS將PPD亞慢性毒性的NOAEL視為8 mg/kg bw/day作為MoS計算，故未以不確定因子進行校正。
Resorcinol	為期17天口服毒性研究中，大鼠的NOAEL為27.5 mg/kg bw/day，考慮口服生物可用率50%及試驗天數之不確定因子，將27.5*50%*17/90=2.6 mg/kg bw/day。
Ammonium Laureth Sulfate	105週大鼠口服毒性得知NOAEL約為100 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，將100*50% =50 mg/kg bw/day。
Sodium Bisulfite	參照世界衛生組織食品添加劑聯合專家委員會在三代動物研究中，NOAEL為72 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，將72*50% =36 mg/kg bw/day。
m-Aminophenol	管飼13週動物試驗得知NOAEL 20 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，20*50% =10mg/kg bw/day。
Disodium EDTA	為期13週餵食大暑試驗中得知NOAEL為692 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，692*50% =346 mg/kg bw/day。

Hydrogen Peroxide (28% Solution)	一項90天小鼠飲水試驗結果顯示，飲用水中過氧化氫的NOAEL為26 mg/kg bw，考慮口服生物可用率50%等不確定因子，將26*50% =13 mg/kg bw/day。
Glycerin	人類患者口服甘油50天時，NOAEL為2200 mg/kg bw/day，考慮口服生物可用率50%及試驗天數等不確定因子，將2200*50% *50/90 =611.1 mg/kg bw/day。
Urea	大鼠口服試驗的NOAEL約為2250 mg/kg bw/day(未說明天數)，考慮口服生物可用率50%等不確定因子， 將2250*50% =1125mg/kg bw/day。。

玩色染髮-瞬時棕染髮劑安全評估結論

安全評估結論簡述

經分析所有可取得之安全性資料，根據上述評估計算結果並根據當前科學知識據以結論，推定玩色染髮-瞬時棕染髮劑在預期正常合理使用條件下，本產品為可安全使用之產品，不致對人體健康造成傷害。

標籤警語和使用說明

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

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

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

*一旦皮膚測試的結果出現異常，請前往醫院皮膚科進行診治。

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

安全評估理由

玩色染髮-瞬時棕染髮劑的安全性評估基於每種成分的毒理學特徵並評估所收集之產品數據。

1. 該產品在符合化粧品優良製造規範之場所和生產設施中生產，並進行微生物品質管理以及倉儲管理作業。
2. 根據本產品「玩色染髮-瞬時棕染髮劑」之化粧品的物理/化學特性、安定性試驗報告、第二劑微生物檢測報告及防腐效能試驗評估，結果由數據顯示產品符合規格特性，證實了「玩色染髮-瞬時棕染髮劑」產品配方具有足夠安定性及微生物安全性。由六個月之加速安定性試驗推測本產品於架儲期間品質穩定，上市後將同時進行長期安定性試驗確認之。
3. 玩色染髮-瞬時棕染髮劑第一劑經評估屬於低微生物風險產品，故無需進行防腐效能試驗及微生物檢測。第二劑微生物檢測報告結果符合我國化

粧品微生物容許量基準之要求。防腐效能試驗報告顯示通過 ISO 11930:2019 Criteria A 之標準。

Table B.1 — Evaluation criteria

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

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

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

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

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

(請簽名並加上日期)

_____

安全資料簽署人員簽名及日期

附錄 1：產品及各別成分之物理及化學特性資料

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

INCI name：Ammonia

SAFETY DATA SHEET

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

1.1 Product identifiers

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

1.2 Other means of identification

No data available

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

Identified uses : Reagent for analysis, Chemical production

1.4 Details of the supplier of the safety data sheet

1.5 Emergency telephone

SECTION 2: Hazards identification

2.1 GHS Classification

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

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

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

2.2 GHS Label elements, including precautionary statements

Pictogram

Signal word: Danger

Hazard statement(s)

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

Precautionary statement(s)

Prevention

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

Response

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

Storage

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

Disposal

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

2.3 Other hazards - none

SECTION 3: Composition/information on ingredients

Substance / Mixture : Mixture

3.2 Mixtures

Hazardous ingredients

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

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

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

SECTION 4: First aid measures

4.1 Description of first-aid measures

General advice
First aiders need to protect themselves.

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

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

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

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

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

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

SECTION 5: Firefighting measures

5.1 Extinguishing media

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

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

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

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

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

SECTION 6: Accidental release measures

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

6.2 Environmental precautions
Do not empty into drains.

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

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling

Advice on safe handling
Observe label precautions.

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

7.2 Conditions for safe storage, including any incompatibilities

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

Recommended storage temperature see product label.

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

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

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

Personal protective equipment

Eye/face protection
Tightly fitting safety goggles

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

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

Body Protection
protective clothing

Respiratory protection
required when vapours/aerosols are generated.

Control of environmental exposure
Do not empty into drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

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

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

9.2 Other safety information

Minimum ignition energy	380 - 680 mJ

SECTION 10: Stability and reactivity

10.1 Reactivity

No data available

10.2 Chemical stability

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

10.3 Possibility of hazardous reactions

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

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

10.4 Conditions to avoid
Heating.

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

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

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Mixture

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

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

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

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
No data available

Carcinogenicity
No data available

Reproductive toxicity
No data available

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

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information

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

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

Components

ammonia solution

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

Skin corrosion/irritation
Causes skin burns.

Serious eye damage/eye irritation
Causes serious eye damage.

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
No data available

Carcinogenicity
No data available

Reproductive toxicity
No data available

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

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

SECTION 12: Ecological information

12.1 Toxicity

Mixture
No data available

12.2 Persistence and degradability
Biodegradability Remarks: No data available

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

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

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

Discharge into the environment must be avoided.
No data available

Components

ammonia solution

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

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product

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

SECTION 14: Transport information

14.1 UN number

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

14.2 UN proper shipping name

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

14.3 Transport hazard class(es)

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

14.4 Packaging group

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

14.5 Environmental hazards

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

14.6 Special precautions for user

None

14.7 Incompatible materials

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

SECTION 15: Regulatory information

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

No data available

SECTION 16: Other information

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

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

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

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

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

附錄 2：各成分之毒理相關資料

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

INCI name：Ammonia

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

Safety Assessment of
Ammonia and Ammonium Hydroxide as Used in Cosmetics

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

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

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

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INTRODUCTION

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

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

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

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

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

CHEMISTRY

Definition and General Characterization

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

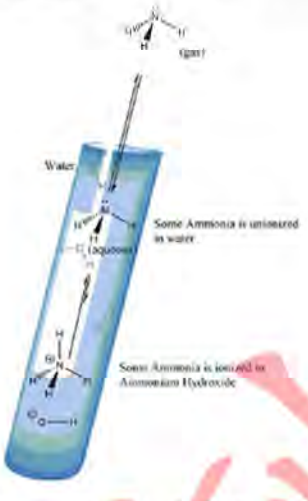


Figure 1. The aqueous relationship of Ammonia and Ammonium Hydroxide

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

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

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

Chemical and Physical Properties

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

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

Method of Manufacture

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

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

Composition

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

Impurities

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

USE

Cosmetic

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

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

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

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

Noncosmetic

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

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

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

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

TOXICOKINETIC STUDIES

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

Absorption, Distribution, Metabolism, and Excretion

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

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

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

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

Animal

Inhalation

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

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

Parenteral

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

Human

Oral

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

TOXICOLOGICAL STUDIES

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

Acute Toxicity Studies

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

Dermal

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

Oral

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

Inhalation

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

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

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

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

Short-Term Toxicity Studies

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

Dermal

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

Oral

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

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

Inhalation

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

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

Risk Assessment

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

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

Subchronic Toxicity Studies

Dermal

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

Oral

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

Inhalation

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

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

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

Chronic Toxicity Studies

Dermal

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

Oral

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

Ammonium Sulfate (included as a potentially similar ammonium salt)

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

Inhalation

Human

Risk Assessment

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

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

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

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

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental/reproductive toxicity studies are summarized in Table 7.

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

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

GENOTOXICITY STUDIES

In Vitro

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

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

In Vivo

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

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

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

CARCINOGENICITY STUDIES

Carcinogenicity and tumor promotion studies are summarized in Table 8.

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

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

Tumor Promotion

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

OTHER RELEVANT STUDIES

Neurotoxicity

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

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

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

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

Cytotoxicity

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

Effect on Mitosis

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

Permeation of Blood Brain Barrier

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

Generation of Free Radicals

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

Immunological Effects

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

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

Neurological Effects

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

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

DERMAL IRRITATION AND SENSITZATION STUDIES

Dermal irritation studies are summarized in Table 9.

Irritation

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

Sensitization

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

OCULAR IRRITATION STUDIES

Ocular irritation studies are summarized in Table 10.

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

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

MUCOUS MEMBRANE IRRITATION STUDIES

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

CLINICAL STUDIES

Case Reports

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

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

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

Other Clinical Reports

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

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

EPIDEMIOLOGICAL STUDIES

Non-Cancer Endpoints

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

SUMMARY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Request for Additional Data

- Dermal absorption data
- Sensitization data

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

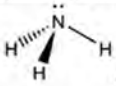
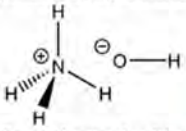
Ingredient CAS No.	Definition & Idealized Structures	Function
Ammonia	Ammonia is an inorganic gas that conforms to the formula:  (See also Ammonium Hydroxide)	External Analgesics; Fragrance Ingredients; pH Adjusters
Ammonium Hydroxide	Ammonium Hydroxide is an inorganic base that conforms to the formula: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

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

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

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

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

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

Table 4. Acute Oral Toxicity Studies

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

Table 5. Acute Inhalation Toxicity

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

Table 5. Acute Inhalation Toxicity

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

Table 5. Acute Inhalation Toxicity

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

Table 6. Short-Term and Subchronic Toxicity Studies

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

Table 6. Short-Term and Subchronic Toxicity Studies

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

Table 6. Short-Term and Subchronic Toxicity Studies

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

Table 6. Short-Term and Subchronic Toxicity Studies

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

Table 7. Developmental and Reproductive Toxicity Studies

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

Table 8. Carcinogenicity and Tumor Promotion Studies

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

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

Table 9. Dermal Irritation Studies

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

Table 9. Dermal Irritation Studies

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

Table 10. Ocular Irritation Studies

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

Table 11. Other Clinical Reports

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

Table 11. Other Clinical Reports

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

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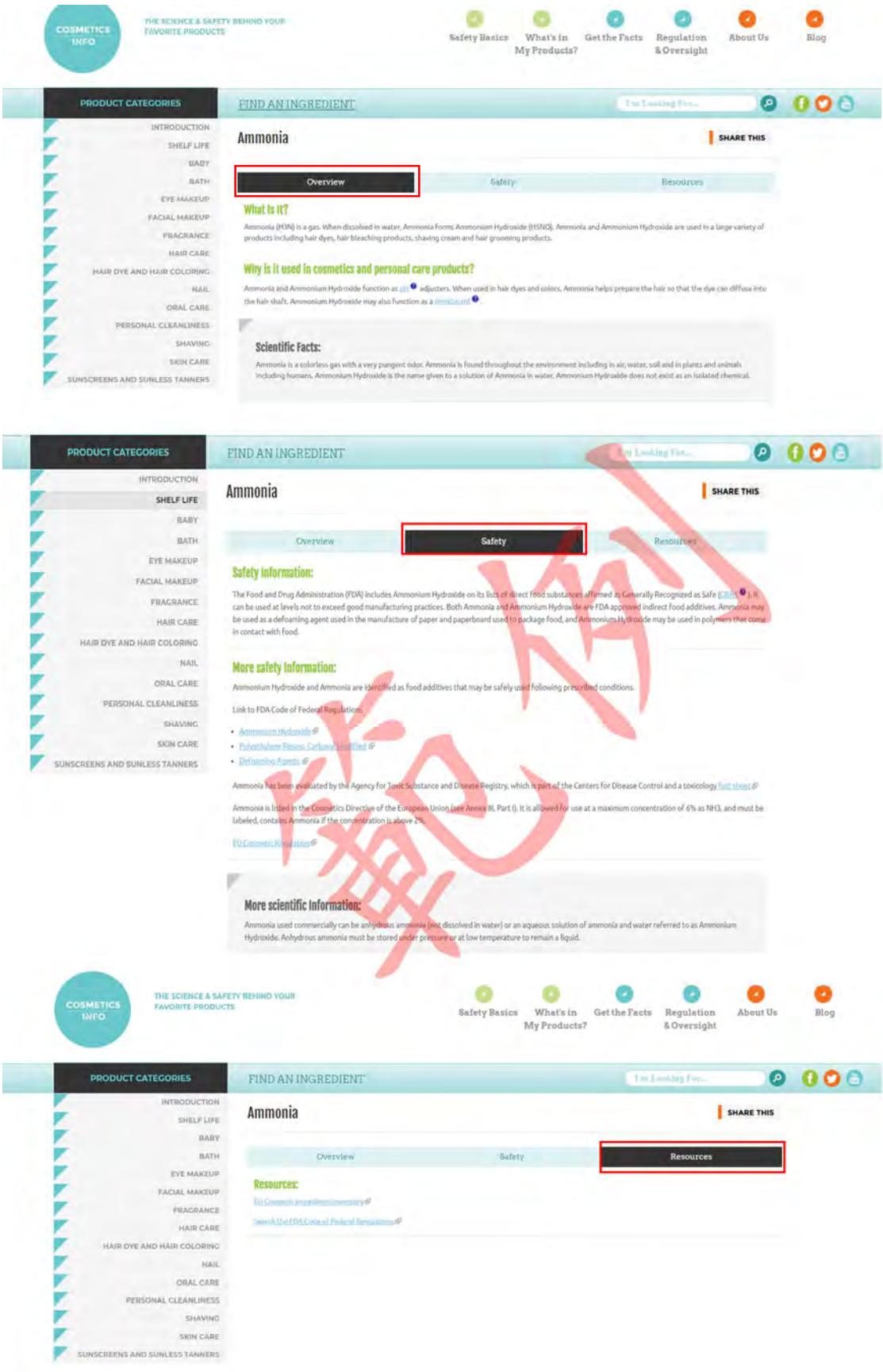

附錄 3　Fragrance IFRA 符合性聲明

CERTIFICATE OF CONFORMITY

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

CERTIFYING PARTY:

CERTIFICATE DELIVERED TO:
GRACEFRUIT LTD

SCOPE OF THE CERTIFICATE:
FIG & VANILLA FRAGRANCE 454155

COMPULSORY INFORMATION:

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

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

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

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

EU COSMETIC INFORMATION:

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

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

Regulatory Affairs Department

ANNEX 1

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

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

IFRA CONFORMITY CERTIFICATE

Product: **FIG & VANILLA FRAGRANCE 454155**

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

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