ReReview Summaries

Ascorbic Acid & Ascorbates
Glyceryl Monoesters – with use
Glyceryl Monoesters – no use
Isopropanolamines
Waxes

EXPERT PANEL MEETING
June 9-10, 2025

Safety Assessment of Ascorbic Acid and Ascorbates as Used in Cosmetics

Status: Extended Re-Review Summary for Panel Approval
Release Date: May 16, 2025
Panel Meeting Date: June 9 – 10, 2025

History
Original Safety Assessment – published 2005
Most Recent Action – new data considered at the September 2024 Panel meeting; not re-opened

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Preethi Raj, M.S., former Senior Scientific Analyst/Writer, CIR, and Priya Ferguson, M.S., Senior Scientific Analyst/Writer, CIR.

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ASCORBIC ACID AND ASCORBATES

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published the Final Report of the Safety Assessment of L-Ascorbic Acid, Calcium Ascorbate, Magnesium Ascorbate, Magnesium Ascorbyl Phosphate, Sodium Ascorbate, and Sodium Ascorbyl Phosphate as Used in Cosmetics in 2005.[1] The Panel concluded, based on the available data contained in the report, that these ingredients are safe as used in cosmetic products.

Because it has been at least 15 years since the final report was published, in accordance with Cosmetic Ingredient Review (CIR) Procedures, the Panel considered whether the safety assessment should be reopened. At the September 2024 meeting, the Panel discussed updated (2023) frequency of use as reported in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database[2] and maximum concentrations of use provided in response to a survey conducted by the Personal Care Products Council.[3] Reported frequencies of use have increased significantly from the last review. For example, according to VCRP data, Ascorbic Acid was reported to be used in 1267 formulations in 2023 as compared to 431 formulations in 2001, and Sodium Ascorbyl Phosphate was reported to be used in 355 formulations in 2023, as compared to 0 uses in 2001. Maximum reported concentrations of use have also changed. The maximum concentrations of use of Ascorbic Acid increased; Ascorbic Acid was reported to be used at a maximum of 17% in skin fresheners in 2023, while in 2000, it was reported to be used at up to 10% in face and neck products and body and hand products. However, the maximum concentrations of use for the other ingredients decreased. For example, Magnesium Ascorbyl Phosphate was reported to be used at up to 3% in several leave-on product categories in 2000, but at only up to 0.5% in moisturizing products in 2023. The cumulative frequency and concentration of use data are presented in Table 1, and the two ingredients with no uses reported in 2023 or in 2000/2001 are listed in Table 2.

In August 2024, an extensive search of the world's literature was performed for studies dated 2000 forward, and a considerable amount of new data were found. The information that was found, including dermal penetration, acute and short-term toxicity, in vitro genotoxicity, in vitro anti-carcinogenicity, dermal irritation, sensitization, photoprotection, and ocular irritation studies as well as a case report, was similar to and primarily additive to the substantial data set included in the original safety assessment. Although the Panel was of the opinion that these new data served to reaffirm the existing conclusion of safety, they thought it was important that this information was captured robustly. Accordingly, these studies are summarized in Tables 3 - 9.

In summary, the Panel reviewed 2023 frequency and concentration of use data and the new, available, relevant safety data. After considering this information, as well as the information provided in the original safety assessment, the Panel reaffirmed the 2005 conclusion. The Panel discussed the possibility for these ingredients to be used in cosmetic products which may be incidentally inhaled. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings This resource document also notes that airbrush technology presents a potential safety concern. Although frequency and/or concentration of use data are now available (and in some cases mandated) for ingredients marketed for use with airbrush delivery systems in certain product categories, no data are available for consumer habits and practices thereof, product particle size, or other relevant particle data (e.g., diameter). As a result of deficiencies in these critical data needs, the data profile is incomplete, and the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Accordingly, the Panel has concluded the data are insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

Table 1. Frequency (2023/2001) and concentration (2022/2000) of use according to likely duration and exposure and by product category

	Ascorbic Acid				Magnesium Ascorbyl Phosphate				Sodium Ascorbate				Sodium Ascorbyl Phosphate			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2023[2]	**2001**[1]	**2023**[3]	**2000**[1]	**2023**	**2001**[1]	**2023**	**2000**[1]	**2023**[2]	**2001**[1]	**2023**[3]	**2000**[1]	**2023**[2]	**2001**[1]	**2023**[3]	**2000**[1]
Totals*	**1267**	**431**	**0.000005 – 17*****	**0.00001 – 10**	**206**	**37**	**0.00001 – 0.5**	**0.001 – 3**	**32**	**6**	**0.001 – 0.1**	**0.0003 – 0.3**	**355**	**NR**	**0.001 – 2**	**0.01 – 3**
summarized by likely duration and exposure**																
Duration of Use																
Leave-On	*837*	*42*	*0.000005 – 17*	*0.00001 - 10*	*184*	*33*	*0.00001 – 0.5*	*0.001 – 3*	*28*	*6*	*0.001 – 0.1*	*0.0003*	*271*	*NR*	*0.001 – 2*	*0.01 – 3*
Rinse-Off	*427*	*388*	*0.00001 – 11.6****	*0.0001 - 5*	*22*	*4*	*0.00001*	*0.001 – 0.5*	*4*	*NR*	*0.001 – 0.01*	*0.3*	*82*	*NR*	*0.003 – 0.93*	*NR*
Diluted for (Bath) Use	*3*	*1*	*0.0001 – 0.0004*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*2*	*NR*	*NR*	*NR*
Exposure Type*																
Eye Area	38	NR	0.001 – 0.1	0.00001 – 0.001	19	1	0.001 – 0.025	0.001 – 0.1	NR	NR	NR	NR	17	NR	0.1 – 0.91	0.01
Incidental Ingestion	89	3	0.0015 – 0.0045	0.001	1	NR	NR	NR	1	1	NR	0.0003	3	NR	0.095 – 0.93	NR
Incidental Inhalation-Spray	13; 438[a] 156[b]	4; 11[a]; 7[b]	0.00005 – 0.015; 0.0001 – 17[a]	0.001 – 0.05[a]; 0.0001 -10[b]	62[a]; 65[b]	1; 20[a]; 9[b]	NR	0.05 – 3; 0.001 – 3[a]; 0.02 – 3[b]	11[a]; 9[b]	4[a]; 1[b]	NR	NR	1; 107[a]; 99[b]	NR	0.05; 0.006[a]	0.05; 3[a]; 0.1 – 1[b]
Incidental Inhalation-Powder	1; 156[b]; 1[c]	9; 7[b]	0.001 – 0.5; 0.00005 – 10.5[c]	0.0001 – 10[b]	1; 65[b]	9[b]	0.022; 0.000073 – 0.034[c]	0.1 – 3; 0.02 – 3[b]	9[b]	1[b]	0.001 – 0.1[c]	NR	99[b]	NR	0.0048; 0.005 – 0.5[c]	0.1 – 1[b]
Dermal Contact	803	30	0.000005 - 17	0.00001 - 10	192	37	0.00001 – 0.5	0.001 – 3	27	5	0.001 – 0.1	NR	303	NR	0.0048 – 2	0.01 – 3
Deodorant (underarm)	17[a]	NR	0.005 – 0.05	NR	1[a]	NR	NR	NR	3[a]	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	84	50	0.0001 – 23.4	0.0001 – 0.05	5	NR	0.00001	0.001	1	NR	NR	NR	45	NR	0.001 – 0.017	0.05
Hair-Coloring	276	348	0.03 – 11.6***	0.3 – 0.6	1	NR	NR	NR	3	NR	NR	0.3	NR	NR	NR	NR
Nail	15	NR	0.001 – 0.01	NR	7	NR	0.0005	0.05	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	119	6	0.00001 – 0.3	0.001	3	NR	NR	NR	1	1	0.001 – 0.01	0.0003	24	NR	0.024 – 0.93	NR
Baby Products	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1	NR	NR	NR
as reported by product category																
Baby Products																
Baby Lotions/Oils/Powders/Creams	1	NR	NR	NR												
Other Baby Products													1	NR	NR	NR
Bath Preparations (diluted for use)																
Bath Oils, Tablets, and Salts	1	NR	0.0001 – 0.0004	NR												
Bubble Baths	NR	1	NR	NR												
Other Bath Preparations	2	NR	NR	NR									2	NR	NR	NR
Eye Makeup Preparations																
Eyebrow Pencil	NR	NR	NR	0.0005												
Eyeliner	1	NR	0.1	0.001									3	NR	0.91	NR
Eye Shadow	13	NR	0.001	NR	NR	NR	0.001	NR								
Eye Lotion	12	NR	0.001	0.00001	6	NR	0.025	0.04 – 0.1					4	NR	0.1	0.01
Eye Makeup Remover	NR	NR	0.001	0.001	1	NR	NR	NR								
Mascara					NR	NR	NR	0.05					1	NR	NR	NR
Other Eye Makeup Preparations	12	NR	0.01	0.01	12	1	NR	0.001					9	NR	NR	NR

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	Ascorbic Acid				Magnesium Ascorbyl Phosphate				Sodium Ascorbate				Sodium Ascorbyl Phosphate			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2023[2]	**2001**[1]	**2023**[3]	**2000**[1]	**2023**	**2001**[1]	**2023**	**2000**[1]	**2023**[2]	**2001**[1]	**2023**[3]	**2000**[1]	**2023**[2]	**2001**[1]	**2023**[3]	**2000**[1]
Fragrance Preparations																
Cologne and Toilet Water	NR	NR	spray: 0.001	NR												
Powders (dusting/talcum, excl aftershave talc)	NR	9	NR	NR									NR	NR	0.0048	NR
Other Fragrance Preparation	1	NR	NR	NR												
Hair Preparations (non-coloring)																
Hair Conditioner	19	15	0.001 – 23.4	0.001 – 0.05	2	NR	0.00001	0.001					19	NR	0.0095 – 0.017	NR
Hair Spray (aerosol fixatives)	12	4	aerosol: 0.015	NR									1	NR	NR	0.05
Hair Straighteners	1	NR	NR	NR												
Rinses (non-coloring)	NR	1	NR	NR									1	NR	NR	NR
Shampoos (non-coloring)	32	17	0.0002 – 0.15	0.0001 – 0.01	3	NR	0.00001	0.001					9	NR	0.003 – 0.0095	NR
Tonics, Dressings, and Other Hair Grooming Aids	14	7	0.0001 – 0.21	NR	NR	NR	NR	0.001					11	NR	0.006	NR
Other Hair Preparations	6	6	NR	NR					1	NR	NR	NR	4	NR	0.001	NR
Hair Coloring Preparations																
Hair Dyes and Colors (all types requiring caution statements and patch tests)	274	345	0.2 – 1	0.3 – 0.6					3	NR	NR	0.3				
Hair Tints	NR	3	NR	NR												
Hair Rinses (coloring)	1	NR	0.1	NR	1	NR	NR	NR								
Hair Bleaches	NR	NR	0.03 – 0.1	NR												
Other Hair Coloring Preparation	1	NR	11.6***	NR												
Makeup Preparations																
Blushers (all types)	16	NR	0.002	NR												
Face Powders	1	NR	0.001 – 0.1	NR	1	NR	0.022	0.1 - 3								
Foundations	4	NR	0.0005 – 0.0057	0.1	4	NR	NR	0.02 - 3					1	NR	NR	NR
Leg and Body Paints					2	NR	NR	NR								
Lipstick	78	1	0.0015 – 0.0045	0.001					NR	1	NR	0.0003	1	NR	NR	NR
Makeup Bases	5	1	NR	NR	2	NR	NR	0.02					3	NR	NR	NR
Makeup Fixatives					1	NR	NR	0.02								
Other Makeup Preparations	6	1	0.001	NR	2	1	NR	NR					3	NR	NR	NR
Manicuring Preparations (Nail)																
Basecoats and Undercoats	1	NR	0.01	NR	1	NR	NR	NR								
Cuticle Softeners	4	NR	NR	NR	1	NR	NR	0.05								
Nail Creams and Lotions	1	NR	NR	NR	2	NR	NR	NR								
Nail Polish and Enamel	NR	NR	0.001	NR	1	NR	0.0005	NR								
Other Manicuring Preparations	9	NR	NR	NR	2	NR	NR	NR								
Oral Hygiene Products																
Dentifrices	2	NR	NR	NR									NR	NR	0.095 – 0.93	NR
Mouthwashes and Breath Fresheners	6	2	NR	NR	1	NR	NR	NR	1	NR	NR	NR	2	NR	NR	NR
Other Oral Hygiene Products	3	NR	NR	NR												
Personal Cleanliness Products																
Bath Soaps and Detergents	23	2	0.00001 – 0.3	0.001	2	NR	NR	NR	NR	NR	0.01	NR	7	NR	0.024 – 0.05	NR

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	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2023[2]	**2001**[1]	**2023**[3]	**2000**[1]	**2023**	**2001**[1]	**2023**	**2000**[1]	**2023**[2]	**2001**[1]	**2023**[3]	**2000**[1]	**2023**[2]	**2001**[1]	**2023**[3]	**2000**[1]
Deodorants (underarm)	17	NR	not spray: 0.005 – 0.05	NR	1	NR	NR	NR	3	NR	NR	NR				
Douches	NR	NR	NR	0.001									3	NR	NR	NR
Other Personal Cleanliness Products	4	NR	0.001	NR					NR	NR	0.001	NR	9	NR	NR	NR
Shaving Preparations																
Aftershave Lotion	1	NR	NR	NR									2	NR	NR	NR
Beard Softeners	1	NR	NR	NR												
Shaving Cream	NR	NR	NR	0.001												
Other Shaving Preparations	NR	NR	0.0001	NR									1	NR	NR	NR
Skin Care Preparations																
Cleansing	52	3	0.0001 – 0.3	0.001 - 5	2	4	NR	0.01 – 0.5					28	NR	0.048 – 0.22	NR
Face and Neck (exc shave)	139	3	not spray: 0.001 - 10	0.001 - 10	57	6	not spray: 0.034	0.05 – 3	9	NR	not spray: 0.001	NR	85	NR	not spray: 0.5	NR
Body and Hand (exc shave)	17	3	not spray: 0.00005 – 10.5	0.0001 - 10	8	1	not spray: 0.000073	0.02 – 0.2	NR	1	not spray: 0.1	NR	14	NR	not spray: 0.005	0.1 – 1
Foot Powders and Sprays		1	powder: 0.5	0.1 – 5	NR	2	NR	NR								
Moisturizing	373	2	not spray: 0.000005 – 0.1	0.001 – 0.05	54	18	not spray: 0.00001 – 0.5	0.03 – 3	8	2	NR	NR	81	NR	not spray: 0.019 - 2	3
Night	20	NR	not spray: 0.001 - 10	NR	6	2	not spray: 0.1	0.04	2	2	not spray: 0.001	NR	8	NR	NR	3
Paste Masks (mud packs)	9	NR	0.0004	NR	10	NR	NR	0.02					3	NR	0.007 – 0.1	NR
Skin Fresheners	19	NR	0.001 - 17	NR	NR	NR	NR	0.001					5	NR	NR	NR
Other Skin Care Preparations	47	4	0.003 - 9	0.01	20	1	NR	0.5 – 3	5	NR	0.001	NR	34	NR	NR	NR
Suntan Preparations																
Suntan Gels, Creams, and Liquids	4	NR	aerosol: 0.00005	NR	NR	1	NR	0.05 – 3					NR	NR	aerosol: 0.05 not spray: 0.05	NR
Indoor Tanning Preparations	2	NR	NR	NR												
Other Suntan Preparations	NR	NR	0.0001	NR	1	NR	NR	NR								

NR – not reported

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

**likely duration and exposure is derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

***According to a supplier, a hair color remover product, which is reported to contain up to 70% Ascorbic Acid in solid crystal form, is used at up to 11.6% after dilution in water

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 2. Ingredients not reported to be in use in 2000/2001 or 2023[1-3]

Calcium Ascorbate
Magnesium Ascorbate

Table 3. Dermal penetration studies

Test Article	Vehicle	Test System	Concentration/Dose	Protocol	Results	Reference
			IN VITRO			
Ascorbic Acid	lotion	pig skin	10, 15, 20, or 25%; 300 µl	Franz diffusion cells; 24 h application; the rate of dermal penetration was measured at 1, 2, 4, 6, and 24 h. A serum containing 20% Ascorbic Acid was used for controls.	Kp values for each lotion containing 10, 15, 20, or 25% Ascorbic Acid were 0.512, 1.442, 1.951, and 2.078 mg/h, respectively, compared to 1.544 mg/h for controls. The lotion containing 20% Ascorbic Acid had the highest diffusion percentage of 84.71%. For unknown reasons, concentrations higher than 20% Ascorbic Acid resulted in decreased diffusion percentage.	[4]
Ascorbic Acid		white Yorkshire pig skin (n = 3)	15%; pH levels of 2 – 5		pK_a was 4.2; tissue levels were enhanced only at pH levels less than 3.5.	[5]
Ascorbic Acid		white Yorkshire pig skin (n = 3)	5 - 30%; pH 3.2	24-h application	Ascorbic Acid tissue levels increased with concentration levels up to 20% (the maximum); higher concentrations result in decreased tissue levels.	[5]
Ascorbic Acid		white Yorkshire pig skin (n = 3)	15%	tissues saturated for 5 d	After 3 d, tissue levels were saturated and were approximately 20 times normal tissue levels. The half-life of Ascorbic Acid in tissues was ~ 4 d.	[5]
Magnesium Ascorbyl Phosphate		white Yorkshire pig skin	12%	24-h application	the presence of Ascorbic Acid was not significantly increased in the skin	[5]

Table 4. Acute and repeated dose toxicity studies

Test Article	Vehicle	Animals/Group	Dose	Protocol	LD_{50}/LC_{50}/Results	Reference
			ACUTE TOXICITY			
			DERMAL			
Magnesium Ascorbyl Phosphate	bi-distilled water	Wistar Han rats (5/sex)	2000 mg/kg bw	24-h semi-occlusive application	LD_{50} > 2000 mg/kg bw	[6]
Magnesium Ascorbyl Phosphate	distilled water (26.7%)	Sprague-Dawley rats (5/sex)	2000 mg/kg bw	24-h semi-occlusive application	LD_{50} > 2000 mg/kg bw	[6]
Sodium Ascorbyl Phosphate	bi-distilled water	Wistar rats (5/sex)	2000 mg/kg bw	24-h semi-occlusive application	LD_{50} > 2000 mg/kg bw "Very weak redness" in 2 males and 2 females (1 d after application)	[7]
			ORAL			
Magnesium Ascorbyl Phosphate	distilled water	Wistar Han rats (5/sex)	2000 mg/kg bw	acute oral toxicity study	LD_{50} > 2000 mg/kg bw	[6]
Magnesium Ascorbyl Phosphate	aq. methylcellulose (1%)	Sprague-Dawley rats (5/sex)	2000 mg/kg bw	acute oral toxicity study	LD_{50} > 2000 mg/kg bw	[6]
Sodium Ascorbyl Phosphate	bi-distilled water	Wistar rats (5/sex)	5000 mg/kg bw	acute oral toxicity study	LD_{50} > 5000 mg/kg bw	[7]
			REPEATED-DOSE TOXICITY			
			ORAL			
Sodium Ascorbyl Phosphate		Wistar rats (5/sex)	males: 0, 83, 424, or 1426 mg/kg bw/d females: 0, 90, 512, or 1662 mg/kg bw/d	OECD TG 407; 28-d (7 d/wk) drinking water study	NOAEL (males): 424 mg/kg bw/d NOAEL (females): 90 mg/kg bw/d Urothelial hyperplasia in males and 1 female of the high-dose groups; cystitis in 4 and ulceration of the urothelium in 1 high-dose male 3 females of the 512 mg/kg group had increased macrophages in the cortex of the thymus (group); high-dose females had decreased absolute ovary weight, with no corresponding morphological effects Increased water consumption observed for high dose males and females	[7]

Table 5. Genotoxicity studies

Test Article	Vehicle	Concentration	Test System	Protocol	Results	Reference
			IN VITRO			
Magnesium Ascorbyl Phosphate	deionized water	33 - 5000 µg/plate	*Salmonella typhimurium* TA98, TA100, TA1535, and TA1537	Ames test, with and without metabolic activation	not mutagenic; cytotoxic at >5000 µg/plate	[6]
Magnesium Ascorbyl Phosphate	purified water	5 - 5000 µg/plate	*S. typhimurium* TA98, TA100, TA102, TA1535, and TA1537 and *Escherichia coli* WP2 uvrA/pkM101	Ames test, with and without metabolic activation	not mutagenic; cytotoxic at >5000 µg/plate	[6]
Magnesium Ascorbyl Phosphate	water	8 - 5000 µg/plate	*S. typhimurium* TA98, TA100, TA102, TA1535, and TA1537	Ames test, with and without metabolic activation	not mutagenic; cytotoxic at 5000 µg/plate	[6]
Magnesium Ascorbyl Phosphate	medium	125 - 4000 µg/ml	Chinese hamster cells	chromosome aberration test, with and without metabolic activation	not genotoxic; cytotoxic at >3000 µg/ml	[6]
Magnesium Ascorbyl Phosphate	sterile water	1250 - 5000 µg/ml	human lymphocytes	chromosome aberration test, with (3 h) and without (20 h) metabolic activation	not genotoxic	[6]
Sodium Ascorbyl Phosphate	water	24 - 6000 µg/plate	*S. typhimurium* TA98, TA100, TA1535, and TA1537 and *E. coli* WP2 uvrA	Ames test, with and without metabolic activation	not mutagenic; cytotoxic at ≥3000 µg/plat	[7]
Sodium Ascorbyl Phosphate	distilled water	500 - 3800 µg/ml	Chinese hamster V79 cells	chromosome aberration test, with (4 h) and without (28 h) metabolic activation	not genotoxic; cytotoxic at ≥1000 µg/ml	[7]

Table 6. Anti-Carcinogenicity study

Test Article	Test System	Protocol	Results	Reference
Sodium Ascorbate	neuroblastoma cell lines (n = 5)	Cell lines were treated with 0.5 – 3 mM for 24 h. To confirm the involvement of intracellular iron in the induction of apoptosis, HTLA- 230 and SH-SY-5Y cells were treated with 1.5 and 2 mM Sodium Ascorbate for 24 h.	EC_{50} values were less than 2 mM; morphological inspection of treated cells confirmed that cell death occurred via apoptosis (not necrosis). Treatment with Sodium Ascorbate resulted in a statistically significant reduction in cellular iron levels, resulting in apoptosis, caused by iron transferrin receptor (Tfr)-downregulation.	[8]

Table 7. Dermal irritation, sensitization, and photoprotective effects studies

Test Article	Vehicle	Concentration/Dose	Test Population/System	Protocol	Results	Reference
IRRITATION						
ANIMAL						
Magnesium Ascorbyl Phosphate	distilled water	500 mg	3 New Zealand white rabbits	4-h semi-occlusive application	No irritation was observed at 24, 48, and 72-h	6
Sodium Ascorbyl Phosphate	distilled water	500 mg	6 New Zealand white rabbits	4-h semi-occlusive application	Mean erythema score of 0.6 was reversible within the 3-d observation period; no other signs of irritation were observed	7
HUMAN						
Ascorbic Acid	lotion	20%	34 subjects	SIOPT; application to shaved forearm for 0.5, 24, or 48 h	No erythema, dryness, or edema was observed at any time point.	4
SENSITIZATION						
ANIMAL						
Magnesium Ascorbyl Phosphate	distilled water	induction: 25% (intradermal and topical) challenge: 0, 10, 25, or 50%	guinea pigs; 10 test animals	GPMT	Not a sensitizer. No signs of irritation were seen after intradermal induction; slight to well-defined erythema was seen in 7/10 test animals after topical induction; very small scabs were seen in 2 test animals and 1 control.	6
Magnesium Ascorbyl Phosphate	water	intradermal induction: 5% in FCA and saline solution topical induction: 50% challenge 50% (0.2 g)	Dunkin-Hartley guinea pigs; 10 test animals; 5 controls	GPMT	Not a sensitizer.	6
Magnesium Ascorbyl Phosphate	distilled water	intradermal induction: 10% topical induction: 40% challenge 20 and 40%	albino guinea pigs; 10 test animals; 5 controls	GPMT, with SLS pre-treatment	Not a sensitizer. Slight irritation reported for test and control animals following topical induction	6
Magnesium Ascorbyl Phosphate	petrolatum or water	intradermal induction: 10% (water) topical induction: 55% (pet) challenge 1 and 2.5% (pet)	albino guinea pigs; 20 test animals; 10 controls	GPMT, with SLS pre-treatment	Positive were seen in both test animals and controls # of animals with positive reactions at 24-h post-challenge: 1%, 5/20 animals; 2.5%, 12/20 animals; controls, 7/10 # of animals with positive reactions at 48-h post-challenge: 1%, 0/20 animals; 2.5%, 9/20 animals; controls, 3/10	6
Sodium Ascorbate	ethanol/water (30:70)	0, 5, 10, or 25%	female CBA mice (4/group)	OECD TG 429; mouse LLNA	non-sensitizing SI was < 3% at all 3 test concentrations; an EC50 value could not be determined	9
Sodium Ascorbyl Phosphate	saline (0.9%) and 5% FCA or bidistilled water	intradermal induction: 5% (saline/FCA) topical induction: 50% (water) challenge 50% (water)	Pirbright-Hartley guinea pigs; 30 test animals; 10 controls reactions	OECD TG 406; GPMT	4 animals showed signs of sensitization at 24 and 48 h during the first challenge; no reactions were seen during re-challenge Significant redness and slight edema were observed during induction. (7 test animals died from pneumonia unrelated to treatment)	7

Table 7. Dermal irritation, sensitization, and photoprotective effects studies

Test Article	Vehicle	Concentration/Dose	Test Population/System	Protocol	Results	Reference
PHOTOPROTECTIVE EFFECTS						
IN VITRO						
Magnesium Ascorbyl Phosphate		25, 250, or 500 µM or 1 mM	human keratinocyte cells	Test article was added to cells. or 1 h prior to UVA irradiation. Non-irradiated cells were used as controls. An MTT assay was used to assess cell viability. Cellular levels of glutathione were measured in keratinocytes directly exposed to UVA irradiation and in keratinocytes exposed to Magnesium Ascorbyl Phosphate prior to irradiation.	The cell survival fractions in cells pre-treated with each test concentration prior to irradiation at 8 J/cm^2 were 51.6, 55.5, 64.8, and 76.7%, respectively, compared to 89.9, 48.4, 9.1, and 4.8% after direct irradiation with 4, 8, 16, or 32 J/cm^2 UVA. Glutathione levels in cells treated prior to irradiation with 8 J/cm^2 UVA were 0.328, 0.35, 0.394, and 0.5 mmol/g protein, respectively, compared to 0.3 mmol/g protein in irradiated cells without pretreatment. These results implied that Magnesium Ascorbyl Phosphate may protect keratinocytes against UVA irradiation, possibly through conserving cellular levels of glutathione.	[10]
ANIMAL						
formulation containing either 15% Ascorbic Acid, 1% vitamin E, or 15% Ascorbic Acid and 1% vitamin E	n/a	applied neat	weanling Yorkshire pigs (number not specified)	Test article applied to a 7.5 cm x 10 cm patch on the back for 4 d. Skin was irradiated with solar-stimulated UV irradiation, 1 - 5 MED at 1-MED intervals. On day 3, 30 – 100 mJ/cm^2 radiation was administered at 10 mJ/ cm^2 intervals of solar-stimulated UVR to untreated skin. The antioxidant protection factor was calculated on day 5 as the ratio of the MED in Ascorbic Acid + α-tocopherol - treated skin in comparison with untreated skin.	Treatment with the 15% Ascorbic Acid and 1% vitamin E formulation provided 4-fold protection to erythema, while treatment with each separately resulted in 2-fold protection, compared to vehicle-treated skin. Thymine dimers formation response to UVR was significantly reduced in the skin treated with combined Ascorbic Acid and vitamin E. At 3 and 4 MEDs, only the combination solution of Ascorbic Acid and vitamin E was significantly protective against sunburn.	[11]
HUMAN						
antioxidant mixture comprising 10% Ascorbic Acid (in water, butylene glycol, dipropylene glycol, and ethanol), 0.5% ferulic acid, and 2% phloretin		2 mg/cm^2	10 subjects (Fitzpatrick skin types II and III)	Topical applications were made to 2 separate 7.5 cm^2 areas of the lower back for 4 d. On day 3, an MED was determined for each subject. Subsequently, 6 separate sites near the treatment area were irradiated with 20 – 70 mJ/cm^2 at 10 mJ/cm^2 intervals. On day 4, both test sites received solar-stimulated UV irradiation (1 – 5 MED at 1 MED intervals) and the MED was determined as the spot receiving the lowest dose with erythema extending to the borders	The Ascorbic Acid mixture provided statistically significant protection from UV-induced erythema, sunburn, and DNA damage (measured as thymine dimers and p53 protein levels) at any tested irradiation dose, compared to vehicle control test sites. The UV-induced reduction of Langerhans cells and increase in MMP-9 levels were precluded by treatment with the Ascorbic Acid mixture, rendering cell levels the same as a non-UV-irradiated site.	[12]

Table 7. Dermal irritation, sensitization, and photoprotective effects studies

Test Article	Vehicle	Concentration/Dose	Test Population/System	Protocol	Results	Reference
Ascorbic Acid	water	15%; 2 mg/cm^2	9 subjects (Fitzpatrick skin types II and III)	Topical application for 4 d to separate patches of back skin. Treated sites were not washed for 2 h. On day 4, the vehicle-treated skin received 2 – 6 MED and the skin treated with the Ascorbic Acid solution received 2 – 10 MED, each at 2x-MED intervals. On day 5, skin was evaluated for erythema, and biopsy specimens of skin receiving 6X MED of irradiation were evaluated for presence of sunburn.	The Ascorbic Acid solution provided significant protection against irradiation compared to vehicle-treated skin. Sunburn cell count was also significantly reduced in skin treated with the Ascorbic Acid solution when compared to vehicle controls (8.4 ± 7 vs. 31.5 ± 14.3; $p < .01$).	[13]
Ascorbic Acid		500 mg	12 volunteers	A fixed UVR dose of 120 mJ/cm^2 administered to 2 circular sites of 1 cm diameter on buttock skin. After 6 h of exposure, skin biopsies were taken from irradiated and non-exposed controls. Subjects then ingested Ascorbic Acid supplements for 8 wk prior to a second UVR exposure and retrieval of skin biopsies.	Mild oxidative stress and a significant erythemal response was observed in the gluteal skin of subjects, which peaked within 6 – 24 h after exposure. Ascorbic Acid supplementation had no effect on the MED, with the same median value of 36 mJ/cm^2 at baseline and after 2 mo supplementation. Ascorbic Acid supplementation significantly increased Ascorbic Acid content in the plasma and the skin; UVR exposure did not significantly affect skin Ascorbic Acid content. Total glutathione content of skin prior to UVR exposure was reduced by Ascorbic Acid supplementation. Levels of oxidized glutathione were increased after UVR exposure; Ascorbic Acid supplementation did not significantly affect glutathione oxidation or changes in protein thiol content seen in response to UVR exposure. Ascorbic Acid supplementation also decreased malonaldehyde content of the skin prior to UVR exposure, suggesting a reduction in baseline lipid peroxidation of skin samples. UVR exposure did not significantly affect malonaldehyde content in supplemented or non-supplemented skin. Ascorbic Acid supplementation also did not significantly affect catalase activity in irradiated or non-irradiated skin.	[14]

Table 8. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Protocol	Results	Reference
				IN VITRO		
Ascorbic Acid	lotion	0.31, 0.63, 1.25, 2.5, 5, or 10%	rabbit corneal epithelial cells	MTT assay	A statistically significant dose-dependent decrease in cell viability was observed in the cells that were treated for 48 h. However, at the 10% concentration the cell viability of treated cells was 94%, indicating a lack of ocular irritation.	[4]
				ANIMAL		
Magnesium Ascorbyl Phosphate		100 mg	3 New Zealand white rabbits	Acute eye study; treated eyes were scored 24, 48, and 72 h after instillation	Mean irritation scores (across 3 timepoints) were 0.33 for conjunctival irritation and chemosis in each animal; irritation was fully reversible within 2 d of instillation.	[6]
Magnesium Ascorbyl Phosphate		not stated	3 New Zealand white rabbits	Acute eye study; treated eyes were scored 24, 48, and 72 h after instillation	Mean conjunctival irritation scores (for each animal, across 3 timepoints) were 0.33, 1, 0.67. A diffuse crimson coloration was observed in all 3 animals, and was accompanied by slight swelling in 2 animals. All reactions had resolved within 3 d of instillation.	[6]
Magnesium Ascorbyl Phosphate		57 mg	3 New Zealand white rabbits	Acute eye study; treated eyes were scored 24, 48, and 72 h after instillation	Mean conjunctival irritation, iris irritation, chemosis, and corneal opacity mean scores were 0 for all 3 animals; conjunctival redness and chemosis observed over the first 4 h of exposure resolved within 1 d.	[6]
Sodium Ascorbyl Phosphate		58 mg	6 New Zealand white rabbits	Acute eye study; treated eyes were scored 24, 48, and 72 h after instillation	Mean conjunctival irritation and chemosis scores were 0.8 and 0.1, respectively; all signs of irritation resolved within 3 d.	[7]

Table 9. Case reports

Test Article	Subjects	Protocol/Study Description	Results	Reference
Ascorbic Acid	47-yr old female	The patient presented with eczema for 3 mo, initially consisting of erythematous lesions on the eyelids which spread to the rest of the face and neck folds. Patch tests were performed using European standard series and cosmetic, fragrance, and plant series, as well as 5 cosmetic products used by the subject, according to ICDRG recommendations.	Positive reactions occurred to a cosmetic cream which had been used prior to onset of symptoms. Subsequent patch tests with the individual ingredients of this cream showed positive results only to Ascorbic Acid (5% aq.: + on day 2; ++ on day 3); 20 controls had negative results. Oral provocation tests performed with up to 2000 mg of Ascorbic Acid also had negative results. Discontinuation of the cream resulted in complete resolution of the eczema over 6 mo.	[15]

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Safety Assessment of Glyceryl Isostearates & Glyceryl Stearate/Acetate as Used in Cosmetics

Status: Re-Review Summary for Panel Approval
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History

Original Safety Assessment – published 2004

Most Recent Action – Glyceryl Monoesters report considered at the March 2025 Panel meeting; not re-opened; ingredients in use and not in use split into separate documents

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This summary was prepared by Temima Nguyen, M.S., Scientific Analyst/Writer, CIR.

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GLYCERYL ISOSTEARATES and GLYCERYL STEARATE/ACETATE

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a safety assessment on Glyceryl Isostearates and Glyceryl Stearate/Acetate in 2004.[1] The Panel concluded that Glyceryl Isostearates and Glyceryl Stearate/Acetate are safe as cosmetic ingredients in the present practices of use and concentration as described in that report. It should be noted that the report published in 2004 assessed the safety of 43 ingredients; however, the majority of those ingredients have been included in other safety assessments and therefore were not considered in this re-review.

Because it has been at least 15 years since the final report was published, in accordance with Cosmetic Ingredient Review (CIR) Procedures, the Panel considered whether the safety of these two ingredients should be reassessed. At the March 2025 meeting, the Panel reviewed updated information regarding product types and ingredient use frequencies according to US Food and Drug Administration (FDA) Registration and Listing Data (RLD; 2024)[2] and the Voluntary Cosmetic Registration Program (VCRP; 2023) database,[3] and maximum use concentrations provided in response to the survey conducted by the Personal Care Products Council in 2022.[4] According to RLD submitted to CIR in 2024, Glyceryl Isostearates has 2 uses in makeup preparations and Glyceryl Stearate/Acetate has 4 uses total, in eye makeup preparations, makeup preparations, and skin care preparations. No uses were reported for these ingredients in the VCRP in 2023. The cumulative frequency and concentration of use data are presented in Table 1.

In January 2025, an extensive search of the world's literature was performed for studies dated 1999 forward. No notable new data were found for these two ingredients.

In summary, the Panel reviewed updated frequency and concentration of use data. After considering this information, as well as the information provided in the original safety assessment, the Panel reaffirmed the 2004 conclusion for Glyceryl Isostearates and Glyceryl Stearate/Acetate. Furthermore, the Panel discussed the possibility for these ingredients to be used in cosmetic products which may be incidentally inhaled. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings. This resource document also notes that airbrush technology presents a potential safety concern. Although frequency and/or concentration of use data are now available (and in some cases mandated) for ingredients marketed for use with airbrush delivery systems in certain product categories, no data are available for consumer habits and practices thereof, product particle size, or other relevant particle data (e.g., diameter). As a result of deficiencies in these critical data needs, the data profile is incomplete, and the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Accordingly, the Panel has concluded the data are insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

Table 1. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	Glyceryl Isostearates					Glyceryl Stearate/Acetate				
	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[2]	VCRP (2023)[3]	VCRP (1998)[1]	% (2022)[4]	% (1999)[1]	RLD (2024)[2]	VCRP (2023)[3]	VCRP (1998)[1]	% (2022)[4]	% (1999)[1]
Totals*	**2**	**NR**	**NR**	**NR**	**NR**	**4**	**NR**	**NR**	**NR**	**1-7**
summarized by likely duration and exposure**										
Duration of Use										
Leave-On	***	*NR*	*NR*	*NR*	*NR*	***	*NR*	*NR*	*NR*	*2-7*
Rinse-Off	***	*NR*	*NR*	*NR*	*NR*	***	*NR*	*NR*	*NR*	*1*
Diluted for (Bath) Use	***	*NR*	*NR*	*NR*	*NR*	***	*NR*	*NR*	*NR*	*NR*
Exposure Type										
Eye Area	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Ingestion	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Inhalation-Spray	***	NR	NR	NR	NR	***	NR	NR	NR	2-7[a]; 2[b]
Incidental Inhalation-Powder	***	NR	NR	NR	NR	***	NR	NR	NR	2[b]
Dermal Contact	***	NR	NR	NR	NR	***	NR	NR	NR	1-3
Deodorant (underarm)	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Hair - Non-Coloring	***	NR	NR	NR	NR	***	NR	NR	NR	7
Hair-Coloring	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Nail	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Mucous Membrane	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Baby Products	***	NR	NR	NR	NR	***	NR	NR	NR	NR
as reported by product category										
Eye Makeup Preparations (not children's)						***2***				
Mascara						1	NR	NR	NR	NR
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)						1	NA	NA	NA	NA
Hair Preparations (non-coloring)										
Tonics, Dressings, and Other Hair Grooming Aids						NR	NR	NR	NR	7
Makeup Preparations (not eye; not children's)	***2***					***1***				
Blushers and Rouges (all types)	2	NR	NR	NR	NR	1	NR	NR	NR	NR
Face Powders	2	NR	NR	NR	NR					
Skin Care Preparations						***1***				
Cleansing						NR	NR	NR	NR	1
Face and Neck (excluding shaving preparations)						NR	NR	NR	NR	2
Body and Hand (excluding shaving preparations)						NR	NR	NR	NR	2
Moisturizing						1	NR	NR	NR	3
Suntan Preparations										
Suntan Gels, Creams, and Liquids						NR	NR	NR	NR	3
Indoor Tanning Preparations						NR	NR	NR	NR	2

NA – not applicable (this category was not part of the VCRP); NR – not reported

*The total FOU provided for RLD refers to the ingredient count supplied by FDA, and is not a summation of the number of uses per category because each product may be categorized under multiple product categories. For data supplied via the VCRP or by the Council survey, the sum of all exposure types may not equal the sum of total uses because each ingredient may be used in cosmetics with multiple exposure types.

**Likely duration and exposure are derived from VCRP and survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

***In the RLD each ingredient may be reported under several product categories, making a summation of RLD misleading in comparison to VCRP data. Accordingly, RLD are presented below by product category (as supplied by FDA), but are not summarized by likely duration and exposure.

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

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Safety Assessment of Glyceryl Collagenate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Maleate, and Glyceryl Thiopropionate as Used in Cosmetics

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GLYCERYL COLLAGENATE, GLYCERYL SESQUIOLEATE, GLYCERYL/SORBITOL OLEATE/HYDROXYSTEARATE, GLYCERYL STEARATE/MALEATE, AND GLYCERYL THIOPROPIONATE

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a safety assessment on Glyceryl Collagenate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Maleate, and Glyceryl Thiopropionate in 2004.[1] In that assessment, the Panel concluded that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration as described in that report. It should be noted that the report published in 2004 assessed the safety of 43 ingredients; however, the majority of those ingredients have been included in other safety assessments and therefore were not considered in this re-review.

Because it has been at least 15 years since the final report was published, in accordance with Cosmetic Ingredient Review (CIR) Procedures, the Panel considered whether the safety of these five ingredients should be reassessed. At the March 2025 meeting, the Panel reviewed updated information regarding product types and ingredient use frequencies according to US Food and Drug Administration (FDA) Registration and Listing Data (RLD; 2024)[2] and the Voluntary Cosmetic Registration Program (VCRP; 2023) database,[3] and maximum use concentrations provided in response to the survey conducted by the Personal Care Products Council in 2022.[4] According to these three sources, the ingredients included in this rereview are not reported to be in use; of note, these ingredient were also not in use at the time of the original safety assessment.

In January 2025, an extensive search of the world's literature was performed for studies dated 1999 forward. No notable new data were found for these five ingredients.

In summary, there were no new safety data, and these ingredients are not reported to be in use. In accord with CIR Procedures, the Panel concluded the safety of Glyceryl Collagenate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Maleate, and Glyceryl Thiopropionate has not been documented and substantiated. The CIR Expert Panel cannot conclude that these ingredients are safe for use in cosmetic products until the appropriate data have been obtained and evaluated.

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Safety Assessment of Diisopropanolamine, Triisopropanolamine, Isopropanolamine, and Mixed Isopropanolamines

Status: Extended Re-Review Summary for Panel Approval
Release Date: May 16, 2025
Panel Meeting Date: June 9 – 10, 2025

History
Original Safety Assessment – published 1987
Re-Review – published 2006
Most Recent Action – new data considered at the September 2024 Panel meeting; not re-opened

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Preethi Raj, M.S., former Senior Scientific Analyst/Writer, CIR, and Priya Ferguson, M.S., Senior Scientific Analyst/Writer, CIR.

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ISOPROPANOLAMINES

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published the Final Report on the Safety Assessment of Diisopropanolamine, Triisopropanolamine, Isopropanolamines, and Mixed Isopropanolamines in 1987.[1] The Panel concluded that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration (as described in the safety assessment); these ingredients should not be used in products containing *N*-nitrosating agents. The Panel previously considered a re-review of this report in December 2004, and re-affirmed the 1987 conclusion, as published in 2006.[2]

Because it has been at least 15 years since the re-review was published, in accordance with Cosmetic Ingredient Review (CIR) Procedures, the Panel considered whether the safety assessment should be reopened. At the September 2024 meeting, the Panel reviewed updated (2023) information regarding product types and ingredient use frequencies as reported in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database[3] and maximum use concentrations provided in response to the survey conducted by the Personal Care Products Council.[4] Overall, the reported frequency and concentrations of use for these ingredients have decreased since the previous review. In 2002, Diisopropanolamine was reported to be used in 33 formulations, while Diisopropanolamine had 1 reported use in 2023. The maximum reported concentrations of use in 2004 were 1% Isopropanolamine in hair dyes and colors and 1% Triisopropanolamine in a pump hair spray; the maximum reported concentration of use in 2023 was 0.85% Triisopropanolamine in non-spray tonics, dressings, and other hair grooming aids. Mixed Isopropanolamines did not have reported uses in 2002/2024 or 2023. The cumulative frequency and concentration of use data are presented in Table 1.

In August 2024, an extensive search of the world's literature was performed for studies dated 2001 forward. Considerable new data were found, including data on toxicokinetics, acute toxicity, repeated dose toxicity, developmental and reproductive toxicity, in vitro genotoxicity, carcinogenicity, dermal irritation and sensitization, ocular irritation, clinical studies, and case reports. Although the Panel was of the opinion that these new data served to reaffirm the existing conclusion of safety, they acknowledged it was important that this information was captured robustly. Accordingly, these studies are summarized in Tables 2 – 11.

In summary, the Panel reviewed 2023 frequency and concentration of use data, in addition to any new, available, relevant safety data. After considering this information, as well as the information provided in the original safety assessment, the Panel reaffirmed the 1987 conclusion for the isopropanolamines. The Panel discussed the possibility for these ingredients to be used in cosmetic products which may be incidentally inhaled. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings. This resource document also notes that airbrush technology presents a potential safety concern. Although frequency and/or concentration of use data are now available (and in some cases mandated) for ingredients marketed for use with airbrush delivery systems in certain product categories, no data are available for consumer habits and practices thereof, product particle size, or other relevant particle data (e.g., diameter). As a result of deficiencies in these critical data needs, the data profile is incomplete, and the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Accordingly, the Panel has concluded the data are insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

Table 1. Frequency (2023/2002) and concentration (2023/2004) of use according to likely duration and exposure and by product category

	Diisopropanolamine				Isopropanolamine				Triisopropanolamine			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2023[5]	**2002**[6]	**2023**[7]	**2004**[6]	**2023**[5]	**2002**[6]	**2023**[7]	**2004**[6]	**2023**[5]	**2002**[6]	**2023**[7]	**2004**[6]
Totals*	**1**	**33**	**0.003 – 0.5**	**0.01 – 0.7**	**3**	**27**	**0.015 – 0.11**	**1**	**12**	**25**	**0.000066 – 0.85**	**0.4 – 1**
summarized by likely duration and exposure**												
Duration of Use												
Leave-On	*NR*	*21*	*0.003 – 0.5*	*0.7*	*1*	*27*	*0.11*	*NR*	*11*	*22*	*0.000066 – 0.85*	*0.4 - 1*
Rinse-Off	*1*	*12*	*NR*	*0.01*	*2*	*NR*	*0.015 – 0.016*	*1*	*1*	*3*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type**												
Eye Area	NR	NR	NR	NR	NR	23	NR	NR	3	NR	0.00031 – 0.0004	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	11; 6[a]	0.003 – 0.17	0.7[a]	NR	3[a]; 1[c]	NR	NR	8[a]	9; 12[a]	0.000066 – 0.51; 0.5[a]	0.4-1; 0.7[a]
Incidental Inhalation-Powder	NR	NR	0.5[b]	NR	NR	1[c]	0.11[b]	NR	NR	NR	0.0002[b]	NR
Dermal Contact	NR	19	0.03 – 0.5	0.01	1	4	0.11	NR	4	NR	0.0002 – 0.0004	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	11	0.003	0.7	1	1	0.016	NR	8	25	0.000066 – 0.85	0.4 – 1
Hair-Coloring	NR	3	NR	NR	1	NR	0.015	1	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	1	NR	NR	NR	NR	NR	NR	NR
as reported by product category												
Baby Products												
Other Baby Products					1	NR	NR	NR				
Eye Makeup Preparations												
Eyebrow Pencil									NR	NR	0.00031	NR
Eyeliner					NR	1	NR	NR				
Mascara					NR	22	NR	NR				
Other Eye Makeup Preparations									3	NR	0.0004	NR
Fragrance Preparations												
Cologne and Toilet Water	NR	1	NR	NR								
Other Fragrance Preparation	NR	10	NR	NR								
Hair Preparations (non-coloring)												
Hair Conditioner	NR	1	NR	NR					1	NR	NR	NR
Hair Spray (aerosol fixatives)	NR	NR	pump spray: 0.003	NR					NR	9	aerosol: 0.000066 – 0.51	0.4
Permanent Waves	NR	3	NR	NR								
Shampoos (non-coloring)	1	NR	NR	NR	1	NR	0.016	NR				
Tonics, Dressings, and Other Hair Grooming Aids	NR	5	NR	0.7	NR	1	NR	NR	7	12	spray: 0.5 not spray: 0.85	0.7
Wave Sets	NR	1	NR	NR					NR	3	NR	NR
Other Hair Preparations	NR	1	NR	NR					NR	1	NR	pump spray: 1
Hair Coloring Preparations												
Hair Dyes and Colors (all types requiring caution statements and patch tests)	NR	3	NR	NR	NR	NR	0.015	1				
Hair Tints					1	NR	NR	NR				

Table 1. Frequency (2023/2002) and concentration (2023/2004) of use according to likely duration and exposure and by product category

	Diisopropanolamine				Isopropanolamine				Triisopropanolamine			
	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2023[5]	**2002**[6]	**2023**[7]	**2004**[6]	**2023**[5]	**2002**[6]	**2023**[7]	**2004**[6]	**2023**[5]	**2002**[6]	**2023**[7]	**2004**[6]
Shaving Preparations												
Aftershave Lotion	NR	2	NR	NR								
Other Shaving Preparations	NR	3	NR	NR								
Skin Care Preparations												
Cleansing	NR	NR	NR	0.01								
Face and Neck (exc shave)	NR	NR	not spray: 0.5	NR					NR	NR	not spray: 0.0002	NR
Body and Hand (exc shave)	NR	NR	not spray: 0.5 spray: 0.17	NR	NR	1	not spray: 0.11	NR				
Moisturizing					NR	1	NR	NR	1	NR	NR	NR
Paste Masks (mud packs)	NR	1	NR	NR								
Skin Fresheners	NR	1	NR	NR								
Other Skin Care Preparations	NR	1	NR	NR								
Suntan Preparations												
Suntan Gels, Creams, and Liquids	NR	NR	not spray: 0.03	NR	NR	1	NR	NR				

NR – not reported

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

**likely duration and exposure are derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] It is possible these products are powders, but it is not specified whether the reported uses are powders.

[c] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

Table 2. ADME studies

Test Article	Vehicle	Animals	Concentration/Dose	Protocol	Results	Reference
^{14}C-labelled Triisopropanolamine salt (concomitantly with 2,4-dichlorophenoxyacetic acid)	water	4 male Fischer 344 rats	10.7 mg/kg bw	OECD TG 417; single gavage administration	Approximately 80% of ^{14}C Triisopropanolamine was excreted in urine within the first 24 h post-dosing; 81 – 85% was excreted by 72 h. Feces accounted for 4 – 7% and expired $^{14}CO_2$ accounted for 3 – 5% of the excreted dose. Less than 1% of the radioactive dose remained in the tissues and carcass of rats that were killed 72 h post-dosing.	[8]

ADME = absorption, distribution, metabolism, and excretion; OECD = Organisation for Economic Co-operation and Development; TG = test guidelines

Table 3. Acute toxicity studies

Test Article	Vehicle	Animals/Group	Concentration/Dose	Protocol	LD_{50}/LC_{50}/Results	Reference
DERMAL						
Diisopropanolamine	no vehicle	male New Zealand white rabbits (4/group)	100%; 0, 4000, 8000, or 16,000 mg/kg	occlusive applications; 24-h patches; application to intact skin	LD_{50}: 8000 mg/kg bw Two animals in the 8000 mg/kg group and all animals in the 16,000 mg/kg group died; erythema and necrosis was observed at all dose levels; congestion of lungs, livers, spleens, and kidneys, mottled livers, and opaque stomachs were also observed.	[9]
ORAL						
Diisopropanolamine	olive oil	Wistar rats (5/sex/group)	0, 1000, or 2000 mg/kg bw	OECD TG 401; single oral dose; gavage	LD_{50} > 2000 mg/kg bw	[9]
Diisopropanolamine	water	rats (5/sex/group)	200, 1600, 3200, or 6400 mg/kg bw	single dose of 200, 1600, 3200, or 6400 mg/kg bw; gavage	LD_{50} approximately 6000 mg/kg bw in 6400 mg/kg bw group: respiration; dilated stomach and intestinal irritation in 3200 mg/kg group: 1 female died within first 24 h	[9]
INHALATION						
nebulized Isopropanolamine (MMAD ≥ 1 - ≤ 2 μm);	air	male Swiss Webster mice (4/group)	230 – 1005 mg/m^3	OECD TG 403; nose/head-only, 3-h exposure to nebulized test substance; animals given 20 min recovery period	LC_0 > 1005 mg/m^3 RD_{50}: 440 mg/m^3; post-exposure recovery of the respiratory frequency was moderate to good no mortality occurred; concentrations of mild sensory and pulmonary irritation observed (assessed via measurement of decreased respiratory frequency)	[10,11]
aerosolized Isopropanolamine	air	male Fischer 344 rats (number not specified)	1126 ppm (3460 mg/m^3)	OECD TG 403; 6-h exposure; 14-d observation period	LC_{50} > 1126 ppm (3460 mg/m^3)	[10]
vaporized Isopropanolamine	air	rats (6/sex/group; strain not specified)	1.95 mg/l	OECD TG 403; 8-h exposure; 7-d observation period	LC_0 calculated: 610 ppm No mortality or abnormalities were observed	[10]

LC_0 = maximum tolerable concentration; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; MMAD = mass median aerodynamic diameter; OECD = Organisation for Economic Co-Operation and Development; RD_{50} - concentration capable of evoking a 50% decrease in mean breathing frequency; TG = test guidelines

Table 4. Repeated dose toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
DERMAL							
Diisopropanolamine	NR	Fischer 344 rats (5/sex/group)	4 wks	0, 100, 500, or 750 mg/kg/d	test substance applied under occlusive conditions to a clipped 2 cm^2 area for 6 h/d, 5 d/wk for 4 wks	During the course of the study, slight erythema was noted in 2 males and 2 females from the 500 mg/kg/d group, all 750 mg/kg males, and three 750 mg/kg females. Erythema and scabs were mostly noted from day 19 onwards for males and females in the 500 and 750 mg/kg/d groups. Very slight hyperkeratosis occurred in 2 males and 2 females in the 500 mg/kg/d group and slight hyperkeratosis occurred at the test site of all rats in the 750 mg/kg/d group. On day 26, light fissuring and scales were seen in 2 females from the 750 mg/kg/d group. No systemic or treatment-related effects upon hematology, urinalysis, body and organ weight, or gross pathology were noted.	12
Triisopropanolamine	distilled water	Fischer 344 rats (5/sex/group)	28 d	0, 7.5, 25, or 75%	OECD TG 410; animals administered test substance under semi-occlusive conditions 5 d/wk for 28 d (patches applied for 6 h); negative controls treated with distilled water	NOAEL (systemic toxicity): ≥ 3000 mg/kg bw/d Triisopropanolamine NOAEL (local toxicity): 300 mg/kg bw/d (based on dermal irritation) Slight erythema and scabs were observed at the test sites of 2 male rats in the 1000 mg/kg group. From the 3000 mg/kg group, similar results were seen in 2 males on day 4 (resolved by day 11), 3 male rats on day 18 (resolved by day 28), and 1 female rat on day 25 (still present at day 28). Microscopically, 2 males and 1 female from the 1000 mg/kg bw/d group also exhibited very slight epidermal hyperplasia, asdid 1 control female. Epidermal hyperplasia was observed at treatment sites for 3 males and 4 females in the 3000 mg/kg bw d group. No other treatment-related or systemic effects were observed.	8
ORAL							
Isopropanolamine	water	Wistar rats (5/sex/group)	14 d	0, 300, 650, or 1000 mg/kg bw/d	dose-range finding study; animals treated via gavage	NOAEL = 1000 mg/kg bw/d Treatment-related effects included slightly lower food consumption in 650 and 1000 mg/kg bw/d males and females and an increased average concentration of bile acids in 2 females from the 1000 mg/kg bw/d group (3.8 and 5.6 times that of controls).	10
Triisopropanolamine	water	female New Zealand white rabbits (3-5/group)	21 d	0 or 1000 mg/kg bw/d	dose-range finding study; animals treated via gavage	All treated animals had reduced food consumption, body weight, feces or diarrhea throughout the course of the study. Two treated rabbits died on day 3 and day 5 of treatment, respectively.	8

Table 4. Repeated dose toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
Diisopropanolamine	drinking water	Fischer 344 rats (10/sex/group)	90 d	0, 100, 500, 1000 mg/kg	OECD TG 408; rats administered test substance via drinking water; additional recovery groups from the 0 and 1000 mg/kg bw/d groups were maintained for at least 28 d post-treatment	NOAEL: 100 and 500 mg/kg bw/d for males and females, respectively Rats given 1000 mg/kg bw/d consumed less food and water and consistently weighed less than controls. Male and females that were treated with 1000 mg/kg bw/d Diisopropanolamine had increased relative kidney weights by ~ 21 and ~14%, respectively, compared to controls. without corresponding histopathological effects. Increased absolute kidney weights in 100 mg/kg males were also statistically significant, but these rats weighed more than controls and the relative kidney weights were similar to that of controls. After the recovery period, the increase in kidney weight seen in both males and females reduced by half.	[12]
Triisopropanolamine	water and feed	Beagle dogs (4/sex/group)	102 – 104 d	500, 2000, or 7500 ppm (corresponding to mean daily intakes of 16.8 and 19.7 mg/kg bw/d, 71.2 and 78.3 mg/kg bw/d, and 272 and 288 mg/kg bw/d Triisopropanolamine for males and females, respectively)	test substance administered via feed and water	NOEL: 7500 ppm for both males and females No mortality occurred and no statistically or toxicologically significant effects were observed at any dose level	[8]

NOAEL = no-observable-adverse-effect-level; NOEL = no-observed-effect-level; NR = not reported; OECD = Organisation for Economic Co-Operation and Development; TG = test guidelines

Table 5. Developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	Reference
Diisopropanolamine	water	female Sprague-Dawley rats (25/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 414; prenatal developmental toxicity study; test substance administered via gavage on GD 6-20; appropriate controls used	NOAEL for maternal and fetal toxicity: 1000 mg/kg bw/d The mean relative kidney weight of 1000 mg/kg-treated dams was 3.9% greater than control dams, which was not statistically significant. Skeletal malformations, and abnormalities of the heart and kidney occurred in the fetuses of control dams. Among the fetuses of treated dams, one fetus from the 100 mg/kg/d group had left hydroureter (enlarged and blocked ureter), one fetus from the 300 mg/kg/d group had wavy ribs of moderate to severe degree, and one fetus from the 1000 mg/kg/d group had bilateral hydroureter. Fetuses from all groups (including controls) had minor skeletal variations, most of which were delayed ossification of skull bones. There were no statistically significant differences between the incidence of fetal abnormalities in the treated groups compared to controls.	[12]
Isopropanolamine	water	Wistar rats (12/sex/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 422; developmental and reproductive toxicity assay; administration via gavage; dosing during 2-wk premating period and continued until 2 wks post-mating for males (38 d); dosing throughout gestation and until day 4 of lactation for females (45 d)	NOAEL for maternal and developmental toxicity: 1000 mg/kg bw/d NOAEL for general systemic toxicity: 300 mg/kg bw/d (based on statistically significantly reduced hemoglobin and hematocrit values in 1000 mg/kg bw/d males, which were indicative of a mild anemic process)	[10]
Isopropanolamine	water	female Wistar rats (22/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 414; prenatal developmental toxicity study; test substance administered via gavage on days 6 – 20 post-coitum	NOAEL for maternal and developmental toxicity: ≥ 1000 mg/kg bw/d No maternal or developmental toxicity was observed at up to the highest tested dose.	[10]
Isopropanolamine	water	Wistar rats (25 sex/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 443: extended one-generation reproductive toxicity assay; gavage administration; F1 males dosed for 7 d/wk for a minimum of 11 wk (prior to and during mating period); females dosed 7 d/wk for a minimum of 16 wks (at least 21 d after delivery)	NOAEL (general toxicity for F_0 and F_1): 100 mg/kg bw/d (based on histopathological findings in kidneys of males starting from 300 mg/kg/d) NOAEL (F_0 reproductive toxicity): 300 mg/kg bw/d for males and females (based on low reproductive performance in 1000 mg/kg group, (likely caused by disturbance in spermatogenesis)) NOAEL (F_1 developmental toxicity, until weaning): 300 mg/kg bw/d (based on low gestation index in 1000 mg/kg group) NOAEL (F_1 developmental toxicity, post-weaning): 1000 mg/kg bw/d (based on no adverse treatment-related effects)	[10]

Table 5. Developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	Reference
Triisopropanolamine	water	Wistar rats (25/sex/group)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 414; prenatal developmental toxicity study; test substance administered via on days 6 – 15 post-coitum	NOAEL for maternal toxicity: 400 mg/kg bw/d (based on decreased weight gain and food consumption in the 1000 mg/kg group) NOEL for fetal toxicity: 1000 mg/kg bw/d (considered not determinable due to absence of adverse toxic effects) A statistically significant reduction in food consumption and body weight gain was observed in 1000 mg/kg bw/d dams, which was considered treatment related. There were no substance-related and/or biologically relevant differences between the groups in terms of conception rate, mean number of corpora lutea and implantation sites, or in the values calculated for the pre- and the post-implantation losses and the number of resorptions and viable fetuses. Any differences were considered incidental and within the normal range of deviations for animals of this strain and age. No adverse effects were observed in pups.	[8]
Triisopropanolamine	diet	rats (25/sex/group; strain not specified)	males: 0, 39.7, 160, 609 mg/kg bw/d females: 0, 43.7, 182, or 700 mg/kg bw/d	one-generation reproductive toxicity study; animals treated for 5 wks prior to mating, during mating, gestation and lactation; 20 offspring/sex/group given the same doses 90 d post-weaning	reproductive NOAEL in males: 609 mg/kg bw/d reproductive NOAEL in females: 7000 mg/kg bw/d No adverse effects observed.	[13]
Triisopropanolamine	water	Sprague-Dawley rats (25/sex/group)	0, 500, 2000, or 7500 ppm/d	one-generation reproductive toxicity study; test substance dissolved in water and administered via diet for 5 wks; parents were mated to produce offspring which were fed same diet for 90 d post-weanign	NOEL parental and fetal toxicity: 7500 ppm No differences in treated animals and controls were attributed to administration of Triisopropanolamine in gestation length, the number of litters, or any other reproductive performance parameters. No treatment-related effects were observed in the pups of the parental generation, even after being fed with Triisopropanolamine for 90 d.	[8]

NOAEL = no-observable adverse effect level; NOEL = no observed effect level; NR = not reported; OECD = Organisation for Economic Co-Operation and Development; TG = test guidelines

Table 6. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
IN VITRO						
Diisopropanolamine	water	0, 100, 333, 1000, 3333, or 10,000 µg/plate	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537	OECD TG 471; Ames assay performed with and without metabolic activation; appropriate positive and negative controls used	non-genotoxic	[9]
Diisopropanolamine	water	up to 5000 µg/plate	*S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537	Ames assay performed with and without metabolic activation; appropriate positive and negative controls used	non-genotoxic	[9]
Diisopropanolamine	water	up to 5000 µg/ml	Chinese hamster ovary cells	OECD TG 476; cell gene mutation assay performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[9]
Diisopropanolamine	cell culture medium	up to 5000 µg/ml	rat lymphocytes	chromosomal aberration assay performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[9]
Isopropanolamine	water	up to 5000 µg/plate	*S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537; *Escherichia coli* WP2	OECD TG 471; Ames assay performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[10]
Isopropanolamine	water	up to 5000 µg/plate	*S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538; *Escherichia coli* WP2	OECD TG 471; Ames assay performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[10]
Isopropanolamine	water	up to 4000 µg/plate	*S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537	OECD TG 471; Ames assay performed with and without metabolic activation; appropriate positive and negative controls used	non-genotoxic	[10]
Isopropanolamine	water	up to 2500 µg/ml	Chinese hamster ovary cells	OECD TG 476; cell gene mutation assay (HGPRT locus) performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[10]
Isopropanolamine	water	up to 2500 µg/ml	rat lymphocytes	OECD TG 473; in vitro chromosomal aberration assay performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[10]
Triisopropanolamine	water	0, 100, 333, 1000, 3333, or 10,000 µg/plate	*S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537	OECD TG 471; Ames assay performed with and without metabolic activation; appropriate positive and negative controls used	non-genotoxic	[14]
Triisopropanolamine	water	0, 50, 167, 500, 1667, or 5000 µg/ml	Chinese hamster ovary cells	OECD TG 476; mammalian gene mutation assay performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[8]
Triisopropanolamine	water	0, 50, 167, 500, 1670, or 5000 µg/ml	rat lymphocytes	OECD TG 473; in vitro mammalian chromosomal aberration assay performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic	[8]
IN VIVO						
Triisopropanolamine	water	0, 500, 1000, or 2000 mg/kg bw/d	NMRI mice (5/sex/group)	OECD TG 474; mammalian erythrocyte micronucleus assay; single dose of test substance given to mice via gavage; polychromatic and nonchromatic erythrocytes in bone marrow measured 24 and 48 h after exposure; appropriate positive and negative controls used	non-genotoxic	[8]

HGPRT = hypoxanthine-guanine phosphoribosyltransferase; OECD = Organisation for Economic Co-operation and Development; TG = test guidelines

Table 7. Carcinogenicity Studies

Test Article	Vehicle	Animals/Group	Procedure	Results	Reference
1% Diisopropanolamine	diet	20 male rats (strain not specified)	animals administered test substance in diet for 94 wks; control animals fed diet without test substance	no significant differences between tumor incidence in control or treated groups; 16/20 animals survived	[13]
2% Triisopropanolamine	diet	male Wistar rats (number of animals not stated)	animals administered test substance in diet for 104 wks	no histological evidence of increased liver foci observed	[13]

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population/System	Protocol	Results	Reference
IRRITATION						
ANIMAL						
Diisopropanolamine	none	100%: 0.5 g	6 small white Russian rabbits (sex not specified)	OECD TG 404; semi-occlusive conditions; applications for 4 h to a 6 cm^2 shaved area of the trunk	slight erythema was observed in 4/6 animals after 1 h, which was fully reversible within 48 h; Diisopropanolamine was not considered irritating	[9]
Diisopropanolamine	water	80%	2 Vienna white rabbits (sex not specified)	OECD TG 404; occlusive conditions; applications for 20 h 2.5 cm^2 area; test sites scored 24 and 48 h, and up to 8 d after application	erythema (accompanied by scale formation) seen in both animals after 20 h of exposure was reversible in 1 animal over the 8-d period; Diisopropanolamine was deemed slightly irritating.	[9]
Isopropanolamine	none	100%	6 Vienna white rabbits (sex not specified)	occlusive conditions; applications for 20 h to 2.5 cm^2 area; test sites scored 24, 48, and 72 h, and up to 8 d after application	bleeding was observed after 5 min (3/6 animals) or 15 min (4/6 animals) and scale and crust formation was observed at the end of 8 d, 1 animal after 15 min of application exhibited anemic necrosis; 20-h application led to severe edema and erythema marked by grey-blackish, relocatable necrosis beyond the application area; Isopropanolamine was classified as a Category 1B corrosive agent based on GHS criteria	[10]
Triisopropanolamine	water	15, 30, 45, 60, or 75%; 4 ml/kg	Male Fischer 344 rats (2/group)	semi-occlusive conditions; applications made to a 5 cm^2 clipped area of the back for at least 6 h/d, for 4 d; animals observed for irritation daily	very slight erythema was observed at the test site of 1 of the 2 rats that received 4 doses of 75% Triisopropanolamine	[8]
Triisopropanolamine	none	100%	6 small white Russian rabbits (3/sex)	semi-occlusive conditions; applications made to a 6 cm^2 clipped area of the back for 4 h; sites scored 24, 48, and 72 h post-application	mean erythema and edema scores and the PDII were 0 at all time points	[8]
Triisopropanolamine	NR	NR	6 Vienna white rabbits (sex not specified)	OECD TG 404; occlusive conditions; applications made to a 2.5 cm^2 area; sites scored 24, 48, and 72 h after application	no erythema or edema was observed in animals exposed for up to 15 min; all 4 animals exposed for 20 h had blotched skin after 2 – 3 d, skin and erythema which expanded beyond the application site which resolved within 6 d.for 3 animals, and persisted in 1 animal	[8]

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population/System	Protocol	Results	Reference
Triisopropanolamine	water	99.6%	1 New Zealand white rabbit (sex not specified)	-10 open applications of 0.1 ml applied to the ear over 14 d, -10 semi-occlusive applications of 0.5 ml applied to intact skin to a 1 in^2 area on the shaved abdomen over 14 d -3 consecutive, semi-occlusive daily applications of 0.5 ml applied to abraded skin to a 1 in^2 area on the shaved abdomen over 3 d test sites were examined 24 h after patch removal and up to 10 d after the last application; test sites were scored on a range of 1 -6 for hyperemia, edema, necrosis, exfoliation, scab and scar formation	slight redness, very slight swelling, and very slight exfoliation and superficial burn were seen with repeated application on confined skin; after 3 applications to abraded test sites or 9 applications to intact test sites a moderate burn developed which resulted in scar formation; no other effects were noted; Triisopropanolamine was considered a possibly weak irritant.	[8]
SENSITIZATION						
ANIMAL						
Diisopropanolamine	distilled water	50%; 0.4 ml	male Hartley guinea pigs (10/group)	OECD TG 406; Buehler assay; occlusive applications in 25 mm patches; positive controls treated with liquid epoxy resin in di(propylene) glycol methyl ether; challenge applications applied 2 wks after induction	non-sensitizing; positive control produced expected results	[9]
Triisopropanolamine	water	22.9%; 0.1 ml	male Hartley guinea pigs (10/group)	EPA OPPTS 81-6; semi-occlusive conditions; 15 mm^2 gauze patches; induction patches made over a period of 10 d; adjuvant administered during 3rd application; challenge patches applied after 2-wk non-treatment period; positive controls treated with 10% solution of epoxy resin	non-sensitizing; positive controls produced expected results	[8]

EPA = Environmental Protection Agency; GHS = globally harmonized system; NR = not reported; OECD = Organisation for Economic Co-operation and Development; OPPTS = Office of Prevention, Pesticides, and Toxic Substances; PDII = primary dermal irritation index; TG = test guidelines

Table 9. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Protocol	Results	Reference
IN VITRO						
Diisopropanolamine	NR	100%; 0.1 ml	4 New Zealand white rabbit eyes	isolated rabbit eye test; test substance applied topically to central part of cornea for 10 s; treated eyes washed with saline, corneal opacity, thickness, and corneal swelling, and fluorescein penetration were evaluated for 4 h, after which the corneas were excised and stained to examine histopathological changes	test substance considered to be slightly irritating	[15]
ANIMAL						
Diisopropanolamine	none	100%; 0,1 ml	3 New Zealand White rabbits (sex not stated)	test substance instilled to the lower conjunctival sac of the right eye; treated eyes held shut for 1 s and rinsed with warm saline water for 10 s; reactions in the cornea, iris, and conjunctiva were scored 1, 24, 48, and 72 h after exposure	test substance considered to be slightly irritating	[15]
Diisopropanolamine	none	100%; 100 mg	6 short white Russian rabbits (sex not stated)	OECD TG 405; test substance administered for 72 h; treated eyes washed with saline and observed for up to 21 d	irreversible effects were observed in exposed eyes included heavy erythema, iritis, opacity, and chemosis; bleeding in the mucous membrane was observed in 5 animals; circum-corneal injections occurred in 4 animals after 7 d; 1 circum-corneal injection and eye reactions were not reversible within 21 d	[9]
Diisopropanolamine	none	100%; 50 µl	2 Vienna white rabbits (sex not stated)	OECD TG 405; test substance (powdered formed) applied to eyes of rabbits; eyes unrinsed and observed for up to 5 d; contralateral eyes received talcum powder (control)	fading conjunctival hemorrhage in both test eyes was not fully reversible in 1 animal; weak chemosis and erythema were also observed in talcum controls within 24 h	[9]

Table 9. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Protocol	Results	Reference
Isopropanolamine	none	100%; 50 µl	2 Vienna white rabbits (sex not stated)	test substance applied to eyes; eyes unrinsed and observed for up to 8 d; contralateral eyes treated with saline (control); eyes scored for chemosis, corneal opacity, conjunctival irritation, and iridial irritation at 24 and 48 h	mean scores for rabbit 1: opacity: (3/4); iritis: (2/2); erythema: (3/3) mean scores for rabbit 2: opacity: (3/4); iritis: (0/2); erythema: (3/3) Based on GHS criteria, Isopropanolamine was considered a Category 1 ocular irritant	[10]
Triisopropanolamine	none	100%; 0.1 g	2 Vienna white rabbits (sex not stated)	test substance applied to eyes of rabbits; eyes washed with saline 72 h after exposure; untreated eyes served as controls; eyes scored via Draize system 1, 24, 48, and 72 h and 5, 7, 10, 12, 14, 19, and 21 d after application	severe ocular irritant corneal opacity, chemosis, and iris effects were reversible within 10 d and conjunctival irritation resolved within 12 d for 5 animals; these effects were not reversible in 1 animal after 21 d and were severe (scores up to 3 for corneal parameters)	[8]
Triisopropanolamine	none	100%; 50 µl	2 Vienna white rabbits (sex not stated)	test substance applied to eyes of rabbits; eyes unrinsed and observed for up to 8 d (readings were taken 1, 24, 48, and 72 h and 8 d after exposure); contralateral eyes served as controls	slight opacity, moderate erythema, and chemosis were observed in the eyes of both animals; although opacity persisted in 1 animal, all other symptoms resolved by the end of the 8-d observation period Category 2 eye irritant based on GHS criteria	[8]

GHS = globally harmonized system; NR = not reported; OECD = Organisation for Economic Co-operation and Development; TG = test guidelines

Table 10. Occupational exposure studies

Ingredient	Study Type	Study Details	Results	Reference
Isopropanolamine	multi-center patch testing	Isopropanolamine was patch tested (as a metal-working fluid component) in 139 metalworkers at 2% in petrolatum.	Four questionable reactions were observed and 1 patient tested (+), resulting in a percent positive rate of 0.7%.	[16]
Isopropanolamine	nasal provocation assay	A patient diagnosed with occupational rhinitis (alone or with asthma) was subject to a nasal provocation test using 0.5% Isopropanolamine. Response of the nasal mucosa (nasal resistance) was measured by posterior rhinomanometry. Data from the patient's medical records including occupational exposure and clinical history were also accounted for.	Isopropanolamine did not produce nasal irritation in the tested patient.	[17]
Isopropanolamine	occupational survey	The potential hazards of Isopropanolamine use in the milling department of a titanium dioxide plant were evaluated in an occupational study conducted by NIOSH.	Nine out of 15-randomly surveyed individuals in the plant reported having health issues; of these men, 5 had present dermatitis and 3 had dermatitis in the past. In 4 instances, moderate cases of definite contact dermatitis were traceable to direct contact with Isopropanolamine, or Isopropanolamine-contaminated dust. One case reported headache, epigastric pain, sore throat, and eye irritation when working around Isopropanolamine, another case mentioned a history of dermatitis related to Isopropanolamine exposure without persistent symptoms. Symptoms in 3 other cases were deemed unrelated to occupational exposure. Workers were recommended to use protective gear and employ good work practices to minimize the risk of contact dermatitis from direct Isopropanolamine exposure.	[18]

NIOSH = National Institute for Occupational Safety and Health

Table 11. Clinical studies/case reports

Ingredient	Subjects	Study Details	Reference
Diisopropanolamine	87-yr-old man	An 87-yr-old man used the same compress for lumbago for 3 wk. During the last 10 d of use, pruritic eruptions appeared on the areas the compress had been applied (bilateral lower back and upper buttock); diffuse erythema developed on the trunk and extremities. The dermatitis was treated with topical steroids. A patch test was performed with the compress ingredients and the Japanese baseline series. Positive reactions were observed on day 2 and day 4 in response to 1% Diisopropanolamine in petrolatum, fragrance mix in 8% petrolatum, and 0.05% aqueous mercuric chloride.	[19]
Diisopropanolamine	60-yr-old man	A 60-yr-old man developed erythema after applying an indomethacin ointment on his lower legs. Treatment with oral histamine and topical steroids was ineffective; treatment with oral prednisone resolved symptoms. Of the patch tested ingredients in the indomethacin ointment, positive reactions were observed in response to 1% Diisopropanolamine pet.; 11 controls had negative reactions to 1% Diisopropanolamine and 1 had a false positive reaction.	[20]

Table 11. Clinical studies/case reports

Ingredient	Subjects	Study Details	Reference
Diisopropanolamine	78-yr-old woman and 76-yr-old woman	A 78-yr-old woman presented with edematous erythema and itching on the left buttock and right knee after using a therapeutic tape to treat osteoarthritis for 1 wk. Additionally, a 76-yr-old woman developed erythema and papules on the waist after using the same therapeutic tape to alleviate lumbago for 2 wk. Positive reactions were only observed in response to Diisopropanolamine in subsequent patch tests; contact dermatitis was attributed to Diisopropanolamine exposure in both cases.	21
Diisopropanolamine	15-yr-old girl	A 15-yr-old girl experienced irritation on her eyelids and face for 6 mo, which was attributed to use of her personal care products. When tested with her previously used cosmetics, the subject only had a positive reaction to her eye gloss; ingredients in the eye gloss were individually patch tested in the affected individual. An undiluted, open, patch test of Diisopropanolamine produced an allergic response, which was considered more severe than just irritation, as the reaction was eczematous and spread beyond the patch test site.	9
Diisopropanolamine	24 subjects	Six out of 24 volunteers were patch tested with undiluted Diisopropanolamine exhibited irritation responses. No irritation occurred in a group of 61 volunteers patch tested with 1% aqueous Diisopropanolamine solution. No further details were provided.	9

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Safety Assessment of Beeswax, Copernicia Cerifera (Carnauba) Wax, Euphorbia Cerifera (Candelilla) Wax, and Rhus Succedanea Fruit Wax as Used in Cosmetics

Status: Extended Re-Review Summary for Panel Approval
Release Date: May 16, 2025
Panel Meeting Date: June 9-10, 2025

History
Original Safety Assessment – published 1984
Original Re-Review – published 2005
Most Recent Action – new data considered at the March 2025 Panel meeting; not re-opened

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This summary was prepared by Temima Nguyen, M.S., Scientific Analyst/Writer, CIR.

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BEESWAX, COPERNICIA CERIFERA (CARNAUBA) WAX, EUPHORBIA CERIFERA (CANDELILLA) WAX, AND RHUS SUCCEDANEA FRUIT WAX

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published the Safety of Candelilla Wax, Carnauba Wax, Japan Wax, and Beeswax in 1984[1] The Panel concluded that these ingredients are safe in cosmetics in the present practices of concentration and use, as stated in that assessment. The Panel previously considered a rereview of this report in and re-affirmed the 1984 conclusion, as published in 2005.[2] Between the publication of the 1984 report and the 2005 re-review, Candelilla Wax, Carnauba Wax, and Japan Wax were re-named Euphorbia Cerifera (Candelilla) Wax, Copernica Cerifera (Carnauba) Wax, and Rhus Succedanea Fruit Wax, respectively.

Because it has been at least 15 years since the previous re-review was published, in accordance with Cosmetic Ingredient Review (CIR) Procedures, the Panel considered whether the safety assessment should be reopened. At the March 2025 meeting, the Panel reviewed updated information regarding product types and ingredient use frequencies according to the US Food and Drug Administration (FDA) Registration and Listing Data (RLD; 2024)[3] and Voluntary Cosmetic Registration Program (VCRP; 2023) database,[4] and maximum use concentrations provided in response to the survey conducted by the Personal Care Products Council in 2022.[5] According to 2002 VCRP Beeswax, Copernicia Cerifera (Carnauba Wax), Euphorbia Cerifera (Candelilla) Wax, and Rhus Succedanea Fruit Wax were used in 1074, 1194, 701, and 528 formulations, respectively. However, frequencies of use differ from what was reported at the time of the first re-review; 2023 VCRP data indicated that these ingredients were used in 1758, 808, 703, and 16 formulations, respectively. In 2003, Beeswax had the highest concentration (used at up to 56% in lipsticks and lip glosses), while in 2022, Rhus Succedanea Fruit Wax had the highest concentration of use in 2022 (used at up to 37.9% in eyebrow pencils). In 2024, RLD collected indicate frequencies of use greater than 5000 formulations for three of the ingredients, i.e., Beeswax, Copernicia Cerifera (Carnauba) Wax, and Euphorbia Cerifera (Candelilla) Wax; Rhus Succedanea Fruit Wax was reported to be used in 300 formulations. The data also suggest that these ingredients are used in children's eye and non-eye makeup preparations, hair sprays, airbrush products (foundations, leg and body paints, makeup bases), oral products, and tattoo preparations. The cumulative frequency and concentration of use data are presented in Table 1.

In January 2025, an extensive search of the world's literature was performed for studies dated 2000 forward, and new data were found. The information that was found included impurities and specifications, acute toxicity, dermal irritation and sensitization to propolis, ocular irritation, and case reports that indicated allergies to propolis which can be found in Beeswax (if contaminated), Carnauba Wax, and Candelilla Wax. Although the Panel was of the opinion that these new data served to reaffirm the existing conclusion of safety, they acknowledged it was important that this information was captured robustly. Accordingly, these studies are summarized in Tables 2-8.

In summary, the Panel reviewed updated frequency and concentration of use data, in addition to any new, available, relevant safety data. After considering this information, as well as the information provided in the original safety assessment, the Panel reaffirmed the 1984 conclusion for Beeswax, Euphorbia Cerifera (Candelilla) Wax, Copernica Cerifera (Carnauba) Wax, and Rhus Succedanea Fruit Wax. During its deliberations, the Panel expressed concern regarding heavy metals and pesticides that may be present in these ingredients. They stressed that the cosmetics industry should continue to minimize impurities in cosmetic formulations according to limits set by the US FDA and the EPA. However, specifically for Beeswax, impurities such as propolis should be avoided. The contamination of Beeswax with this substance appeared to cause multiple reactions based on the case reports. Furthermore, the Panel discussed the possibility for these ingredients to be used in cosmetic products which may be incidentally inhaled. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings. This resource document also notes that airbrush technology presents a potential safety concern. Although frequency and/or concentration of use data are now available (and in some cases mandated) for ingredients marketed for use with airbrush delivery systems in certain product categories, no data is available for consumer habits and practices thereof, product particle size, or other relevant particle data (e.g., diameter). As a result of deficiencies in these critical data needs, the data profile is incomplete, and the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Accordingly, the Panel has concluded the data is insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

TABLES

Table 1. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[3]	**VCRP (2023)[4]**	**VCRP (2002)[2]**	**% (2022)[5]**	**% (2003)[2]**	**RLD (2024)[3]**	**VCRP (2023)[4]**	**VCRP (2002)[2]**	**% (2022)[5]**	**% (2003)[2]**
	BEESWAX					**COPERNICIA CERIFERA (CARNAUBA) WAX**				
Totals*	**8872**	**1758**	**1074**	**0.00015 - 35**	**1 - 56**	**5199**	**808**	**1194**	**0.05 – 30**	**0.07 - 20**
summarized by likely duration and exposure**										
Duration of Use										
Leave-On	***	*1544*	*958*	*0.00015 – 35*	*1 – 56*	***	*793*	*1177*	*0.05 – 30*	*0.1 - 20*
Rinse-Off	***	*210*	*116*	*0.0004 – 25.5*	*1 – 2*	***	*15*	*16*	*0.25 – 4.5*	*0.07 – 0.2*
Diluted for (Bath) Use	***	*4*	*NR*	*NR*	*NR*	***	*NR*	*1*	*NR*	*NR*
Exposure Type										
Eye Area	***	296	222	0.00015 – 35	2 - 19	***	360	603	0.15 – 30	1 – 6
Incidental Ingestion	***	270	224	0.49 – 25.5	2 - 56	***	229	481	0.33 – 7	0.07 – 9
Incidental Inhalation-Spray	***	9; 371[a]; 193[b]	25; 175[a]; 125[b]	5; 0.001 – 14[a]	1; 1 – 4[a]; 1 – 10[b]	***	3; 64[a]; 23[b]	2; 13[a]; 4[b]	0.5; 0.7 – 8[a]	0.1 – 4[a]
Incidental Inhalation-Powder	***	14; 193[b]; 26[c]	6; 125[b]	0.34 – 6; 1.5 – 13.5[c]	2; 1 – 10[b]	***	7; 23[b]	1; 4[b]	6.8 – 7.1; 0.05 – 1[c]	0.8 – 1
Dermal Contact	***	1170	679	0.00015 – 27	1 – 19	***	358	559	0.05 – 12.5	0.1 – 20
Deodorant (underarm)	***	24[a]	1[a]	3.5	NR	***	3[a]	NR	NR	NR
Hair - Non-Coloring	***	114	21	0.001 - 14	1	***	41	1	4 – 8	NR
Hair-Coloring	***	86	24	0.01 – 1.5	NR	***	2	8	NR	NR
Nail	***	2	10	7.5	NR	***	2	2	NR	NR
Mucous Membrane	***	289	228	0.0004 – 25.5	2 – 56	***	229	482	0.33 – 7	0.07 - 9
Baby Products	***	31	4	2 – 13.5	NR	***	4	NR	NR	0.8 – 1
as reported by product category										
Baby Products	***35***					***7***				
Baby Lotions/Oils/Powders/Creams	30	26	4	2 – 13.5	NR	7	4	NR	NR	0.8 – 1
Baby Wipes	1	NA	NA	NR	NA					
Other Baby Products	5 (l.o.); 1 (r.o.)	5	NR	NR	NR	2 (l.o.)	NR	NR	NR	NR
Bath Preparations	***19***					***7***				
Bath Oils, Tablets, and Salts	4	NR	NR	NR	NR	1	NR	1	NR	NR
Bubble Baths	1	NR	NR	NR	NR					
Other Bath Preparations	16	4	NR	NR	NR	6	NR	NR	NR	NR
Eye Makeup Preparations (not children's)	***1424***					***2090***				
Eyebrow Pencil	291	48	15	7.8 – 9.8	NR	408	52	36	4 – 12.5	NR
Eyeliner	307	19	29	1.5 – 12.5	2	590	66	317	2 – 9	1
Eye Shadow	366	68	23	0.33 – 13.8	2	264	41	59	0.15 – 6.8	NR
Eye Lotion	22	19	1	0.00015 – 1.5	NR	9	3	NR	NR	NR
Eye Makeup Remover	4	NR	NR	NR	NR	1	NR	NR	NR	NR
False Eyelashes	4	NA	NA	NR	NA	4	NA	NA		NA
Mascara	414	115	116	11.4 – 35	19	776	176	143	2 – 30	2 – 6
Eyelash and Eyebrow Adhesives, Glues, and Sealants	20	NA	NA	NR	NA	9	NA	NA	NR	NA
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)	23	NA	NA	NR	NA	66	NA	NA	NR	NA
Eyelash Cleansers	1	NA	NA	NR	NA					

Table 1. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[3]	**VCRP (2023)[4]**	**VCRP (2002)[2]**	**% (2022)[5]**	**% (2003)[2]**	**RLD (2024)[3]**	**VCRP (2023)[4]**	**VCRP (2002)[2]**	**% (2022)[5]**	**% (2003)[2]**
Other Eye Makeup Preparations	141	27	38	2.3 – 5	3	133	22	48	3.5 – 4.5	5
Children's Eye Makeup Preparations	***9***					***2***				
Children's Eyeshadows	8	NA	NA	NR	NA	2	NA	NA	NR	NA
Other Children's Eye Makeup	1	NA	NA	NR	NA					
Fragrance Preparations	***151***					***5***				
Cologne and Toilet Water	1	NR	NR	NR	NR	NR	NR	1	NR	NR
Perfumes	31	6	18	NR	1					
Powders (dusting/talcum, excl aftershave talc)	2	NR	NR	NR	NR					
Sachets	NR	NR	9	NR	NR					
Other Fragrance Preparation	118	2	6	5	NR	5	3	1	0.5	NR
Hair Preparations (non-coloring)	***421***					***110***				
Hair Conditioners	19 (l.o.); 24 (r.o.)	8	4	0.01 – 2	NR	8 (l.o.); 5 (r.o.)	3	NR	NR	NR
Hair Sprays (aerosol fixatives)	58	NR	NR	NR	NR	1	NR	NR	NR	NR
Hair Straighteners	7	4	NR	NR	NR	1	1	NR	NR	NR
Permanent Waves	3	NR	NR	NR	NR					
Rinses (non-coloring)	10	NR	NR	NR	NR	1	NR	NR	NR	NR
Shampoos (non-coloring)	6	1	NR	NR	NR	1 (r.o.)	NR	1	NR	NR
Tonics, Dressings, and Other Hair Grooming Aids	137	83	17	0.001 – 14	NR	37	28	NR	NR	NR
Wave Sets	11	NR	NR	NR	NR	NR	2	NR	8	NR
Other Hair Preparations	141 (l.o.); 27 (r.o.)	18	NR	NR	1	54 (l.o.); 5 r.o.)	7	8	4	NR
Hair Coloring Preparations	***1119***					***182***				
Hair Dyes and Colors (all types requiring caution statements and patch tests)	947	83	20	0.75 – 1.5	NR	151	NR	NR	NR	NR
Hair Tints	87	2	1	NR	NR	21	1	NR	NR	NR
Hair Rinses (coloring)	9 (r.o.)	NR	NR	0.01	NR					
Hair Shampoos (coloring)	1 (r.o.)	NR	NR	NR	NR					
Hair Color Sprays (aerosol)	7	NR	1	NR	NR					
Hair Lighteners with Color	7	NR	NR	0.2	NR					
Hair Bleaches	7	NR	NR	NR	NR	1	NR	NR	NR	NR
Eyelash and Eyebrow Dyes	8	NA	NA	NR	NA	2	NA	NA	NR	NA
Other Hair Coloring Preparation	30 (l.o.); 22 (r.o.)	1	2	NR	NR	6 (l.o.); 1 (r.o.)	1	NR	NR	NR
Makeup Preparations (not eye; not children's)	***3219***					***2382***				
Blushers and Rouges (all types)	263	49	13	6.5 – 11	19	186	13	10	2 - 6.8	4
Face Powders	190	14	2	0.34 – 6	2	116	3	1	6.8 – 7.1	
Foundations	262 (traditional application); 8 (airbrush application)	10	14	9	5	317 (traditional application)	26	NR	7.6	6 – 20
Leg and Body Paints	63 (traditional application); 1 (airbrush application)	1	NR	NR	NR	2	NR	NR	NR	NR
Lipstick and Lip Glosses	2073	269	224	2 – 12.2	56	1718	228	479	1 – 7	1 – 9

Table 1. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[3]	**VCRP (2023)[4]**	**VCRP (2002)[2]**	**% (2022)[5]**	**% (2003)[2]**	**RLD (2024)[3]**	**VCRP (2023)[4]**	**VCRP (2002)[2]**	**% (2022)[5]**	**% (2003)[2]**
Makeup Bases	153 (traditional application); 2 (airbrush application)	4	25	9	3	84 (traditional application)	NR	7	NR	NR
Makeup Fixatives	143	NR	NR	NR	NR	5	1	2	NR	NR
Other Makeup Preparations	213 (l.o.)	125	27	25	9	151 (l.o.); 1 (r.o.)	36	45	1.1 – 4	2 – 6
Makeup Preparations for Children (not eye)	***487***					***148***				
Children's Blushers and Rouges (All Types)	1	NA	NA	NR	NA					
Children's Face Paints	5	NA	NA	NR	NA	1	NA	NA	NR	NA
Children's Face Powders	1	NA	NA	NR	NA					
Children's Foundations	1	NA	NA	NR	NA					
Children's Lipsticks and Lip Glosses	474	NA	NA	NR	NA	147	NA	NA	NR	NA
Other Children's Makeup	11	NA	NA	NR	NA					
Manicuring Preparations	***30***					***2***				
Basecoats and Undercoats	2	NR	NR	NR	NR					
Cuticle Softeners	4	NR	5	7.5	NR					
Nail Creams and Lotions	2	2	5	NR	NR	NR	1	NR	NR	NR
Nail Polish and Enamel	6	NR	NR	NR	NR	2	1	1	NR	NR
Nail Polish and Enamel Removers	3	NR	NR	NR	NR					
Other Manicuring Preparations	13	NR	NR	NR	NR	NR	NR	1	NR	NR
Oral Products	***21***									
Dentifrices						NR	1	NR	0.33	NR
Mouthwashes and Breath Fresheners	NR	1	NR	NR	NR					
Other Oral Products	21	NR	NR	0.49 – 25.5	2	NR	NR	2	4.5	0.07
Personal Cleanliness	***103***					***22***				
Bath Soaps and Body Washes	17	3	2	0.0004	NR	4	NR	NR	NR	NR
Deodorants (underarm)	57 (not spray); 1 (spray)	24	1	3.5 (not spray)	NR	10	3	NR	NR	NR
Douches	NR	1	NR	NR	NR					
Feminine Deodorants	1 (l.o.)	1	NR	NR	NR					
Disposable Wipes						1	NA	NA	NR	NA
Other Personal Cleanliness Products	8 (l.o.); 22 (r.o.)	10	2	20	NR	1 (l.o.); 6 (r.o.)	NR	NR	NR	NR
Shaving Preparations	***43***					***3***				
Aftershave Lotions	2	4	8	3	NR	1	NR	NR	NR	NR
Beard Softeners	15	10	NR	NR	NR	2	1	NR	NR	NR
Pre-shave Lotions (all types)						2	NR	NR	NR	NR
Shaving Creams (aerosol, brushless, lather)	7	1	NR	NR	NR	1	NR	NR	NR	NR
Shaving Soaps (cakes, sticks, etc.)	1	NR	NR	NR	NR					
Other Shaving Preparation Products	19	3	1	NR	NR					
Skin Care Preparations	***1726***					***273***				
Cleansing	147	38	72	0.5 – 6.6	2	13	3	3	0.25	0.2
Depilatories	120	49	1	3 – 19	2	3	3		3	NR
Face and Neck (excluding shaving preparations)	414 (l.o.); 82 (r.o.)	105	32	2- 8.6 (not spray)	1	102 (l.o.); 8 (r.o.)	15	2	0.21 (not spray)	NR

Table 1. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[3]	**VCRP (2023)[4]**	**VCRP (2002)[2]**	**% (2022)[5]**	**% (2003)[2]**	**RLD (2024)[3]**	**VCRP (2023)[4]**	**VCRP (2002)[2]**	**% (2022)[5]**	**% (2003)[2]**
Body and Hand (excluding shaving preparations)	192 (l.o.); 20 (r.o.)	87	93	1.5 – 12 (not spray)	10	34 (l.o.); 2 (r.o.)	8	2	0.05 – 1 (not spray)	NR
Foot Powders and Sprays	9	NR	NR	NR	NR	NR	NR	NR	0.5 – 3.5 (not spray)	NR
Moisturizing	699	263	102	0.0005 – 27 (not spray)	1	95	30	5	NR	NR
Night	34	23	48	0.5 (not spray)	4	4	4	5	NR	0.2
Paste Masks (mud packs)	36	5	11	5	1	NR	NR	1	NR	NR
Skin Fresheners	13	1	NR	NR	NR	NR	2	NR	NR	NR
Other Skin Care Preparations	258 (l.o.); 27 (r.o.)	115	74	1.5 – 2	4	44 (l.o.); 10 (r.o.)	19	9	0.7	NR
Suntan Preparations	***46***					***3***				
Suntan Gels, Creams, and Liquids	30	1	7	NR	NR	3	NR	1	2 (not spray)	0.1
Indoor Tanning Preparations	10 (traditional application)	NR	1	NR	NR					
Other Suntan Preparations	6	NR	NR	NR	NR	NR	NR	2	NR	4
Tattoo Preparations	***14***									
Temporary Tattoo Inks	2	NA	NA	NR	NA					
Other Tattoo Preparations	12	NA	NA	NR	NA					
Other Preparations (i.e., those preparations that do not fit another category)	***169***	NA	NA	NR	NA	***36***	NR	NA	NR	NA
	EUPHORBIA CERIFERA (CANDELILLA) WAX					**RHUS SUCCEDANEA FRUIT WAX**				
Totals*	**5394**	**713**	**701**	**0.005 – 25**	**0.03 - 27**	**300**	**16**	**528**	**0.98 – 37.9**	**1 - 34**
summarized by likely duration and exposure**										
Duration of Use										
Leave-On	***	*674*	696	0.2 – 25	0.2 – 27	***	16	527	0.98 – 37.9	1 – 34
Rinse-Off	***	*38*	5	0.005 – 3.1	0.03 – 12	***	NR	NR	NR	NR
Diluted for (Bath) Use	***	*1*	NR	NR	NR	***	NR	1	NR	NR
Exposure Type										
Eye Area	***	150	93	0.3 – 18.1	2 – 18	***	6	362	0.98 – 37.9	11 – 34
Incidental Ingestion	***	265	504	2.6 – 20.7	0.03 – 27	***	1	143	5.5	NR
Incidental Inhalation-Spray	***	20; 65[a]; 24[b]	3; 9[a]	0.5; 25[a]	0.2 – 8[a]; 0.3[b]	***	4[a]; 3[b]	1[a]	NR	1[b]
Incidental Inhalation-Powder	***	24[b]; 12[c]	1	2 – 4.2; 0.2 – 10	1; 0.3[b]; 3	***	3[b]	NR	NR	1[b]
Dermal Contact	***	375	149	0.01 – 18.1	0.2 – 18	***	14	384	0.98 – 37.9	1 – 34
Deodorant (underarm)	***	7[a]	NR	NR	NR	***	NR	NR	NR	NR
Hair - Non-Coloring	***	20	2	0.005 – 25	2	***	NR	1	NR	NR
Hair-Coloring	***	7	NR	NR	0.4	***	NR	NR	NR	NR
Nail	***	NR	2	2	9	***	NR	NR	NR	NR
Mucous Membrane	***	284	504	0.05 – 20.7	0.03 – 27	***	1	144	5.5	NR
Baby Products	***	14	NR	NR	NR	***	NR	NR	NR	NR

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	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[3]	VCRP (2023)[4]	VCRP (2002)[2]	% (2022)[5]	% (2003)[2]	RLD (2024)[3]	VCRP (2023)[4]	VCRP (2002)[2]	% (2022)[5]	% (2003)[2]
as reported by product category										
Baby Products	***9***									
Baby Lotions/Oils/Powders/Creams	5	12	NR	NR	NR					
Baby Wipes										
Other Baby Products	4 (l.o.)	2	NR	NR	NR					
Bath Preparations (diluted for use)	***3***									
Bath Oils, Tablets, and Salts	1	NR	NR	NR	NR	NR	NR	1	NR	NR
Bubble Baths										
Other Bath Preparations	2	1	NR	NR	NR					
Eye Makeup Preparations	***1236***					***239***				
Eyebrow Pencil	231	22	4	0.33 – 18.1	NR	146	3	56	9 – 37.9	34
Eyeliner	313	46	17	3.4 – 11	5 – 12	17	1	276	0.98 – 10	11
Eye Shadow	228	24	16	0.3 – 10.3	3 – 5	29	NR	23	5	NR
Eye Lotion	5	3	NR	NR	NR					
Eye Makeup Remover	1	NR	NR	NR	NR					
False Eyelashes	1	NA	NA	NR	NA					
Mascara	403	46	44	0.5 – 6.6	3 – 8	34	1	NR	NR	NR
Eyelash and Eyebrow Adhesives, Glues, and Sealants	2	NA	NA	NR	NA					
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)	42	NA	NA	NR	NA					
Eyelash Cleansers										
Other Eye Makeup Preparations	70	9	12	10	2 – 18	20	1	7	NR	NR
Children's Eye Makeup Preparations	***7***									
Children's Eyeshadows	7	NA	NA	NR	NA					
Other Children's Eye Makeup										
Fragrance Preparations	***32***									
Cologne and Toilet Water										
Perfumes	26	16	3	NR	NR					
Powders (dusting/talcum, excl aftershave talc)										
Other Fragrance Preparation	7	4	NR	0.5	NR					
Hair Preparations (non-coloring)	***124***					***6***				
Hair Conditioners	3 (l.o.); 24 (r.o.)	7	NR	0.01 – 2	NR					
Hair Sprays (aerosol fixatives)	3	NR	NR	NR	NR					
Hair Straighteners										
Permanent Waves										
Rinses (non-coloring)	2	NR	NR	NR	NR					
Shampoos (non-coloring)	1 (l.o.)	NR	NR	0.0005	NR					
Tonics, Dressings, and Other Hair Grooming Aids	21	11	2	25	NR	1	NR	1	NR	NR
Wave Sets	2	NR	NR	NR	NR					
Other Hair Preparations	59 (l.o.); 14 (r.o.)	2	NR	8.5	2	4 (l.o.); 1 (r.o.)	NR	NR	NR	NR
Hair Coloring Preparations	***46***									
Hair Dyes and Colors (all types requiring caution statements and patch tests)	28	NR	NR	NR	NR					
Hair Tints	12	2	NR	NR	NR					

Table 1. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[3]	**VCRP (2023)[4]**	**VCRP (2002)[2]**	**% (2022)[5]**	**% (2003)[2]**	**RLD (2024)[3]**	**VCRP (2023)[4]**	**VCRP (2002)[2]**	**% (2022)[5]**	**% (2003)[2]**
Hair Rinses (coloring)										
Hair Shampoos (coloring)										
Hair Color Sprays (aerosol)										
Hair Lighteners with Color										
Hair Bleaches	3	NR	NR	NR	NR					
Eyelash and Eyebrow Dyes										
Other Hair Coloring Preparation	2 (l.o.); 1 (r.o.)	5	NR	NR	0.4					
Makeup Preparations (not eye; not children's)	***3502***					***44***				
Blushers and Rouges (all types)	310	27	14	3 – 8.6	2 – 8	7	2	NR	NR	NR
Face Powders	87	NR	1	2 – 4.2	3					
Foundations	408 (traditional application)	8	14	8.9	3 – 10					
Leg and Body Paints	NR	2	NR	NR	NR					
Lipstick and Lip Glosses	2533	265	504	2.6 – 20.7	5 – 27	41	1	143	5.5	
Makeup Bases	NR	1	13	3.5	NR	1 (traditional application)	NR	NR	NR	NR
Makeup Fixatives	12	1	NR	NR	NR					
Other Makeup Preparations	277 (l.o.); 4 (r.o.)	46	41	NR	6 – 10	4 (l.o.)	NR	19	NR	7
Makeup Preparations for Children (not eye)	***11***					***3***				
Children's Blushers and Rouges (All Types)										
Children's Face Paints	1	NA	NA	NR	NA					
Children's Face Powders										
Children's Foundations										
Children's Lipsticks and Lip Glosses	10	NA	NA	NR	NA	3	NA	NA	NR	NA
Other Children's Makeup										
Manicuring Preparations (Nail)	***2***					***1***				
Basecoats and Undercoats										
Cuticle Softeners	NR	NR	NR	2	NR	1	NR	NR	NR	NR
Nail Creams and Lotions	1	NR	NR	NR	NR					
Nail Polish and Enamel	NR	NR	1	NR	9					
Nail Polish and Enamel Removers										
Other Manicuring Preparations	1	NR	1	NR	NR					
Oral Hygiene Products										
Dentifrices										
Mouthwashes and Breath Fresheners										
Other Oral Products	NR	NR	NR	3.1	0.03 – 12					
Personal Cleanliness Products	***48***					***2***				
Bath Soaps and Body Washes	12	12	NR	0.05	NR					
Deodorants (underarm)	26 (not spray)	7	NR	NR	NR					
Douches										
Feminine Deodorants	NR	1	NR	NR	NR					
Disposable Wipes										
Other Personal Cleanliness Products	11 (r.o.)	5	NR	NR	NR	2 (r.o.)	NR	NR	NR	NR

Table 1. Frequency (RLD/VCRP) and concentration of use according to likely duration and exposure and by product category

	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[3]	**VCRP (2023)[4]**	**VCRP (2002)[2]**	**% (2022)[5]**	**% (2003)[2]**	**RLD (2024)[3]**	**VCRP (2023)[4]**	**VCRP (2002)[2]**	**% (2022)[5]**	**% (2003)[2]**
Shaving Preparations						***1***				
Aftershave Lotions	1	NR	NR	NR	NR					
Beard Softeners	3	2	NR	NR	NR					
Pre-shave Lotions (all types)	1	NR	NR	NR	NR					
Shaving Creams (aerosol, brushless, lather)	1	NR	NR	NR	NR					
Shaving Soaps (cakes, sticks, etc.)										
Other Shaving Preparation Products	1	NR	NR	NR	NR	1	NR	NR	NR	NR
Skin Care Preparations	***438***					***9***				
Cleansing	30	6	2	0.01 – 0.063	1					
Depilatories	2									
Face and Neck (excluding shaving preparations)	138 (l.o.); 19 (r.o.)	11	NR	3.3 – 10 (not spray)	NR	2 (l.o.)	3	NR	NR	1
Body and Hand (excluding shaving preparations)	57 (l.o.); 1 (r.o.)	12	NR	0.2 – 2.3 (not spray)	0.3	3 (l.o.)	NR	NR	NR	NR
Foot Powders and Sprays										
Moisturizing	136	49	4	0.2 – 5 (not spray)	NR	2	2	NR	NR	NR
Night	8	4	2	NR	2	1	2	NR	NR	NR
Paste Masks (mud packs)	5	1	3	NR	2					
Skin Fresheners	4	NR	NR	NR	NR					
Other Skin Care Preparations	105 (l.o.); 19 (r.o.)	41	2	NR	0.3 – 5	1 (l.o.)	NR	2	NR	NR
Suntan Preparations	***8***									
Suntan Gels, Creams, and Liquids	**7**	NR	1	NR	8					
Indoor Tanning Preparations										
Other Suntan Preparations	1	NR	NR	NR	0.2 – 4					
Tattoo Preparations										
Temporary Tattoo Inks										
Other Tattoo Preparations										
Other Preparations (i.e., those preparations that do not fit another category)	***28***	NA	NA	NR	NA	***2***	NA	NA	NR	NA

NR – not reported; NA – not applicable (this category was not part of the VCRP)
l.o. – leave-on; r.o. – rinse-off
*The total FOU provided for RLD refers to the ingredient count supplied by FDA, and is not a summation of the number of uses per category because each product may be categorized under multiple product categories. For data supplied via the VCRP or by the Council survey, the sum of all exposure types may not equal the sum of total uses because each ingredient may be used in cosmetics with multiple exposure types.
**Likely duration and exposure are derived from VCRP and survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)
***In the RLD each ingredient may be reported under several product categories, making a summation of RLD misleading in comparison to VCRP data. Accordingly, RLD are presented below by product category (as supplied by FDA), but are not summarized by likely duration and exposure.
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 2. Impurities and specifications*

Ingredient	Data	Reference
Beeswax	Specifications of Beeswax according to European legislation: -glycerol and other polyols: not more than 0.5% (as glycerol) -ceresin, paraffins, and certain other waxes: absent -fats, Japan wax, rosin, and soaps: absent -arsenic: not more than 3 mg/kg -lead: not more than 5 mg/kg -mercury: not more than 1 mg/kg	6
Beeswax	Beeswax may be contaminated by persistent lipophilic acaricides. The active varroacide substances coumaphos, fluvalinate, and bromopropylate were the main acaricide residues found in commercial Beeswax samples from European countries and were detected in levels ranging from 0.05 – 16.40 mg/kg, less than 0.01 to 15 mg/kg, and 0.07 – 15 mg/kg, respectively. Other contaminants reported include z-chlorfenvinphos (0.16 – 4.82 mg/kg), amitraz (0.10 – 0.56 mg/kg), lindane (0.04 – 0.29 mg/kg), endosulfan sulphate (0.12 – 0.36 mg/kg), lead (0.06 – 6.2 mg/kg), cadmium (0.01 – 0.1 mg/kg), and mercury (0.0001 – 0.06 mg/kg).	1
Beeswax	Heavy metal concentrations of Beeswax comb samples (n = 15) of different ages were measured between 2018 to 2022 in Egypt. Concentrations at year 1 were as follows: iron (2.1 ppm), chromium (1.01 ppm), zinc (0.36 ppm), copper (0.65 ppm), nickel (0.89 ppm), manganese (0.22 ppm), lead (0.04 ppm), cadmium (0.024 ppm), cobalt (0.027 ppm). Concentrations at year 5 were as follows: iron (5.04 ppm), chromium (2.7 ppm), zinc (2.5 ppm), copper (2.6 ppm), nickel (2.5 ppm), manganese (1.2 ppm), lead (0.19 ppm), cadmium (0.05 ppm), cobalt (0.05 ppm).	2
Beeswax	Amounts of trace metals in Beeswax samples of different countries of origin were evaluated. The highest amounts observed were as follows: iron (334,000 µg/kg; Poland), zinc (729,000 µg/kg; Italy), copper (40,930 µg/kg; Croatia), manganese (41,904 µg/kg; Slovakia), nickel (17,830 µg/kg; Croatia), chromium (56,280 µg/kg; Croatia), lead (6510 µg/kg; Italy), arsenic (140 µg/kg; Italy), cadmium (289 µg/kg; Italy), mercury (1700 µg/kg; Spain).	7
Beeswax	According to a review article on the toxic compounds present in bee products, Beeswax may contain polycyclic aromatic hydrocarbons, polychlorinated naphthalenes, *Clostridium botulinum* spores, pesticides, and other inorganic contaminants.	4
Beeswax	According to a review article on residues found in different samples of Beeswax in Europe, 68 different residues were found. These residues include acaricide, insecticides, antiparasitics, molluscicides, fungicides, nematicides, antimicrobials, ovicides, etc.	5
Beeswax	Monitoring of lipophilic acaricides was performed in commercial Swiss Beeswax. In 2019, *tau*-fluvalinate, coumaphos, and thymol residues were found in average amounts of 0.38, 0.41, and 17.4 mg/kg, respectively (number of samples evaluated not stated).	6
Beeswax	Swiss commercial Beeswax samples from 19 manufacturers were evaluated for pesticides. Mean values of 401, 236, 106 and 3 µg/kg were obtained for coumaphos, *tau*-fluvalinate, bromopropylate and N-(2,4-dimethylphenyl)-formamide, respectively. For other pesticides, the mean values were 203 µg/kg synergist piperonyl butoxide, 120 µg/kg repellent N,N-diethyl-3-methylbenzamide), 19 µg/kg (chlorfenvinphos and 4 µg/kg (E)-fenpyroximate, while the means for acrinathrin, azoxystrobin, bendiocarb, boscalid, chlorpyrifos, flumethrin, permethrin, propoxur and thiacloprid were below the limit of quantification.	7
Beeswax	Thirty-five Beeswax samples from Spain were collected in 2016 to evaluate pesticide incidence. The compounds coumaphos (detected in 100% of samples), fluvalinate (detected in 86% of samples), and amitraz (detected in 83% of samples) were the pesticides most frequently detected, with maximum concentrations of 26,858, 3593 and 6884 ng/g, respectively. Chlorfenvinphos, acrinathrin and flumethrin, also acaricides, were detected in 77, 71 and 54% of samples, respectively.	8
Copernicia Cerifera (Carnauba) Wax	Specifications of carnauba wax according to European legislation: -arsenic: not more than 3 mg/kg -lead: not more than 2 mg/kg -mercury: not more than 1 mg/kg	8
Euphorbia Cerifera (Candelilla) Wax	Specifications of candelilla wax according to European legislation: -glycerol and other polyols: not more than 0.5% (as glycerol) -ceresin, paraffins, and certain other waxes: absent -fats, Japan wax, rosin, and soaps: absent -arsenic: not more than 3 mg/kg -lead: not more than 2 mg/kg -mercury: not more than 1 mg/kg	9

*According to the re-review published in 2005, the Panel reviewed impurities data and reminded manufacturers that cosmetic products containing plant-derived ingredients should be formulated to limit the presence of heavy metal/pesticide residues as follows: lead ≤10 ppm, arsenic ≤3 ppm, mercury ≤1 ppm, and total PCB/pesticide contamination ≤40 ppm, with ≤10 ppm for any specific residue.

Table 3. CFR Citations

Ingredient	Data	Reference
Beeswax	Beeswax is used as an active ingredient in OTC drug products (insect bite and sting drug products and skin protectant drug products); there are inadequate data to establish the general recognition of safety and effectiveness of Beeswax for these uses	21CFR310.545
Beeswax	White and yellow Beeswax may be used at up to 5% in combination with one more emollient (that are also listed in 21CFR349.13) in OTC ophthalmic drug products	21CFR310.545
Beeswax Copernicia Cerifera (Carnauba) Wax	Residues resulting from the use of carnauba wax or Beeswax as either an inert or an active ingredient in a pesticide chemical formulation, including antimicrobial pesticide chemicals, are exempted from the requirement of a tolerance under FFDCA section 408, if such use is in accordance with good agricultural or manufacturing practices.	40CFR180.950
Copernicia Cerifera (Carnauba) Wax	Carnauba wax is approved as a direct human food ingredient used as an anticaking agent	21CFR184.1978
Rhus Succedanea Fruit Wax	Rhus Succedanea Fruit Wax may be used as an adhesive in articles intended for use in packaging, transporting, or holding food when used in accordance with certain conditions	21CFR175.105
Rhus Succedanea Fruit Wax	Rhus Succedanea Fruit Wax may be used as diluents in color additive mixtures for coloring eggshells subject to the condition that there is no penetration of the color additive mixture of any of its components through the eggshell into the egg	21CFR73.1

CFR = Code of Federal Regulations; FFDCA = Federal Food Drug, and Cosmetic Act; OTC = over-the-counter

Table 4. Acute toxicity studies

Test Article	Vehicle	Animals/Group	Concentration/Dose	Protocol	LD_{50}/LC_{50}/Results	Reference
DERMAL						
Beeswax	arachis oil	female Wistar rats (1 animal at low dose; 5 animals at high dose)	300 and 2000 mg/kg bw	OECD TG 420; acute oral toxicity assay; gavage administration	LD_{50} > 2000 mg/kg bw; no deaths or signs of systemic signs of toxicity observed	10

LD_{50} = median lethal dose; OECD = Organisation for Economic Co-operation and Development; TG = test guideline

Table 5. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
IN VITRO						
Beeswax	tetrahydrofuran	experiment 1: 1.5, 5, 15, 50, 150, 500, 1500 and 5000 µg/plate experiment 2: 15, 50, 150, 500, 1500, 5000 µg/plate	*Salmonella typhimurium* TA 1535, TA 1537, TA 98, TA 100 and *Escherichia coli* WP2	OECD TG 417; 2-part Ames assay; negative control: vehicle; positive controls: benzo(a)pyrene and 2-aminoathracene	non-mutagenic; controls gave expected results	10

OECD = Organisation for Economic Co-operation and Development; TG = test guideline

Table 6. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population/System	Protocol	Results	Reference
IRRITATION						
IN VITRO						
Beeswax	none	100%; 10 ± 5 mg (26 mg/cm^2)	EpiSkin^{TM} tissues (n = 3/group)	OECD TG 439; in vitro skin irritation assay; 15-min exposure period; 42-h post-treatment incubation; tissue viability calculated after incubation; negative control: phosphate-buffered saline; positive control: sodium lauryl sulfate	non-irritating; tissue viability of test article, negative control, and positive control was 100, 96.1, and 2.7%, respectively	10
SENSITIZATION						
ANIMAL						
Beeswax	tetrahydrofuran	2.5, 5, and 10%	female CBA/Ca mice (5/group)	OECD TG 429; local lymph node assay; negative control: vehicle: positive control: hexyl cinnamic aldehyde	non-sensitizing; controls gave expected results	10

OECD = Organisation for Economic Co-operation and Development; TG = test guideline

Table 7. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Protocol	Results	Reference
IN VITRO						
Beeswax	none	100%; 50 mg	EpiOcular^{TM} tissues (n = 2/group)	OECD TG 492; reconstructed human cornea-like epithelium test; 6-h treatment period; 18-h post incubation period; tissue viability evaluated after incubation; negative control: water; positive control: methyl acetate	no indication of irritation; tissue viability of the test substance, negative control and positive control was 96, 100, and 31.8%, respectively	10

OECD = Organisation for Economic Co-operation and Development; TG = test guideline

Table 8. Clinical studies

Ingredient	Subjects	Protocol/Study Description	Results/Case Report Summary	Reference
RETROSPECTIVE AND SINGLE OR MULTI-CENTER STUDIES				
Allergy				
Beeswax	95 patients	retrospective study; patch tests performed in 95 atopic patients using yellow and white Beeswax	A retrospective study was performed using a cohort of 95 patients with a suspicion of contact allergic cheilitis (n = 55), eczema around the lips or on the face (n = 32), or a suspicion of contact allergy to products containing Beeswax (n = 8). Occlusive patch tests were performed using yellow Beeswax, white Beeswax, and propolis (only 84 subjects tested for propolis). In the cohort, 17/95 patients showed positive results to yellow and/or white Beeswax. Positive patch tests to propolis were seen in 16/84 patients. In 16 of the 17 positive reactions to white or yellow Beeswax, the reactions were determined to be clinically relevant (clinical relevance was assessed by checking products used with regard to Beeswax).	11
Beeswax	58 patients	cross-sectional study evaluating allergic response to propolis and Beeswax in beekeepers	An 18-mo cross-sectional study was performed in beekeepers in India. Patch tests using 10% propolis in petroleum, royal jelly (tested as-is), and Beeswax (tested as-is) were performed in bee workers with clinical features of contact dermatitis (n = 58). Six positive reactions were observed for propolis and 0 positive reactions were observed for Beeswax and royal jelly.	12
Beeswax	2828 patients	multi-center study evaluating prevalence of allergy and cross-reactions to Beeswax and yellow and white Beeswax	The prevalence of propolis allergy and cross-reactions to Beeswax were evaluated in 2828 subjects via patch testing (subjects undergoing patch testing as part of the investigation for contact dermatitis in UK centers). Patch tests were performed using 10% propolis in petroleum and pure yellow and white Beeswax. Fifty-five subjects had a positive patch test to propolis, and 13 subjects had a positive reaction to Beeswax. Fifty-one subjects reacted to propolis only, 9 to Beeswax only, and 4 to both allergens.	13
Euphorbia Cerifera (Candelilla) Wax	146 patients	retrospective study evaluating the prevalence and common allergens associated with cheilitis in a specialist contact dermatitis clinic	The clinic's patch test database was used to pull data on patients (n = 146) with cheilitis over a 19-yr period (1982 – 2001), all of who had patch testing done for potential allergens. A positive allergic patch test reaction was thought to be relevant in 22 patients. Two of the 22 patients had positive patch tests to candelilla wax.	14
Wound Prevention/Healing				
Beeswax	90 mothers	randomized controlled trial evaluated the effectiveness of Beeswax in preventing nipple pain and cracks in the early post-partum period	Ninety primiparous mothers that met qualification criteria were randomly divided into Beeswax (n = 30), breast milk (n = 30), and control (n = 30) groups (mothers who were not allergic to honey or honey products were included in the study). Mothers in each group were evaluated for nipple pain and cracks on post-partum day 1, 3, 5, 7, and 10. Beeswax barriers were prepared by melting 100% Beeswax and molding into nipple shapes. Participants were instructed to wash hands before breastfeeding and allow 20-25 s for drying before application of the barrier. The barriers were worn at all times outside of breastfeeding and bathing. On post-partum day 10, nipple pain and cracks occurred highest in the control group (53.3%), whereas nipple pain and cracks were encountered least in the Beeswax group (20%) on post-partum observation days. None of the participants in this study experienced any Beeswax-related allergic reactions. In addition, no adverse effects were observed among newborns whose mothers used the Beeswax barrier.	15

Table 8. Clinical studies

Ingredient	Subjects	Protocol/Study Description	Results/Case Report Summary	Reference
			CASE REPORTS	
Beeswax	60-yr-old male	case report on subject with worsening dermatitis following use of cream containing Beeswax	A 60-yr-old male with chronic venous insufficiency and stasis dermatitis in both legs presented with worsening dermatitis following use of an ointment containing 7% Beeswax, 8% cetylpalmitate, 60% peanut oil, and 25% distilled water. Treatment with this ointment plus 1% hydrocortisone resulted in severe deterioration of the dermatitis. Discontinuation of this ointment resulted in regression of symptoms. Patch tests were performed on the individual ingredients of the ointment, the ointment itself, the ointment in combination with hydrocortisone, hydrocortisone, and propolis (Beeswax tested at 30% in petroleum and propolis tested at 10% in petroleum). Positive reactions were obtained for Beeswax, the ointment, the ointment with hydrocortisone, and propolis. The patient was diagnosed with allergic contact dermatitis to Beeswax, which was likely contaminated with propolis.	16
Beeswax	29-yr-old female	case report on subject with chronic cheilitis due to Beeswax-containing lip balm	A 29-yr-old woman with a nut allergy and asthma presented with chronic, relapsing cheilitis and perioral dermatitis. The patient reported the use of various lip balms without improvement. Patch tests revealed positive results for several substances including fragrances and lip balm containing 30% white Beeswax. Ingredient testing confirmed allergic reactions to the lip balm and to 30% white Beeswax in petroleum.	17
Beeswax	44-yr-old female	case report on subject with dermatitis and cheilitis due to lip balm and candy containing Beeswax	A 44-yr-old woman with a history of atopic dermatitis was patch-tested (with her own products and standard series) after presenting with face and neck dermatitis and pronounced cheilitis. The patient developed reactions to her lip balm and two other substances. When testing the individual ingredients of the lip balm, the patient had a positive reaction to white Beeswax. The skin condition cleared upon lip balm discontinuation; however, dry and chapped lips still occurred. It was subsequently discovered that wine gums often consumed by the patient were coated in white Beeswax. The cheilitis cleared completely following discontinuation of the candy. The patient was again patch tested 6 mo later to evaluate if cross-reaction to propolis was present. Positive reactions were seen to 10% propolis in petroleum, 20% white Beeswax, and 30% yellow Beeswax in petroleum.	18
Beeswax	45-yr-old female	case report on beekeeper with edematous facial eczema	A 45-yr-old woman with a history of facial eczema and previous positive patch testing to several substances (fragrance mix I, balsam of Peru, isoeugenol, and eugenol) presented with severe edematous facial eczema. The patient reported reactions following exposure to beehives. Patch tests were performed using standard series, cosmetic/perfume series, personal perfume, and semi-open tests with the patient's own products (including propolis and Beeswax from her hives). The patient tested positive for the previously positive substances, as well as propolis and Beeswax. Chinese-type propolis and white Beeswax provided by a cosmetics laboratory yielded negative results.	19
Beeswax	26-yr-old male	case report on dental technician with a history of atopic dermatitis following occupational exposure to Beeswax and propolis	A 26-yr-old dental technician with a history of atopic eczema presented with chronic pulpitis and fingertip/nail eczema on the right hand. The patient's job involved the manufacture of dental molds. Patch testing with a standard series, dental series, and 10% propolis yielded positive reactions to propolis and a borderline reaction to bisphenol. It was discovered that the dental molding process involved molding Beeswax. The patient was diagnosed with allergic contact dermatitis secondary to occupational exposure to propolis.	20

Table 8. Clinical studies

Ingredient	Subjects	Protocol/Study Description	Results/Case Report Summary	Reference
Beeswax	81-yr-old male	case report on healthy man with chronic dry lips with fissures and scaling following use of bee's ointment and honey ingestion	An 81-yr-old healthy man who presented with chronic dry lips with fissures and scaling was being treated with hydrocortisone and different types of emollients, including a bee's ointment, with no relief. Patch testing was performed with a Swedish baseline series, 5% carvone in petroleum, 10% propolis in petroleum, and the patient's own products. The patient showed an extreme positive reaction to propolis and a doubtful reaction to *Myroxylon pereirae*, but remained negative to his own products, including the bee's ointment (which according to the ingredient label contained propolis). The patient reported consumption of a honey sandwich, daily, for many years. Further patch testing was performed with his own honey, *Myroxylon pereirae*, white Beeswax, and yellow Beeswax. The patient showed positive reactions to yellow Beeswax, his own honey, and *Myroxylon pereirae.* Symptoms cleared after stopping honey ingestion.	21
Beeswax and Euphorbia Cerifera (Candelilla) Wax	32-yr-old female	case report on atopic patient with severe cheilitis following use of lip balms containing Beeswax and candelilla wax	A 32-yr-old atopic female patient presented with severe, chronic cheilitis and mild facial and hand dermatitis. The patient had tried multiple (n = 6) lip balms for atopic cheilitis treatment. Clinical examination showed pronounced lip dermatitis complicated by bacterial infection. Patch tests were performed using a baseline, fragrance, and bakery series, as well as 4 out of the 6 lip balms used. Positive reactions were observed for all lip balms, propolis, and several other substances. Additional patch tests were performed and positive reactions were observed for several lip balm ingredients including 30% Beeswax in petroleum and 41% candelilla wax in petroleum.	22
Beeswax and Copernicia Cerifera (Carnauba) Wax	6-yr-old female	case report on girl with cheilitis and facial/upper extremity dermatitis due to vitamins containing Beeswax and carnauba wax	A 6-yr-old girl with a history of mild atopic dermatitis since infancy presented with recurrent episodes of cheilitis accompanied by facial and upper extremity dermatitis. Patch tests were performed with selected chemicals. Clinically relevant positive reactions were observed for propolis and cinnamaldehyde. A provocative use test with the child's lip balm (containing natural and artificial flavors and menthol in a wax base) yielded positive results. Significant improvement was noted following discontinuation of the lip balm. Further discussion revealed the use of multivitamins containing an unspecified amount of carnauba wax and Beeswax. Discontinuation of the vitamins results in clearance of both cheilitis and dermatitis.	23
Copernicia Cerifera (Carnauba) Wax	33-yr-old female	case report on woman with desquamative cheilitis and perioral dermatitis after use of lip balm containing carnauba wax	A 33-yr-old woman with a history of atopic dermatitis and asthma presented with desquamative cheilitis and perioral dermatitis after starting a lip balm for cracked lips. The patient was patch-tested with the European baseline series, individual components of fragrance mix I and II, her own lipsticks, lip balm, and toothpaste. Patch tests were positive for nickel sulfate in 5% petroleum and for the hypoallergenic lip balm. Further patch testing was performed on the ingredient of the lip balm. A positive reaction was obtained for carnauba wax.	24
Copernicia Cerifera (Carnauba) Wax	21-yr-old female	case report of woman with rash on eyelids due to mascara containing carnauba wax	A 21-yr-old woman presented with a 1-yr history of a bilateral scaly rash on both upper and lower eyelids. Patch testing was performed using the European standard series, a medicaments series, and her own eye cosmetics (including a mascara and its constituents, including carnauba wax)). Positive reactions were observed to the mascara, 50% carnauba wax in mineral oil, and 10% coathylene in petroleum.	25
Euphorbia Cerifera (Candelilla) Wax	11-mo-old male	case report on boy with rash following use of emollient cream containing candelilla wax	An 11-mo-old boy was prescribed an unscented emollient to treat dry skin accompanying atopic dermatitis. A generalized, papular, itchy rash formed 2 wk after starting use, and usage of cream was discontinued. At age 4, as parents struggled to find suitable creams and sunscreens for the child, a patch test was performed using a baseline series as well as the emollient cream. Positive results were obtained for the emollient cream, as well as to a fragrance mix and *Myroxylon pereirae* resin. Additional patch tests were performed on the individual ingredients of the cream. Strong positive reactions were obtained for 2 of the ingredients (candelilla wax in 41% petroleum and sucrose distearate in 10% petroleum). Cosmetics without fragrances, candelilla wax, and sucrose distearate were eventually advised and well-tolerated by the child.	26

Table 8. Clinical studies

Ingredient	Subjects	Protocol/Study Description	Results/Case Report Summary	Reference
Euphorbia Cerifera (Candelilla) Wax	25-yr-old female	case report on woman with cheilitis following use of lip balm containing candelilla wax	A 25-yr-old woman with a history of atopic dermatitis presented with recurrent episodes of cheilitis. Patch testing was performed with the European baseline series, a cosmetic extended series, and the patient's own products. Positive reactions were observed to the patient's lip balm and thiomersal. Patch tests were performed on the individual ingredients of the lip balm (including candelilla wax). A positive reaction to 10% candelilla wax in paraffin and octyldodecanol were observed. Discontinuation of lip balm resulted in cheilitis clearance.	27
Euphorbia Cerifera (Candelilla) Wax	25-yr-old female	case report on woman with lip and eye dermatitis due to products containing candelilla wax	A 25-yr-old atopic female presented with a history of intermittent pruritic dermatitis on the lips and eyelids with occasional involvement on the trunk and limbs. Over the years, the patient was treated with immunosuppressive, steroidal, and antibiotic treatments. Patch testing was performed using an allergen screening series, several supplemental series (e.g., corticosteroid, cosmetics), and 37 of her own personal products. Patch tests revealed a positive reaction to 50% candelilla wax in petroleum, a lipstick containing candelilla wax, and several other substances.	28

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