化粧品產品資訊檔案(範例)

<燙髮劑 1 號>

＜PIF **無特定之格式**，本範例**僅提供參考用**＞

中華民國 112 年 10 月

目　錄

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I. 產品敘述

(1) 產品基本資料

項目	內容描述
產品名稱(中文/英文)	燙髮劑 1 號(第一劑、第二劑) Waving Solution No.1 (First dose、Second dose)
產品類別	頭髮用化粧品類
產品劑型	第一劑-液劑、第二劑-液劑
用途	燙髮
製造作業場所資訊	製造廠名稱：XX 化粧品股份有限公司 廠址：○○市○○區○○路○○號 國別：台灣
包裝作業場所資訊	包裝廠名稱：YY 股份有限公司 廠址：○○市○○區○○路○○號 國別：台灣
產品製造業者資訊	製造業者：AJP 化粧品股份有限公司 地址：oo 市 oo 路 oo 段 XX 號 公司負責人：李○基 聯絡電話：02-2xxx-xxxx 統一編號：0123XXXX

(2) 完成產品登錄之證明文件

登錄號碼：0123XXXXTEST2000000000

NO.		登錄編號	中文品名	產品種類	產品劑型	案件狀態	提交日期	提交結果	版次	登錄期限
1.		0123XXXXTEST2000000000	燙髮劑1號			結案	1091012	成功	01	

產品基本資訊 | 全成分

案件資訊

* 登錄編號：	0123XXXXTEST2000000000	* 聯絡人：	OOO
提交日期：	1091012	登錄期限：	1130701
案件狀態：	結案	版次：	01

廠商資訊

公司名稱：	AJP化粧品股份有限公司	電話：	02-2XXX-XXXX
地址：	oo市oo路oo段XX號		

產品資訊

* 國產/輸入：	國產 輸入		
* 是否為組合式產品：	是	產品品牌：	
* 產品類型：	單一產品		

	*中文品名	英文品名
產品名稱：	燙髮劑1號	Waving Solution No.1
組合式產品1：	燙髮劑第一劑	
*產品種類：	燙髮劑 查詢	*產品劑型： 液劑 查詢
*產品用途：	燙髮 查詢	
*製造作業場所：	XX化粧品股份有限公司 查詢	*包裝作業場所： YY股份有限公司 查詢
組合式產品2：	燙髮劑第二劑	
*產品種類：	燙髮劑 查詢	*產品劑型： 液劑 查詢
*產品用途：	燙髮 查詢	
*製造作業場所：	XX化粧品股份有限公司	*包裝作業場所： YY股份有限公司

製造、包裝作業場所： 製造、包裝作業場所維護

若查無製造場所或包裝場所時，請先至「製造場所維護作業」確認對應之製造場所或包裝場所已選擇場所類別或已建立資料

* 使用注意事項：
一、使用前請詳閱說明書並依據使用方法正確使用。
二、不得使用於眉毛、睫毛等頭髮以外之毛髮。
三、燙髮一星期前後，不可連續進行染髮。
四、燙髮操作時應戴手套。
五、應避免燙髮劑接觸臉部或頭部，若不慎接觸時，應立即沖洗。

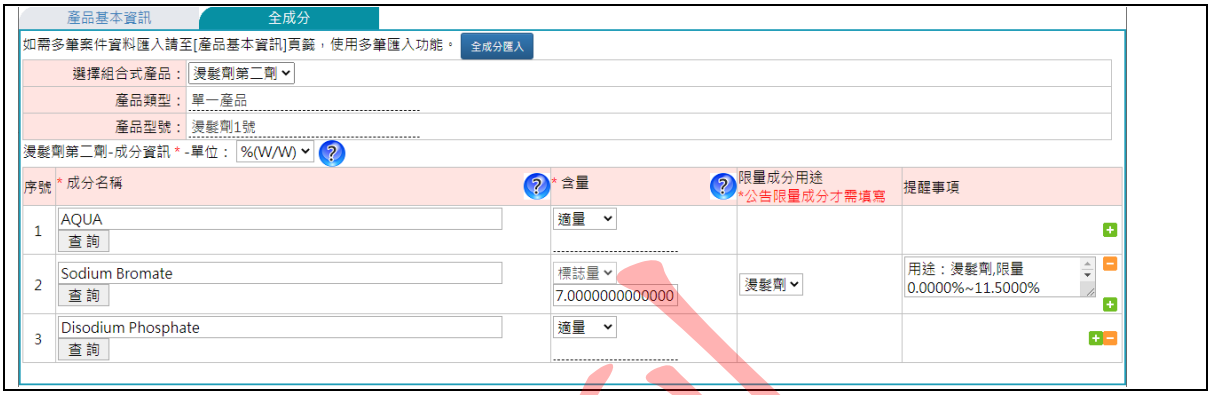
產品基本資訊 | 全成分

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

選擇組合式產品： 燙髮劑第一劑
產品類型： 單一產品
產品型號： 燙髮劑1號

燙髮劑第一劑-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	AQUA 查詢	適量		
2	Ammonia 查詢	標誌量 1.6000000000000	其他	用途：染髮劑,限量 0.0000%~6.0000%
3	Ammonium Thioglycolate 查詢	適量		
4	Polysorbate 80 查詢	適量		
5	Sorbitan Stearate 查詢	適量		
6	Paraffinum Liquidum 查詢	適量		
7	Lanolin Wax 查詢	適量		


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

(3) 全成分名稱及其各別含量

第一劑

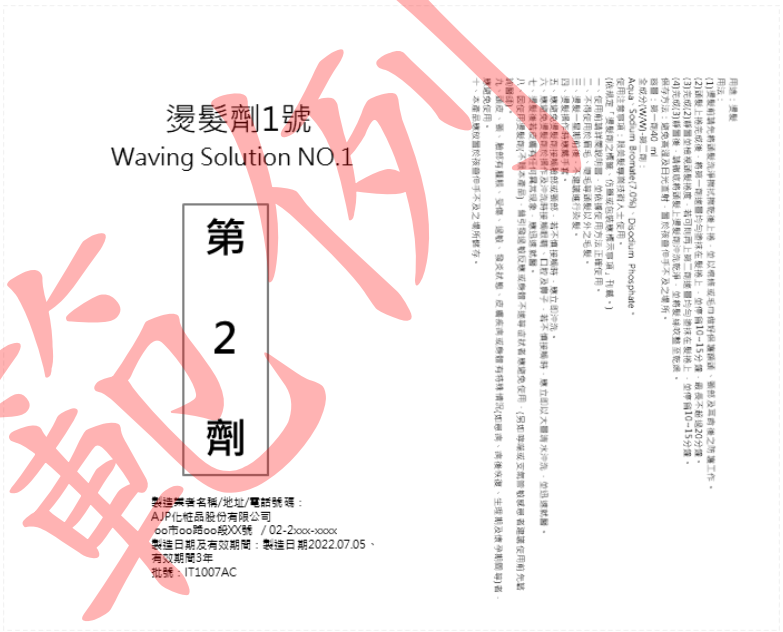
	INCI Name	Cas No.	w/w%	功能
1	Aqua	7732-18-5	84.3	溶劑
2	Ammonium Thioglycolate (50% Solution)	5421-46-5	10.0	還原劑
3	Polysorbate 80	9005-65-6	2.0	界面活性劑-乳化
4	Ammonia (28% Solution)	7664-41-7	1.6	鹼劑
5	Sorbitan Stearate	1338-41-6	1.0	界面活性劑-乳化
6	Paraffinum Liquidum	8012-95-1 / 8042-47-5	0.6	皮膚調理-潤膚
7	Lanolin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

第二劑

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

(4) 產品標籤、仿單、外包裝或容器

項目	資料
內包裝/容器第一劑(正反面)	
內包裝/容器第二劑(正反面)	

標籤/仿單	 燙髮劑1號 Waving Solution NO.1 第 1 劑 製造廠商名稱/地址/電話號碼： AJP化粧品股份有限公司 oo市oo路oo段XX號 /02-2xxx-xxxx 製造日期及有效期間：製造日期2022.07.05、 有效期間3年 批號：IT1007AC  燙髮劑1號 Waving Solution NO.1 第 2 劑 製造廠商名稱/地址/電話號碼： AJP化粧品股份有限公司 oo市oo路oo段XX號 /02-2xxx-xxxx 製造日期及有效期間：製造日期2022.07.05、 有效期間3年 批號：IT1007AC

外盒	
標籤、仿單	內容物：燙髮劑(第一劑、第二劑) 品名：燙髮 1 號 (第一劑、第二劑) 用途：燙髮 用法： (1)燙髮前請先將頭髮洗淨擦拭擦乾後上捲，並以棉條或毛巾做好保護額頭、頸部及耳背後之防護工作。 (2)頭髮上捲完成後，將第一劑適量均勻塗抹在髮捲上，並停留 10~15 分鐘，最長不超過 20 分鐘。 (3)完成(2)靜置並檢視頭髮捲度，若可則再上第二劑適量均勻塗抹在髮捲上，並停留 10~15 分鐘。 (4)完成(3)靜置後，請徹底將頭髮上燙髮劑沖洗乾淨，並將髮絲吹整至乾燥。 保存方法：避免高溫及日光直射，置於孩童伸手不及之場所。 製造業者名稱/地址/電話號碼： AJP 化粧品股份有限公司 / oo 市 oo 路 oo 段 XX 號 / 02-2xxx-xxxx 製造日期及有效期間：製造日期 2022.07.05、有效期間 3 年 批號：IT1007AC 容量：第一劑 40 ml / 第二劑 40 ml 全成分(W/W)-第一劑： Aqua、Ammonium Thioglycolate (50%)(10.0%)、Polysorbate 80、Ammonia (28%)(1.6%)、Sorbitan Stearate、Paraffinum Liquidum、Lanolin Wax。 全成分(W/W)-第二劑： Aqua、Sodium Bromate(7.0%)、Disodium Phosphate。

	使用注意事項：限美髮專業技術人士使用。 (依規定「燙髮劑之標籤、仿單或包裝應標示事項」刊載。) 一、使用前請詳閱說明書，並依據使用方法正確使用。 二、不得使用於眉毛、睫毛等頭髮以外之毛髮。 三、燙髮一星期前後，不建議進行染髮。 四、燙髮操作時應戴手套。 五、應避免燙髮劑接觸臉部或頸部，若不慎接觸時，應立即沖洗。 六、應避免燙髮劑於操作及沖洗時接觸眼睛、口腔及鼻子，若不慎接觸時，應立即以大量清水沖洗，並迅速就醫。 七、燙髮後若皮膚有任何異常現象，應迅速就醫。 八、因使用燙髮劑(不限本產品)，曾引發過敏反應或身體不適等症狀者應避免使用，(另如哮喘或支氣管敏感患者建議使用前先諮詢醫師)。 九、頭皮、頸、臉部有腫脹、受傷、過敏、發炎狀態、皮膚疾病或身體有特殊情況(如患病、病後恢復、生理期及懷孕期間等)者，應避免使用。 十、本產品應放置於孩童伸手不及之場所儲存。

(5) 製造場所符合化粧品優良製造準則之證明文件或聲明書

衛 生 福 利 部

化 粧 品 優 良 製 造 證 明 書

證號：(C)GMPOOOO-OOO

製造廠（場所）名稱：

製造廠（場所）地址：

核定劑型及作業項目：

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

衛生福利部

發 證 日 期：　　年　　月　　日
有 效 日 期：　　年　　月　　日

XXXX(流水號)

符合化粧品優良製造準則聲明書(**範例**)

符合化粧品優良製造準則聲明書

Declaration of Conformity

本業者/本廠生產之化粧品符合中華民國之化粧品優良製造準則，產品資料如下：

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

一、製造廠名稱：

Manufacturer's Name

二、製造廠地址：

Manufacturer's Address

三、製造劑型：

Product forms

四、作業項目：

The process of operations

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

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

立聲明書人： (Signature)

Applicant

申請廠商蓋公司章

負責人/代表人： (Signature)

Person in charge

負責人或代表人章

統一編號或身分證字號：

Company Tax ID No. / ID Number

地址：

Address:

中 華 民 國 年 月 日

Date year month day

(6) 製造方法、流程

第一劑

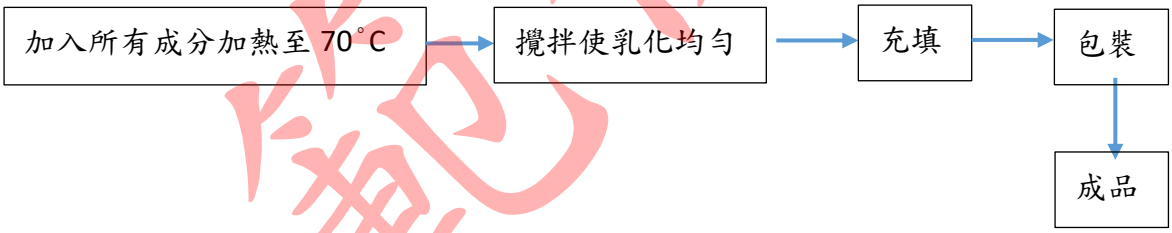
	INCI Name	Cas No.	w/w%
1	Aqua	7732-18-5	84.3
2	Ammonium Thioglycolate (50% Solution)	5421-46-5	10.0
3	Polysorbate 80	9005-65-6	2.0
4	Ammonia (28% Solution)	7664-41-7	1.6
5	Sorbitan Stearate	1338-41-6	1.0
6	Paraffinum Liquidum	8012-95-1 / 8042-47-5	0.6
7	Lanolin Wax	68201-49-0	0.5

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

製造方法：

1.加入第一劑所有成分加熱至 70°C，攪拌使其乳化均勻，冷卻至室溫即可。

製程流程圖：



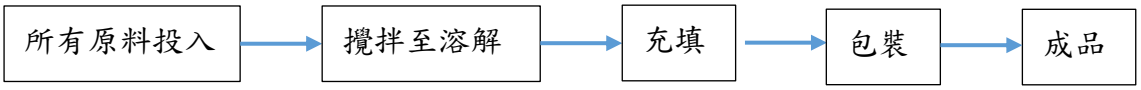
第二劑

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

製造方法：

1.依序將 1~3 項，攪拌至溶解即可。

製程流程圖：



(7) 使用方法、部位、用量、頻率及族群

使用方法：

(1)燙髮前：請先將頭髮洗淨擦拭，濕度呈半乾燥狀態。

(2)頭髮上捲完成後，將第一劑均勻塗抹在頭髮上，並停留 10~15 分鐘。

(3)完成(2)靜置後再上第二劑，並停留 10~15 分鐘。

(4)完成(3)靜置後，請徹底將頭髮上燙髮劑沖洗乾淨，並將髮絲吹整至乾燥。

使用部位：頭髮。

用量：每次燙髮使用第一劑 40 ml、使用第二劑 40 ml。

使用族群：適用於頭髮及頭皮無受損之成年人。

使用頻率：每 3 個月 1 次 (每次燙髮至少間隔 3 個月) 。

(8) 產品使用不良反應資料

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

II. 品質資料

(9) 產品及各別成分之物理及化學特性

成品規格檢驗報告

第一劑

燙髮劑 1 號第一劑成品 CoA			
檢測項目	**規格**	**實際檢驗結果**	**檢驗方法**
外觀	流動液體	流動液體	目視
顏色	乳白色不透明	乳白色不透明	目視
氣味	"氨"刺激氣味	有刺激氣味	嗅覺
pH (at 25 °C)	9.5 ± 0.5	9.57	使用已校正之 pH meter 依 pH meter 檢測方法測定
微生物規格	生菌數< 1000 CFU/g 不得檢出： 大腸桿菌 金黃色葡萄球菌 綠膿桿菌 白色念珠菌	生菌數 未檢出 (<10 CFU/g)； 大腸桿菌 陰性； 金黃色葡萄球菌 陰性； 綠膿桿菌 陰性； 白色念珠菌 陰性；	參考衛生福利部食品藥物管理署 109.07.28 及 111.04.21 公布建議檢驗方法-化粧品中微生物檢驗方法及化粧品中白色念珠菌之檢驗方法。
檢測人員/日期		（請簽名並加上日期）	
複核人員/日期		（請簽名並加上日期）	

第二劑

燙髮劑 1 號第二劑成品 CoA			
檢測項目	**規格**	**實際檢驗結果**	**檢驗方法**
外觀	流動液體	流動液體	目視
顏色	乳白色微透明	乳白色微透明	目視
氣味	無	無添加香精	嗅覺
pH (at 25 °C)	5.5 ± 0.5	5.61	使用已校正之 pH meter 依 pH meter 檢測方法測定
微生物規格	生菌數 < 1000 CFU/g 不得檢出： 大腸桿菌 金黃色葡萄球菌 綠膿桿菌 白色念珠菌	生菌數 未檢出 (<10 CFU/g)； 大腸桿菌 陰性； 金黃色葡萄球菌 陰性； 綠膿桿菌 陰性； 白色念珠菌 陰性；	參考衛生福利部食品藥物管理署 109.07.28 及 111.04.21 公布建議檢驗方法-化粧品中微生物檢驗方法及化粧品中白色念珠菌之檢驗方法。
檢測人員/日期		(請簽名並加上日期)	
複核人員/日期		(請簽名並加上日期)	

各成分物理化學特性

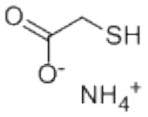
Aqua CoA			
檢測項目	**規格**	**實際檢驗結果**	**檢驗方法**
pH (at 25 °C)	6.0~8.5	6.85	使用已校正之線上(on line) pH meter 測定
導電度(at 25 °C)	<10 µS/cm	7.5 µS/cm	使用已校正之線上(on line)導電度計測定
微生物規格	生菌數 < 100 CFU/ml	生菌數 未檢出 (<10 CFU/ml)；	參考環境保護署環境檢驗所公告之水中總菌落數檢測方法測定
檢測人員/日期		(請簽名並加上日期)	
複核人員/日期		(請簽名並加上日期)	

INCI name：Ammonium Thioglycolate (50% Solution)

CAS No.: 5421-46-5

Molecular Formula: $C_2H_7NO_2S$

Molecular Fomula:109.15

Chemical Structure: 

AMMONIUM THIOGLYCOLATE Typical Properties

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

INCI name：Polysorbate 80

Certificate of Analysis

Product Name:TWEEN® 80

TEST SPECIFICATION

hydroxyl value 74.7

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

INCI name：Ammonia (28% Solution)

Product Name: AMMONIA 28% Solution AR

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

Description

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

Properties

Chemical Formula:

Molecular Weight: 35.05

Product Code: AA005

CAS No.: 1336-21-6

General Information:

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

Hazard and Safety Data

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

Quality Specification

Typical Assay: 28.0 - 30.0 % w/w

Specific Properties and Impurities [Typical levels]:

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

INCI name：Sorbitan Stearate

Certificate of Analysis

(Representative Sample Certificate)

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

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

INCI name：Paraffinum Liquidum

Certificate of Analysis

(Representative Sample Certificate)

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

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

INCI name：Lanolin Wax

Certificate of Analysis

(Representative Sample Certificate)

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

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

INCI name：Sodium Bromate

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

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

INCI name：Disodium Phosphate

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

(10) 成分之毒理資料

- 由 AJP 化粧品股份有限公司及安全資料簽署人員查詢蒐集之各個成分毒理資料，另存放於燙髮劑 1 號成分毒理資料檔案夾(附錄 2)。
- 安全資料簽署人員依據上述資料內容摘錄各成分相關毒理資料如下：

1. INCI name：Ammonium Thioglycolate (50% Solution)

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

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

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

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

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

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

2. INCI name：Polysorbate 80

- 暴露途徑：經皮膚吸收、眼睛接觸吸收、吸入。[2]
- 不純物：製造過程中，需將聚山梨酯(Polysorbate)進行蒸餾以去除不需要的水溶性副產物，例如：1,4-二噁烷。由於聚乙二醇(Polyethylene glycol, PEG)是環氧乙烷與水的縮合產物，其鍊長取決於聚合的環氧乙烷之摩爾數，因此它們可能含有 1,4-二噁烷不純物（乙氧基化的副產物）。1,4-二噁烷是已知的動物致癌物，美國食品藥物管理局(U.S. Food and Drug Administration, FDA)一直在定期監測化粧品中 1,4-二噁烷的含量，根據化粧品行業報告顯示已知 1,4-二噁烷可能是 PEG 中的製程中生成之不純物，因此，在摻入化粧品配方前須另進行純化步驟以降低其殘留量。[1]
- 急性毒性：無 Polysorbate 80 之研究數據，而類似的聚山梨酯類成分 Polysorbate 81 的口服 LD_{50} 對大鼠> 20 000 mg/kg；乙氧基化脫水山梨糖醇單硬脂酸酯(sorbitan monostearate, ethoxylated)在大鼠中的急性皮膚 LD_{50}> 2000 mg/kg；乙氧基化脫水山梨糖醇單硬脂酸酯(sorbitan monostearate, ethoxylated)給藥 4 小時，吸入 LC_{50} 為 5.1 mg/L；Polysorbate 20 對小鼠的靜脈注射 LD_{50} 為 1420 mg/kg。[1]
- 重複劑量毒性：90 天以狗為試驗對象對於 Polysorbate 80 最高口服 NOAEL 為 5 mL/kg bw/day，大鼠 4 週試驗中對於 Polysorbate 80 的最高口服 NOAEL 為 5 mL/kg bw/day。鼻腔給藥方式給予小鼠 0.2% Polysorbate 80 的 NOAEL 為 10 µL /鼻腔/day。在對 Sprague-Dawley 大鼠（n = 6 /性別）高脂餵食 28 天後，口服 28 天的 Polysorbate 80 (148、740 或 3700 mg/kg bw/day)，無不良反應或致命的報導，但尚不清楚大鼠在施用 Polysorbate 80 期間是否繼續高脂飲食。對大鼠使用 Polysorbate 80 進行的亞慢性研究(NTP, 1992a)顯示，無觀察到的不良反應，其 NOAEL 相當於 4500mg/kg bw/day。在大鼠膳食亞慢性研究(BIBRA, 1981)中，確定的 NOAEL 相當於 1460 mg/kg bw/day。[1]
- 生殖毒性：在一項生殖和發育研究中，在妊娠第 6 天，透過管飼法對 25 隻 Crl：CD BR VAF/Plus TM 大鼠餵食 Polysorbate 80（在蒸餾水中濃度為 500 和 5000 mg/kg bw/day；5 mL），對照組接受 5 mL/kg 蒸餾水。據實驗結果顯示母親和發育中胎兒的 NOAEL >5000 mg/kg bw/day。未觀察到產婦死亡或與治療有關的毒性中毒臨床症狀，對體重增加、器官重量(非不利的相對肝臟重量增加)以及飼料和水的消耗沒有影響，在實驗組和對照組之間沒有觀察到畸形的差異。[1]

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

- 參考資料：

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

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

https://cosmeticsinfo.org/ingredient/polysorbate-80

3. INCI name：Ammonia

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

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

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

4. INCI name：Sorbitan Stearate

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

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

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

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

5. INCI name：Paraffinum Liquidum

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

影響提供證據並推論，高或中黏度礦物油不會產生生殖或發育毒性。[1]

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

1. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS); Scientific Opinion on the use of high viscosity white mineral oils as a food additive on request from the European Commission. EFSA Journal, 7(11), 1387, [39 pp.], doi:10.2903/j.efsa, 2009.
2. Critical Reviews in Toxicology Mineral oil in food, cosmetic products, and in products regulated by other legislations Mineral oil in food, cosmetic products, and in products regulated by other legislations, Critical Reviews in Toxicology. January, 2020.
3. Mineral Hydrocarbons In Cosmetic LIP Care Products., COSMETICS EUROPE RECOMMENDATION N°14, 17-09, 2018.
4. Scientific opinion on the safety assessment of medium viscosity white mineral oils with a kinematic viscosity between 8.5~11 mm²/s at 100 °C for the proposed uses as a food additive. EFSA Journal, 2013.

6. INCI name：Lanolin Wax

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

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

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

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

7. INCI name：Sodium Bromate

- 急性毒性：使用溴酸鈉(Sodium Bromate)進行試驗非常少，大多數研究都以溴酸鉀(Potassium Bromate)為主。在大鼠中，溴酸鉀的口服 LD_{50} 為 200~400 mg，導致 100%死亡率的口服致死劑量為 700 mg/kg。在小鼠中，口服 LD_{50} 為 400 mg/kg。在一次胃內給予溴酸鉀後，大鼠、小鼠和倉鼠的 LD_{50} 超過 3700 mg/kg。這些物種的 LD_{50} 值在 300~500 mg/kg 的範圍內。[1]
- 重複劑量毒性：用溴酸鉀進行研究。由對溴酸鈉的研究並參照結果顯示，這兩種物質會都在水中解離，且鈉(Na+)和鉀(K+)離子都是天然存在的物質。Kurokawa 等人評估溴酸鹽的亞慢性效應（1990 年），它們在水中以 0、150、300、600、1250、2500、5000 或 10000 ppm 的濃度，並對 F344 大鼠組（10 隻/性別/組）施用溴酸鉀 13 週。假設平均默認飲用水消耗量為 0.4 L/day，平均默認體重為 0.3 kg，研究顯示與這些濃度相對應的劑量約為 0、16、32、63、140、270、650 或 1080 mg BrO^{3-} /Kg/day。所有暴露於>1,250 ppm 的動物均在 7 週內死亡。觀察到的毒性跡象包括在≥600ppm 雄性大鼠體重減少和雄性及雌性大鼠血清鉀濃度顯著下降，觀察到腎小管的再生變化，該研究將 LOAEL 值確定為 63 mg BrO^{3-} /Kg bw/day，但提供的數據未足以確定在較低劑量下是否會發生影響。中野(1989)等人將雄性 Wistar 大鼠餵食 0.04%溴酸鉀飲用水，在 0.1 L/kg/day 的攝入量下，對應約為 30 mg BrO^{3-}/kg bw/day 的劑量下，長達 15 個月。發現動物的體重增加明顯受到抑制，7~11 週時的腎臟組織學檢查顯示腎內部存在異常變化。15 個月後發現 BUN 增加，皮質小管明顯結構異常。基於體重增加減少和腎臟影響，本研究確定可觀察到不良反應最低劑量(LOAEL)為 30 mg BrO^{3-} /kg bw/day，但無法確定未觀察到不良反應劑量 (NOAEL)。[3]
- 皮膚刺激性：針對天竺鼠刺激性研究發現，溴酸鈉具有刺激性。[1]
- 經皮吸收：在一些動物研究中發現，將溴酸鈉施用於切下的天竺鼠皮膚，通過測量總溴化物(Bromide)而不是溴酸鹽(Bromate)以確定溴酸鹽吸收量。如發生溴酸鹽吸收，則吸收速度很慢（30 分鐘內為 0.12%）。當將溴酸鈉施用在天竺鼠的皮膚上時，血液中沒有檢測到溴酸鹽。[1]
- 人類數據：據研究顯示人類意外或自殺性攝入永久性燙髮劑中和溶液後出現了幾例急性溴酸鹽中毒案例。這些產品通常含有 2%的

溴酸鉀或 10%的溴酸鈉。最常見的急性症狀是嚴重的胃腸道刺激（嘔吐、疼痛和腹瀉）和中樞神經系統抑鬱（嗜睡、低血壓和喪失反射反應），血管內溶血也可能導致貧血。這些影響通常是可逆的。後來的後遺症（通常在幾天內）包括明顯的腎損傷和聽力損失，但如果治療不成功，可能會導致腎衰竭死亡。如果治療成功，腎功能通常在 5~10 天後恢復。發生聽力損失通常是不可逆轉的。這些病例的估計劑量範圍為 20~1000 g BrO^{3-}/kg。[2]

- 其他安全資料：在幾項體內和體外研究中，發現溴酸鹽很難通過皮膚吸收。在哺乳動物細胞試驗和測試的三種細菌菌株中發現溴酸鉀具有致突變性。用於皮膚或皮下注射的溴酸鉀不會致癌，但這與口服給藥後觀察到的陽性結果相反，推測這些氧化劑的高反應性和較差的皮膚吸收，被認為是暴露途徑之間結果差異所造成之結果。根據 CIR 報告數據得出的結論是，溴酸鈉和溴酸鉀可以以不超過 10.17%的濃度（以溴酸鈉計）用於化粧品用燙髮配方。[4]
- 參考資料：

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

8. INCI name：Disodium Phosphate

- 急性毒性：據報導，磷酸鈉鹽(Sodium alts of phosphoric acid)的兔子皮膚單次劑量急性毒性 LD_{50} 範圍> 300 mg/kg ~ > 7940 mg/kg。在急性口服毒性研究中，給大鼠、小鼠、倉鼠和天竺鼠服用磷酸鈉鹽，LD_{50} 範圍為 1300 mg/kg（焦磷酸四鈉 Tetrasodium Pyrophosphate［小鼠］）至 10600 mg/kg（三偏磷酸鈉 Sodium Trimetaphosphate［大鼠］）。磷酸鈉鹽、鉀鹽和鈣鹽具有較低的吸

入毒性。[1]

- 眼睛刺激性：磷酸(Phosphoric Acid)在 70% ~ 85%的濃度範圍對兔子的眼睛有腐蝕性，但在 10%~17%的濃度範圍無刺激性。沒有一種磷酸鹽對兔子的眼睛有腐蝕性。[1]
- 重複劑量毒性：對大鼠餵食（飲食中最多 5%）磷酸二鈉(Disodium Phosphate)或焦磷酸二鈉(Disodium Pyrophosphate) 100 天的研究根據腎組織病理學結果推算出磷酸二鈉之 LOAEL< 2571 mg/kg/d。當將磷酸二鈉、三磷酸五鈉(Pentasodium Triphosphate)或焦磷酸四鈉(Tetrasodium Pyrophosphate)在飲食中以高達 5%的濃度給予大鼠 39 週時，報告得到的 LOAEL 為 495 mg/kg bw/day。在大鼠研究中，每天在飲食中餵食濃度高達 0.75%的磷酸(Phosphoric Acid)，持續時間> 52 週確定的最高 NOAEL 為 338 mg/kg bw/day。
- 皮膚刺激性：磷酸二鈉(Disodium Phosphate)具中度刺激性。[1]
- 皮膚致敏性：磷酸在人類受試者中不致敏，而磷酸鈉（在丙二醇中為 10%）在局部淋巴結試驗亦顯現不致敏。[1]
- 致癌性：非致癌性。[1]
- 遺傳毒性：磷酸及其銨鹽、鈉鹽、鉀鹽和鈣鹽在體外或體內遺傳毒性試驗為陰性。[1]
- 毒物動力學：磷酸鹽從胃腸道吸收，腸道管腔的運輸是一個依賴能量的過程。維生素 D 刺激磷酸鹽吸收。在生理 pH 7.4 下，細胞外磷酸鹽主要以磷酸二鈉鹽和磷酸鈉鹽(4:1)的形式存在。磷酸鹽一旦吸收，就會與鈣結合形成骨骼和牙齒中的磷酸氫鈣。游離正磷酸鹽是膳食吸收的主要形式，攝入大量的磷酸根離子後，腸中大部分的磷酸根離子吸收便會消除。根據另一種來源，成年人中約三分之二的磷酸根吸收是透過胃腸道吸收的，吸收的磷酸根幾乎全部釋放至尿液中。[1]
- 人體數據:依據FDA研究報告指出在確定的使用磷酸鈉片劑的178例患者（佔女性的 71%）中，每年與片劑製備相關的腎臟不良藥物反應的數量不斷增加。2006 年，研究 74 例腎臟不良藥物反應(renal adverse drug reactions, ADRs)中有 9 例(12%來自攝入片劑。片劑製劑中患有腎臟併發症的女性的平均體重為 68.57±1.78 kg，遠低於全國健康和營養檢查調查中同一年齡組的全國平均體重 74±0.5 kg (P = 0.003)。結論是，平均體重低於全國平均體重的女性中，磷酸鈉片引起的腎臟不良藥物反應更為常見。

◆ 其他安全資料：

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

◆ 參考資料：

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

(11) 產品安定性試驗報告

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

產品名稱	燙髮劑 1 號第一劑			
包裝材質	PVC			
試驗時間 / 試驗項目	第 0 個月	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	乳白色不透明	乳白色不透明	乳白色不透明	乳白色不透明
氣味	有刺激氣味	有刺激氣味	有刺激氣味	有刺激氣味
pH (at 25 °C)	9.57	9.46	9.79	9.65
微生物檢測結果	未檢出	未檢出	未檢出	未檢出
包材外觀	無膨脹、變色、腐蝕及脆裂之現象	無膨脹、變色、腐蝕及脆裂之現象	無膨脹、變色、腐蝕及脆裂之現象	無膨脹、變色、腐蝕及脆裂之現象
結果判定	■合格 □不合格	■合格 □不合格	■合格 □不合格	■合格 □不合格
參考試驗方法	ISO/TR 18811 Cosmetics-Guidelines on the stability testing of cosmetics products,2018. 參考 5.3.2 建議之溫度及濕度進行加速安定性試驗			
檢測人員/日期	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)
複核人員/日期	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)

產品名稱	燙髮劑 1 號第二劑			
包裝材質	PVC			
試驗時間 試驗項目	第 0 個月 40 ℃ 75 %RH	第 1 個月 40 ℃ 75 %RH	第 3 個月 40 ℃ 75 %RH	第 6 個月 40 ℃ 75 %RH
外觀	流動液體	流動液體	流動液體	流動液體
顏色	乳白色微透明	乳白色微透明	乳白色微透明	乳白色微透明
氣味	無	無	無	無
pH (at 25 °C)	5.61	5.73	5.58	5.42
微生物檢測結果	未檢出	未檢出	未檢出	未檢出
包材外觀	無變形、變色、腐蝕及脆裂之現象	無變形、變色、腐蝕及脆裂之現象	無變形、變色、腐蝕及脆裂之現象	無變形、變色、腐蝕及脆裂之現象
結果判定	■合格 □不合格	■合格 □不合格	■合格 □不合格	■合格 □不合格
參考試驗方法	ISO/TR 18811 Cosmetics-Guidelines on the stability testing of cosmetics products,2018. 參考 5.3.2 建議之溫度及濕度進行加速安定性試驗			
檢測人員/日期	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)
複核人員/日期	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)	(請簽名並加上日期)

(12) 微生物檢測報告

燙髮劑1號第一劑雖然含氨0.448%，未符合ISO 29621: 2017微生物低風險性含氨≥0.5%之條件，判斷非屬於低微生物風險產品，此類產品仍須進行防腐效能試驗及微生物檢測。

產品名稱	燙髮劑 1 號-第一劑		
產品批號	IT1107AC		
產品製造日期	111.07.05		
包裝材質	PVC	試驗日期	111.07.08
檢測項目	規 格	檢測結果	參考測試方法
生菌數	<1000 CFU/g	未檢出 (<10 CFU/g)	參考衛生福利部食品藥物管理署 109.07.28 及 111.04.21 公布建議檢驗方法-化粧品中微生物檢驗方法及化粧品中白色念珠菌之檢驗方法。
大腸桿菌	不得檢出	未檢出	
綠膿桿菌	不得檢出	未檢出	
金黃色葡萄球菌	不得檢出	未檢出	
白色念珠菌	不得檢出	未檢出	
結果判定	■合格	□不合格	
檢測人員/日期	(請簽名並加上日期)		
複核人員/日期	(請簽名並加上日期)		

產品名稱	燙髮劑 1 號-第二劑		
產品批號	IT1107AC		
產品製造日期	111.07.05		
包裝材質	PVC	試驗日期	111.07.08
檢測項目	規 格	檢測結果	參考測試方法
生菌數	<1000 CFU/g	未檢出 (<10 CFU/g)	參考衛生福利部食品藥物管理署 109.07.28 及 111.04.21 公布建議檢驗方法-化粧品中微生物檢驗方法及化粧品中白色念珠菌之檢驗方法。
大腸桿菌	不得檢出	未檢出	
綠膿桿菌	不得檢出	未檢出	
金黃色葡萄球菌	不得檢出	未檢出	
白色念珠菌	不得檢出	未檢出	
結果判定	■合格 □不合格		
檢測人員/日期	(請簽名並加上日期)		
複核人員/日期	(請簽名並加上日期)		

(13) 防腐效能試驗報告

燙髮劑1號第一劑雖然含氨0.448%，未符合ISO 29621: 2017微生物低風險性含氨≥0.5%之條件，判斷非屬於低微生物風險產品，此類產品仍須進行防腐效能試驗及微生物檢測。

樣品名稱 (Sample Name)	燙髮劑 1 號第一劑				
測試日期(Date Tested): 110/06/01~110/06/30					
試驗參考方法(Method Code): 衛福部食藥署 110.05.13 公告之化粧品防腐效能試驗指引					
測試菌種 (Microbial strains)					
分析時間點 (Assay Time)	大腸桿菌 *Escherichia coli* (ATCC 8739) (CFU/g or ml)	金黃色葡萄球菌 *Staphylococcus aureus* (ATCC 6538) (CFU/g or ml)	綠膿桿菌 *Pseudomonas aeruginosa* (ATCC 9027) (CFU/g or ml)	白色念珠菌 *Candida albicans* (ATCC 10231) (CFU/g or ml)	黑麴菌 *Aspergillus brasiliensis* (ATCC 16404) (CFU/g or ml)
第 0 天	8.4×10^5	9.8×10^5	9.3×10^5	8.9×10^4	9.1×10^4
第 7 天	<10	<10	<10	$6.3X10^2$	$3.5X10^3$
第 14 天	<10	<10	<10	<10	$1.3X10^2$
第 28 天	<10	<10	<10	<10	<10
檢測人員/日期	（請簽名並加上日期）				
複核人員/日期	（請簽名並加上日期）				

樣品名稱 (Sample Name)	燙髮劑 1 號第二劑
測試日期(Date Tested): 110/06/01~110/06/30	
試驗參考方法(Method Code): 衛福部食藥署 110.05.13 公告之化粧品防腐效能試驗指引	

測試菌種 (Microbial strains)					
分析時間點 (Assay Time)	大腸桿菌 *Escherichia coli* (ATCC 8739) (CFU/g or ml)	金黃色葡萄球菌 *Staphylococcus aureus* (ATCC 6538) (CFU/g or ml)	綠膿桿菌 *Pseudomonas aeruginosa* (ATCC 9027) (CFU/g or ml)	白色念珠菌 *Candida albicans* (ATCC 10231) (CFU/g or ml)	黑麴菌 *Aspergillus brasiliensis* (ATCC 16404) (CFU/g or ml)
第 0 天	8.8×10^5	9.2×10^5	9.4×10^5	8.6×10^4	9.7×10^4
第 7 天	<10	<10	<10	$3.7X10^2$	$2.6X10^3$
第 14 天	<10	<10	<10	<10	$1.4X10^2$
第 28 天	<10	<10	<10	<10	<10

檢測人員/日期	(請簽名並加上日期)
複核人員/日期	(請簽名並加上日期)

(14) 功能評估佐證資料

燙髮劑相關功能性測定，如燙髮捲度試驗等。

(15) 與產品接觸之包裝材質資料

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

III. 安全評估資料

(16) 產品安全資料

燙髮劑 1 號每日皮膚暴露量計算

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

基本數據	
平均體重(K)	60 kg
接觸部位	頭皮
日常每日使用劑量(GBC)	4.0 g/day
駐留因子(RBC)	0.1
每日皮膚暴露量(Edermal) Edermal =(GBC* RBC)/K (4.0×0.1)/60 = 0.00667 g/Kg bw/day = 6.67 mg/kg bw/day	

燙髮劑 1 號各個成分 MoS 值計算

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

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

MoS*= PODsys/*SED

PODsys 可以是 BMDL 或者是 NOAEL、LOAEL。

SCCS 化粧品成分測試及其安全性評估指引第 12 版(SCCS/1647/22)提及 90 天口服毒性試驗是化粧品成分最常用的重複劑量毒性試驗，當有科學合理的 90 天研究確認明確的 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 (%)	皮膚吸收指數 DAp(%)	NOAEL (mg /kg bw/day)	SED (mg /kg bw/day)	MoS
Aqua	84.3	-	-	-	>100
Ammonium Thioglycolate (50% Solution)	10.0	1.09	129	0.0036	35487
Polysorbate 80	2.0	100	730	0.1334	5472
Ammonia (28% Solution)	1.6	100	77	0.0299	2577
Sorbitan Stearate	1.0	100	2500	0.0667	37481
Paraffinum Liquidum	0.6	10	600	0.0040	299850
Lanolin Wax	0.5	100	500	0.0334	14993

第二劑

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

INCI name	NOAEL 校正說明
Ammonium Thioglycolate (50% Solution)	對大鼠13週反覆皮膚毒性研究中，系統性NOAEL為180 mg/kg bw/day，考慮每週只進行5天試驗不確定因子，將180*5/7 =129 mg/kg bw/day。
Polysorbate 80	大鼠膳食亞慢性研究(BIBRA, 1981)中，確定的NOAEL相當於1460 mg/kg bw/day(未說明天數)，考慮口服生物可用率50%之不確定因子，將1460*50% =730 mg/kg bw/day。
Ammonia (28% Solution)	參照在飲用水中添加0.01%氨水大鼠試驗8週中，磷酸二銨NOAEL為250 mg/kg bw/day，考慮口服生物可用率50%及試驗天數(8週)之不確定因子，將250*50%*8/13=77 mg/kg bw/day。
Sorbitan Stearate	雄性大鼠餵食5%脫水山梨糖醇硬脂酸酯2年NOAEL為5000 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，將5000*50% =2500 mg/kg bw/day。
Paraffinum Liquidum	在一項為期2年長期研究中，F344大鼠口服高黏度(P-100)和I類中黏度(P-70)白油，NOAEL為1200 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，將1200*50%=600 mg/kg bw/day。
Lanolin Wax	13週大鼠口服毒性得知NOAEL約為1000 mg/kg bw/day，考慮口服生物可用率50%之不確定因子，將1000*50% =500 mg/kg bw/day。
Sodium Bromate	長達15個月Wistar大鼠餵食0.04%溴酸鉀飲用水，確定可觀察到不良反應最低劑量(LOAEL)為30 mg /kg bw/day，考慮LOAEL轉換成NOAEL及口服生物可用率50%之不確定因子，將30/3*50% =5 mg/kg bw/day。
Disodium Phosphate	大鼠口服5%磷酸二鈉39週，報告得到的LOAEL為495 mg/kg bw/day，考慮LOAEL轉換成NOAEL及口服生物可用率50%之不確定因子，495/3*50% =82.5 mg/kg bw/day。

燙髮劑 1 號安全評估結論

安全評估結論簡述

經分析所有可取得之安全性資料，根據上述評估計算結果並根據當前科學知識據以結論，推定燙髮劑 1 號在預期正常合理使用條件下，本產品為可安全使用之產品，對人體健康造成傷害風險低。

標籤警語和使用說明

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

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

安全評估理由

燙髮劑 1 號的安全性評估基於每種成分的毒理學特性並評估所收集之產品數據。

1. 該產品在符合化粧品優良製造規範之場所和生產設施中生產，並進行微生物品質管理以及倉儲管理作業。
2. 由於該產品含有濃度 7% Sodium Bromate 強氧化劑成分，根據 CIR 研究數據，CIR 專家小組得出的結論是，溴酸鈉可以不超過 10.17%的濃度用於化粧品用燙髮配方，我國溴酸鈉限制使用濃度標準為 11.5%，燙髮劑 1 號添加 7% Sodium Bromate 是合乎規範且安全的。
3. 根據本產品「燙髮劑 1 號」之物理/化學特性、安定性試驗報告、微生物檢測報告及防腐效能試驗評估，結果由數據顯示產品符合規格特性，證實「燙髮劑 1 號」產品配方具有足夠安定性及微生物安全性。
4. 燙髮劑 1 號第一劑經評估非屬於低微生物風險產品，故仍需進行防腐效能試驗及微生物檢測。燙髮劑 1 號第一劑及第二劑微生物檢測報告結果符合我國化粧品微生物容許量基準之要求，防腐效能試驗報告顯示符合衛福部食藥署 110.05.13 公告之化粧品防腐效能試驗指引標準 A，表示產品微生物汙染風險受到管控，可保護產品避免受到潛在微生物汙染之風險。

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

(請簽名並加上日期)

_____

安全資料簽署人員簽名及日期

附錄 1 產品及各別成分之物理及化學特性資料

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

INCI name：Ammonia

SAFETY DATA SHEET

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

1.1 Product identifiers

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

1.2 Other means of identification

No data available

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

Identified uses : Reagent for analysis, Chemical production

1.4 Details of the supplier of the safety data sheet

1.5 Emergency telephone

SECTION 2: Hazards identification

2.1 GHS Classification

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

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

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

2.2 GHS Label elements, including precautionary statements

Pictogram

Signal word: Danger

Hazard statement(s)

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

Precautionary statement(s)

Prevention

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

Response

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

Storage

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

Disposal

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

2.3 Other hazards - none

SECTION 3: Composition/information on ingredients

Substance / Mixture : Mixture

3.2 Mixtures

Hazardous ingredients

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

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

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

SECTION 4: First aid measures

4.1 Description of first-aid measures

General advice
First aiders need to protect themselves.

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

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

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

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

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

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

SECTION 5: Firefighting measures

5.1 Extinguishing media

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

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

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

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

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

SECTION 6: Accidental release measures

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

6.2 Environmental precautions
Do not empty into drains.

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

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling

Advice on safe handling
Observe label precautions.

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

7.2 Conditions for safe storage, including any incompatibilities

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

Recommended storage temperature see product label.

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

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

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

Personal protective equipment

Eye/face protection
Tightly fitting safety goggles

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

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

Body Protection
protective clothing

Respiratory protection
required when vapours/aerosols are generated.

Control of environmental exposure
Do not empty into drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

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

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

9.2 Other safety information

Minimum ignition energy	380 - 680 mJ

SECTION 10: Stability and reactivity

10.1 Reactivity

No data available

10.2 Chemical stability

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

10.3 Possibility of hazardous reactions

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

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

10.4 Conditions to avoid
Heating.

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

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

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Mixture

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

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

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

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
No data available

Carcinogenicity
No data available

Reproductive toxicity
No data available

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

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information

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

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

Components

ammonia solution

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

Skin corrosion/irritation
Causes skin burns.

Serious eye damage/eye irritation
Causes serious eye damage.

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
No data available

Carcinogenicity
No data available

Reproductive toxicity
No data available

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

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

SECTION 12: Ecological information

12.1 Toxicity

Mixture
No data available

12.2 Persistence and degradability
Biodegradability Remarks: No data available

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

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

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

Discharge into the environment must be avoided.
No data available

Components

ammonia solution

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

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product

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

SECTION 14: Transport information

14.1 UN number

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

14.2 UN proper shipping name

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

14.3 Transport hazard class(es)

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

14.4 Packaging group

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

14.5 Environmental hazards

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

14.6 Special precautions for user

None

14.7 Incompatible materials

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

SECTION 15: Regulatory information

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

No data available

SECTION 16: Other information

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

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

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

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

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

附錄 2 各成分之毒理相關資料

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

INCI name：Ammonia

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

Safety Assessment of
Ammonia and Ammonium Hydroxide as Used in Cosmetics

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

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

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

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INTRODUCTION

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

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

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

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

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

CHEMISTRY

Definition and General Characterization

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

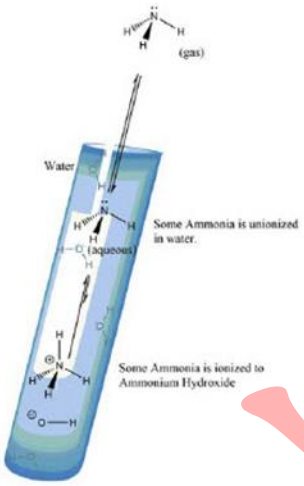


Figure 1. The aqueous relationship of Ammonia and Ammonium Hydroxide

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

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

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

Chemical and Physical Properties

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

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

Method of Manufacture

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

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

Composition

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

Impurities

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

USE

Cosmetic

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

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

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

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

Noncosmetic

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

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

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

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

TOXICOKINETIC STUDIES

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

Absorption, Distribution, Metabolism, and Excretion

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

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

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

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

Animal

Inhalation

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

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

Parenteral

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

Human

Oral

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

TOXICOLOGICAL STUDIES

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

Acute Toxicity Studies

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

Dermal

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

Oral

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

Inhalation

In 10-minute exposure studies involving mice, LC_{50s} of ≤ 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_{50s} 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.[53,63]

Chronic Toxicity Studies

Dermal

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

Oral

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

Ammonium Sulfate (included as a potentially similar ammonium salt)

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

Inhalation

Human

Risk Assessment

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

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

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

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

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental/reproductive toxicity studies are summarized in Table 7.

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

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

GENOTOXICITY STUDIES

In Vitro

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

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

In Vivo

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

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

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

CARCINOGENICITY STUDIES

Carcinogenicity and tumor promotion studies are summarized in Table 8.

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

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

Tumor Promotion

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

OTHER RELEVANT STUDIES

Neurotoxicity

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

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

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

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

Cytotoxicity

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

Effect on Mitosis

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

Permeation of Blood Brain Barrier

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

Generation of Free Radicals

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

Immunological Effects

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

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

Neurological Effects

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

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

DERMAL IRRITATION AND SENSITZATION STUDIES

Dermal irritation studies are summarized in Table 9.

Irritation

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

Sensitization

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

OCULAR IRRITATION STUDIES

Ocular irritation studies are summarized in Table 10.

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

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

MUCOUS MEMBRANE IRRITATION STUDIES

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

CLINICAL STUDIES

Case Reports

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

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

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

Other Clinical Reports

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

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

EPIDEMIOLOGICAL STUDIES

Non-Cancer Endpoints

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

SUMMARY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Request for Additional Data

- Dermal absorption data
- Sensitization data

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

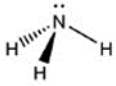
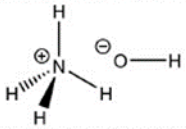
Ingredient CAS No.	Definition & Idealized Structures	Function
Ammonia	Ammonia is an inorganic gas that conforms to the formula:  (See also Ammonium Hydroxide)	External Analgesics; Fragrance Ingredients; pH Adjusters
Ammonium Hydroxide	Ammonium Hydroxide is an inorganic base that conforms to the formula: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

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

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

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

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

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

Table 4. Acute Oral Toxicity Studies

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

Table 5. Acute Inhalation Toxicity

Ingredient	Animals/Protocol	Results
Ammonia (21,400 ppm)	Mice. 30-minute exposure	Signs and symptoms included eye irritation (blinking and scratching), dyspnea, frothing, convulsions, excitation/escape behavior, coma, and death. Histopathology of the lungs of mice that died showed alveolar disruption and loss of septal continuity.[22,47]
Ammonia (8,770-12,940 ppm)	Mice (groups of 20). 10-minute exposure	LC_{50}=10,150 ppm.[46,48,53]
Ammonia (8,723-12,870 ppm)	Mice. 10-minute exposure	At 8,723 ppm, 25% of the animals died. At 12,870 ppm, and 80% of the animals died. LC_{50} = 10,096 ppm.[22,48]
Ammonia (3,600-5,720 ppm)	Mice. 1-h exposure	Nasal and eye irritation, followed by labored breathing, in all groups. Gross examination of surviving mice showed mild congestion of the liver at the intermediate (4550 ppm) and high (5720 ppm) concentrations. LC_{50} = 4837 ppm (95% CI = 4409–5305 ppm).[22,50,53]
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.[22,49,53]
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.[56]
Ammonia (3028-14,044 ppm)	Male and female SPF-bred Wistar rats (Hsd Cpb:WU strain; 5 males, 5 females). Nose-only exposure to 9,222-14,044 ppm for 1 h and 3,028-5,053 ppm for 4 h.	Signs typical of upper respiratory tract irritation. No gross abnormalities in any organ or nasal passages were found at necropsy of surviving rats (2 weeks post-exposure). Rats that died had corneal opacity, collapsed lungs, nasal discharge, reddened larynx, and tracheal epithelial desquamation. LC_{50} (1-h exposure) = = 12,303 mg/m^3 [~17,633 ppm]). LC_{50} (4-h exposure = 4,923 mg/m^3 [~7068 ppm]).[57] -
Ammonia (6210-9840 ppm)	Groups of 10 male CFE rats. 1-h exposure	Signs of eye and nasal irritation observed immediately, followed by labored breathing and gasping. Surviving animals exposed to the low concentration weighed less than controls on day 14, and gross examination showed mottling of the liver and fatty changes at the two highest concentrations. LC_{50} = 7338 ppm (95% CI = 6822–7893 ppm).[22,50-53]
Ammonia (431, 1436, and 4307 ppm)	Rats. Inhalation exposure	Decrease in static muscular tension and other sublethal effects.[53]
Ammonia (1436, 4307, and 6814 ppm)	White rats. Inhalation exposure	Dyspnea, irritation of respiratory tract and eyes, cyanosis of extremities, and increased excitability.[53]
Ammonia (92 mg/m^3 [~132 ppm] to 1243 mg/m^3 [~1785 ppm])	Groups of 4 male specific pathogen free (SPF) Wistar rats of the Hsd Cpb:WU (SPF) strain. Nose-only exposure for 45 minutes	RD_{50} = 972 and 905 mg/m^3 (corresponding to ~1396 and ~1299 ppm, respectively) in rats in dry and wet air, respectively.[22,58]
Ammonia (500 ppm)	Rats. Inhalation exposure	Reduced body weight.[59]
Ammonia (144 ppm)	Rats. Inhalation exposure for 5, 10, 15, 30, or 60 minutes	No effects.[53]
Ammonia (5,200-12,800 ppm)	Rabbits. 1-h exposure	Average survival: 18 h (gassed after cannulation), 33 h (gassed before cannulation). 2- to 3-fold increase in production of respiratory tract fluid. No change in water content of lungs. Increased blood hemoglobin. Increased plasma lipids.[22]
Ammonia (10,360 ppm, average)	Rabbits. 1-h exposure	Congestion of respiratory tract tissues.[22]
Ammonia (50 ppm and 100 ppm)	16 New Zealand White rabbits. Inhalation Exposure for 2.5 h to 3 h	Significant decrease in rate of respiration.[53]
Ammonia (3.5 ppm and 8.7 ppm)	54 rabbits. Exposure for 1 h	Increased respiratory tract fluid output by 2- to 3-fold. No appreciable effect on water content of respiratory tract tissues. Transient decrease in blood hemoglobin. Lipemia also observed.[53]

Table 5. Acute Inhalation Toxicity

Ingredient	Animals/Protocol	Results
Ammonia (5,200-12,800 ppm)	Cats. 1-h exposure	Average survival: 18 h (gassed after cannulation), 33 h (gassed before cannulation). 2- to 3-fold increase in production of respiratory tract fluid. No change in water content of lungs. Increased blood hemoglobin. Increased plasma lipids.[46,60]
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.[53]

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.[4,53,45]
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.[63]
Ammonia (~653 ppm)	Sprague-Dawley or Long-Evans rats (males and females, 15 to 51/group)	Inhalation exposure for 65 days	Lung effects: Focal or diffuse interstitial pneumonitis in all animals. Upper respiratory tract effects: Dyspnea and nasal irritation/discharge.[3,63]
Ammonia (650 ppm; Ct [product of concentration and exposure time (ppm-h)] =1,014,000)	51 rats	Continuously for 65 days	32 of 51 rats dead by day 25 (390,000 ppm-h); 50 of 51 rats dead by day 65 (1,014,000 ppm-h).[46,63]
Ammonia (500 ppm)	27 male rats	Continuous inhalation exposure for up to 8 weeks	After 3 weeks, nasal irritation and inflammation of upper respiratory tract, but no effects observed in bronchioles and alveoli. No lesions observed at 8 weeks.[53,59]

Table 6. Short-Term and Subchronic Toxicity Studies

Ingredient	Animals	Protocol	Results
Ammonia (250 ppm)	F344 rats (6/sex/group)	Exposure in inhalation chamber for 35 days	Increased thickness of nasal epithelium (3 to 4 times) and nasal lesions at 150 ppm.[3,64]
Ammonia (221 ppm; Ct [ppm-h] = 53,040)	Rats, guinea pigs, rabbits, squirrel monkeys, and beagle dogs	5 days per week (8 h per day) for 6 weeks	No effect.[46,63]
Ammonia (10 or 150 ppm)	Sherman rats (5/sex/group)	Inhalation exposure from bedding for 75 days	Increased thickness of nasal epithelium (3 to 4 times) and nasal lesions at 150 ppm.[3,53,64]
Ammonia (50 or 90 ppm)	Male Wistar rats (8-14 per group)	Inhalation exposure continuously for 50 days	None of the animals died and there were no treatment-related effects.[53,70]
Ammonia (12% solution)	50 maleWhite albino mice	Vapor exposure 6 days per week (15 minutes/day) for 4, 5, 6, 7, or 8 weeks	Nasal mucosa adversely affected. Histological changes progressed from weeks 4–8 from crowding of cells forming crypts and irregular arrangements to epithelial hyperplasia, patches of squamous metaplasia, loss of cilia, and dysplasia of the nasal epithelium. One animal that had loss of polarity of the epithelium, hyperchromatism, and mitotic figures with an intact basement membrane also had a carcinoma *in situ* in one nostril. At week 8, one mouse had an invasive adenocarcinoma of the nasal mucosa. Histo-chemical results were also abnormal.[3,90]
Ammonia (78 ppm, 271 ppm, and 711 ppm)	Groups of 10 male Swiss mice	Exposure for 4, 9,or 14 days (6 h/day)	No clinical signs of toxicity were noted for mice exposed to ammonia. Rhinitis and pathologic lesions with metaplasia and necrosis were seen only in the respiratory epithelium of the nasal cavity of mice inhaling 711 ppm, the severity of the lesions increased with duration of exposure, ranging from moderate on day 4, severe on day 9, to very severe on day 14. No lesions were seen in the controls or in mice inhaling the 78 ppm. No effects were seen at 271 ppm, even after 9 days of exposure.[22,65]
Ammonia (303 ppm)	Groups of 16 to 24 male Swiss Webster mice	Exposure for 5 days (6 h/day)	Histopathological findings, which were confined to the respiratory epithelium of the nasal cavity, included minimal exfoliation, erosion, ulceration, and necrosis; moderate inflammatory changes; and slight squamous metaplasia.[22,66]
Ammonia (20 ppm)	Swiss albino mice (males and females, groups of 4)	Exposure for 7, 14, 21, 28, or 42 days	Lung congestion, edema, and hemorrhage observed after 42 days.[3,67]
Ammonia (170 ppm; Ct [ppm-h] =30,600 to 91,800)	Guinea pigs	5 days per week (6 h per day) for 6 weeks	No histopathologic changes.[46,74]

Table 6. Short-Term and Subchronic Toxicity Studies

Ingredient	Animals	Protocol	Results
Ammonia (50 ppm)	Guinea pigs (males and females, groups of 6)	Exposure for 42 days	Lung congestion, edema, and hemorrhage.[3,67]
Ammonia (20 ppm)	Guinea pigs (males and females, groups of 2)	Exposure for 7, 14, 21, 28, or 42 days	Lung congestion, edema, and hemorrhage after 42 days. [3,67]
Ammonia (100 ppm [average range = 20 to 203 ppm; Ct [ppm-h] =100,800) alone and with con 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, 46,129]
Ammonia (10 ppm and 50 to 150 ppm; Ct [ppm-h] = 42,000 to 126,000)	Duroc Pigs (groups of 36)	Continuously for 5 weeks	Excessive nasal, lacrimal and mouth secretions at 50, 100, and 150 ppm; more pronounced at 100 and 150 ppm, gradually diminishing over 1-2 weeks. No histopathologic changes in nasal turbinates or lung.[4,46,71]
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.[53,63]
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).[2,83]
diammonium phosphate (17.9% NH_4 and 46.86% P_2O_5 equivalent)	Groups of Crj: CD(SD) rats (5 males, 10 females [reproductive subgroup])	Administered by gavage daily (doses of 0, 250, 750, and 1500 mg/kg/day) for, at most, 28 days (males) and 53 days (females).	No treatment-related deaths and no signs of overt clinical toxicity. Body weight gain was reduced during the first week of gestation (82% of control) in females dosed with 1500 mg/kg/day, but returned to control levels for remainder of study. Mating performance and fertility were unaffected by treatment, and parental treatment had no apparent effect on the offspring to day 4 of age. NOAEL for reproductive and developmental toxicity = 1500 mg/kg/day; LOAEL = > 1500 mg/kg/day.[4,45]
diammonium phosphate	Groups of 10 (5 males, 5 females) Crj: CD(SD) rats	Administered by gavage daily for, at most, 28 days (males) and 53 days (females). Doses of 0, 250, 750, and 1500 mg/kg/day.	Mating performance and fertility unaffected by dosing. Also, dosing had no apparent effect on offspring up to 4 days of age. NOAEL (for reproductive and developmental toxicity) = 1500 mg/kg/day; LOAEL = 1500 mg/kg/day.[4,55]
Inhalation Study			
Ammonia (7 ppm or 35 ppm)	Female pigs	Exposure for 6 weeks (7 ppm or 35 ppm). Exposure to ~7 ppm or ~35 ppm from 6 weeks prior to breeding until day 30 of gestation	No statistically significant differences in ovarian or uterine weights after 6 weeks of exposure. After exposure from 6 weeks prior to breeding until day 30 of gestation, no statistically significant differences in age at puberty, number of live fetuses, fetal length, or fetus-to-corpus luteum ratio compared to pigs exposed to only about 7 ppm . No unexposed controls were included in this study.[81]

Table 8. Carcinogenicity and Tumor Promotion Studies

Ingredient	Animals	Protocol	Results
		Oral Studies	
Ammonia (dissolved in water)	Mice	Dose of 42 mg ammonium/kg/day by gavage for 4 weeks.	No evidence of carcinogenic effect.[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.[85]
Ammonium ion (and diethyl pyrocarbonate)	Pregnant mice	Exposure (by gavage) during pregnancy and lactation	No lung tumors.[87]
Ammonium Sulfate	Groups of 10 F344/DuCrj rats (male and female)	Dietary concentrations of 0%, 1.5%, 3% daily for 104 weeks	Survival rates of control, 1.5%, and 3% groups were 88%, 78%, and 76%, respectively, for males, and 76%, 80%, and 80%, respectively, for females. Neoplastic lesions (not treatment-related; occur spontaneously in rats of this strain): C-cell adenomas/adenocarcinomas in the thyroids, fibroadenomas/adenomas/adeno-carcinomas in mammary glands, adenomas/adenocarcinomas in pituitary glands, interstitial cell tumors in testes, and endometrial stromal polyps in uteri. The only macroscopic finding at necropsy was massive, nodular or focal lesions suggesting neoplastic change. Ammonium Sulfate classified as non-carcinogenic.[4]
Ammonium Sulfate	Groups of 10 F344/DuCrj rats (male and female)	Dietary concentrations of 0%, 0.1%, 0.6%, and 3% for 52 weeks	Neoplastic lesions reported included malignant pheochromocytoma of the adrenal gland in males of the 3% dietary group, 2 adenomas in the anterior pituitary of females of the 3% dietary group, and uterine endometrial stromal polyp in a female control rat.[4]

Inhalation Study			
Ammonia (12% solution)	10 male mice	Vapor exposure 6 days per week (15 minutes/day) for 4, 5, 6, 7, or 8 weeks	Histological changes progressed from (weeks 4 to 8) from crowding of cells forming crypts and irregular arrangements to epithelial hyperplasia, patches of squamous metaplasia, loss of cilia, and dysplasia of the nasal epithelium. One mouse had a carcinoma *in situ* in 1 nostril. At week 8, 1 mouse with invasive adenocarcinoma of the nasal mucosa. Authors noted that prolonged exposure to Ammonia may interfere with normal protective reflexes of the respiratory nasal mucosa, resulting in the accumulation of particulate matter initiating or promoting a neoplastic process.[90]
Tumor Promotion			
Ammonia (dissolved in water)	Rats	Rats pretreated with the initiator *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG) in drinking water for 4 weeks, prior to receiving 0.01% Ammonia solution in drinking water for 24 weeks	Statistically significantly greater incidence of gastric cancer (70% of rats) and number of tumors per tumor-bearing rat (2.1) than rats that received only MNNG and tap water (31% and 1.3 tumors/rat).[53,88]
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.[10,45]
Ammonium Hydroxide (10% and 12% aqueous)	Female Albino New Zealand White rabbits	Each solution (0.1 ml) applied, under an occlusive patch ("1 x 1"), to the skin for 4 h. There were 3 rabbits per dose, with 2 replicates per rabbit at each concentration.	The 12% solution was corrosive to the skin, but the 10% solution was not.[4]
Human Studies			
Ammonium Hydroxide (saturated aqueous solution)	16 subjects (10 men, 6 women)	Applied (via a chamber) to middle of ventral aspect of forearm	Formation of a well-defined, sub-epidermal blister (positive reaction) observed within a few minutes of chamber application; skin irritation observed in all subjects.[111]

Table 9. Dermal Irritation Studies

Ingredient	Animals/Subjects/Cells	Protocol	Results
Ammonium Hydroxide (1:1aqueous solution)	110 subjects	Test substance (0.5 ml) placed in 8 mm well drilled in acrylic plastic block (3 x 3 x 1 cm) that was strapped to the skin. Block (used to measure minimal blistering time [MBT, indicator of cutaneous irritability, defined as total exposure in well that results in a single bulla, occupying the total area of contact]).	MBT ranged from 3 to 57 minutes. Inflammatory reaction considered slight; healing was rapid and without scarring. Intensity of the dermatitis provoked by a 24-h exposure to sodium lauryl sulfate was strongly correlated with the MBT.[112]
Ammonium Hydroxide solution (50% solution)	Young adults and older adults	Blistering response measured	Mild discomfort during procedure. The initial response, characterized by the appearance of tiny follicular vesicles, occurred more quickly in older adults. The time required to produce a full blister was greatly prolonged in the aged.[113]

Table 10. Ocular Irritation Studies

Ingredient	Animals/Cells	Test Protocol	Results
In Vitro			
Ammonium Hydroxide	Human corneal endothelial cell cultures	^{51}Cr-release assay. Performed by loading the cells with isotope, incubating the cells with Ammonium Hydroxide, and measuring the isotope that was recovered in the medium.	Severe ocular irritant (ED_{50} = 3.9 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.[2,115]
Ammonium Hydroxide (0.3%, 1%, 2.5%, and 10%)	New Zealand albino rabbits (groups of 6)	Draize test. Test substance (0.1 ml) instilled into the eye. In 1 group, eyes rinsed after instillation	Conjunctivitis (at 1% to 10%, but not at 0.3%). Ammonium Hydroxide (10%) produced pannus in 5/6 unwashed rabbit eyes and 2.5% produced pannus in 1/6 unwashed and 6/6 washed eyes. Ammonium Hydroxide at 1% produced pannus in 3/6 washed eyes. Keratoconus was produced by 10% Ammonium Hydroxide in 4/6 unwashed eyes and 2/6 washed eyes and 2.5% produced keratoconus in 2/6 unwashed eyes. Ammonium Hydroxide (10%) caused corneal opacities within 1 h of instillation.[116]
Ammonium Hydroxide (prepared with 3% Ammonia)	3 New Zealand White Albino Rabbits	Draize test. Test substance (100 µl) instilled into eye	Conjunctivitis (score = 3 at 96 h; mean maximum Draize score = 3), chemosis (score = 3 at 96 h; mean maximum score = 4), iritis (score = 1; mean maximum Draize score = 2), corneal opacity (score = 4; mean maximum Draize score = 4), and mean surface of corneal damage (70% corneal damage; mean maximum Draize value = 100%). Risk of serious damage to the eyes.[117]

Table 11. Other Clinical Reports

Ingredient	Number of Subjects	Protocol	Results
Inhalation Exposure			
Ammonia (700 ppm)	Number of subjects not available	Not available	Eye irritation.[124]
Ammonia (500 ppm)	Number of subjects not available	30-minute exposure	Variable lacrimation.[124]
Ammonia (500 ppm)	Number of subjects not available	30-minute exposure	Increased blood pressure and pulse rate.[124]
Ammonia (500 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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