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 6 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 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[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, and photoprotection studies, 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. The Panel concluded these new data served to reaffirm the existing conclusion of safety; accordingly, this safety assessment was not reopened. However, they acknowledged the importance of capturing this information robustly, and therefore these studies are summarized in in Tables 3 - 9.

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. Some products containing these ingredients may be marketed for use with airbrush delivery systems; however, this information is not available from the VCRP or the Council survey. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients used in airbrush delivery systems are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the frequency and concentrations of use of these ingredients, and without consumer habits and practices data or particle size data related to this use technology, the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

In summary, the Panel reviewed 2023 frequency and concentration of use data, in addition to any new relevant safety data. After considering this information, as well as the information provided in the original safety assessment, the Panel reaffirmed the 2005 conclusion stating that that these ingredients are safe as used in cosmetic products.

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

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]
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

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]
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, the concentration 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	24-h application	pK_a was 4.2; tissue levels were enhanced only at pH levels less than 3.5; the researchers stated delivery of topical L-ascorbic acid into the skin is critically dependent on formulation characteristics	[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]

Abbreviations: OECD – Organisation for Economic Co-operation and Development; NOAEL – no-observable-adverse-effect-level; TG – test guideline

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 Tfr-downregulation.	[8]

Abbreviation: Tfr - transferrin receptor

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]

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

Test Article	Vehicle	Concentration/Dose	Test Population/System	Protocol	Results	Reference
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
PHOTOPROTECTIVE EFFECTS						
IN VITRO						
Magnesium Ascorbyl Phosphate		25, 250, or 500 µM or 1 mM	human keratinocyte cells	Test article was added to cells for 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 (365 nm). 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-simulated 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-simulated UV radiation to untreated skin (solar simulator with 295 nm band-pass filter). 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 UV radiation 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

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

Test Article	Vehicle	Concentration/Dose	Test Population/System	Protocol	Results	Reference
			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 (290 – 400 nm). On day 4, both test sites received solar-simulated 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]
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 3, each subject received solar-simulated irradiation to an untreated patch of skin (solar simulators equipped with 295 nm band-pass filters) to determine the MED. 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 UV (270 – 400 nm) 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 UV 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; UV exposure did not significantly affect skin Ascorbic Acid content. Total glutathione content of skin prior to UV exposure was reduced by Ascorbic Acid supplementation. Levels of oxidized glutathione were increased after UV exposure; Ascorbic Acid supplementation did not significantly affect glutathione oxidation or changes in protein thiol content seen in response to UV exposure. Ascorbic Acid supplementation also decreased malondialdehyde content of the skin prior to UV exposure, suggesting a reduction in baseline lipid peroxidation of skin samples. UV exposure did not significantly affect malondialdehyde content in supplemented or non-supplemented skin. Ascorbic Acid supplementation also did not significantly affect catalase activity in irradiated or non-irradiated skin.	[14]

Abbreviations: FCA – Freund's complete adjuvant; GPMT – guinea pig maximization test; LLNA – local lymph node assay; MED – minimal erythema dose; MMP-9 - matrix metalloproteinase-9; MTT - (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide); OECD - Organisation for Economic Co-operation and Development; SIOPT – single-insult occlusive patch test; SI – stimulation index; SLS – sodium lauryl sulfate; TG – test guideline; UV – ultraviolet

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]

Abbreviation: MTT - (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide)

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]

Abbreviation: ICDRG - International Contact Dermatitis Research Group

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