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Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics

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Abstract

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Caprylhydroxamic Acid as used in cosmetic formulations; this ingredient is reported to function as a chelating agent. Positive sensitization results that occurred with the use of a moisturizer containing Caprylhydroxamic Acid appeared to correlate with use on damaged skin. Therefore, the Panel cautioned against the use of Caprylhydroxamic Acid in a manner that would result in increased penetration. A quantitative risk assessment (QRA) was performed, using a weight-of-evidence no-expected-sensitization-induction-level (WoE NESIL) of 1056 μg/cm^2. The Panel concluded that Caprylhydroxamic Acid is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Keywords

Cosmetic Ingredient Review, Expert Panel for Cosmetic Ingredient Safety, Safety, Cosmetics, Caprylhydroxamic Acid

Introduction

This assessment reviews the safety of Caprylhydroxamic Acid as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), this ingredient is reported to function as a chelating agent in cosmetics.[1]

Included in this safety assessment are relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Expert Panel for Cosmetic Ingredient Safety (Panel) typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data were provided by the cosmetics industry, as well as by other interested parties.

Some of the data included in this safety assessment was found on Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS)[2] and the European Chemicals Agency (ECHA)[3] websites. Please note that these websites provide summaries of information from other sources, and it is those summary data that are reported in this safety assessment when NICNAS or ECHA is cited.

Chemistry

Definition and Structure

According to the *Dictionary*, Caprylhydroxamic Acid (CAS No. 7377-03-9) is the organic compound that conforms to the keto form depicted in Figure 1.[1] However, hydroxamic acids may exist in both keto and enol tautomeric forms.[4] The keto form is likely to predominate in acidic formulation, while the enol may dominate under alkaline conditions.

The hydroxamic acid functional group makes Caprylhydroxamic Acid a chelating agent. It is known that some bacteria synthesize and use hydroxamic acids as siderophores (iron scavengers/chelators).[4] Additionally, Caprylhydroxamic Acid forms strong complexes with oxidized transition metals almost instantaneously, and it may react with oxidizers and acids.[2] In general, hydroxamic acids are capable of inhibiting a

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variety of enzymes, including ureases, peroxidases, and matrix metalloproteinases.[5] However, data concerning the effects of Caprylhydroxamic Acid, specifically, on enzyme activity were not found in the published literature.

Caprylhydroxamic Acid is stable under normal environmental and usage conditions.[2] However, at very high or low pH, it may be hydrolyzed to caprylic acid and hydroxylamine. Decomposition products at high temperature are ammonia and oxides of carbon and nitrogen.

Chemical Properties

Caprylhydroxamic Acid is a white to tan crystalline solid,[2,3] with a molecular weight of 159.23 Da. The estimated dissociation constant (pKa) was 9.56,[6] and the estimated log K_{ow} ranged from 1.66 to 2.827.[2,3,6] Additional chemical properties are described in Table 1.

Method of Manufacture

A supplier reports that as a cosmetic ingredient, Caprylhydroxamic Acid is only synthesized via the transamidation of either methyl caprylate or ethyl caprylate with hydroxylamine to yield Caprylhydroxamic Acid; methanol or ethanol, respectively, is a byproduct of the process.[7] Depending on which caprylate ester is used, the reaction is conducted in either methanol or ethanol under refluxing conditions. Caprylhydroxamic Acid is then isolated and purified via recrystallization from ethyl acetate, followed by washing and drying of the crystalline Caprylhydroxamic Acid to obtain the ingredient at a purity of >99%. Figure 2 depicts an example of the synthesis route for the commercial production of Caprylhydroxamic Acid.

Impurities

Caprylhydroxamic Acid is reported to be >99% pure, and it does not contain any "non-hazardous" (> 1% by weight) or "hazardous" impurities.[2] According to NICNAS, formulators should consider monitoring products for formation of hydroxylamine if formulated at pH < 5 or pH > 8, or if formulation intermediates are substantially acidic or basic.

Use

Cosmetic

The safety of the cosmetic ingredient addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are

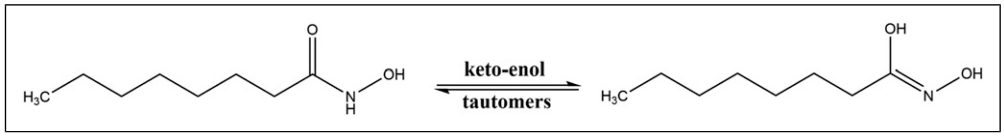

Figure 1. Caprylhydroxamic Acid.

Table 1. Chemical Properties.

Property	Value	Reference
Physical form	Crystalline solid	2,3
Color	White	3
	White to tan	2
Odor	Mild, characteristic	3
Molecular weight (Da)	159.23	6
Density (g/ml @ 25°C)	0.3413 (sample not compressed)	2,3
	0.4789 (sample tamped down)	
Vapor pressure (mmHg @ 25°C)	2.50 x 10^{-6} (estimated)	2
Melting point (°C)	≥78 to ≤81	3
	81	2
	79–81	21
Boiling point (°C)	343.32	21
Water solubility (g/l @ 23°C)	1.55	2,3
Log K_{ow} (@ 25°C)	1.66 (estimated)	2,3
	2.827 ± 0.191 (estimated)	6
Disassociation constants pKa (@ 25°C)	9.56 ± 0.20 (estimated)	6

submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2020 VCRP survey data, Caprylhydroxamic Acid is reported to be used in 269 formulations (Table 2).[8] The results of the concentration of use survey conducted by the Council in 2018 indicate that Caprylhydroxamic Acid is used at maximum leave-on and rinse-off concentrations of 0.25% in body and hand products and 0.3% in bath soaps and detergents, respectively.[9] Caprylhydroxamic Acid is used at up to 0.2% in products applied near the eye (in eyebrow pencils and in "other" eye makeup preparations), at up to 0.3% in formulations that come into contact with mucous membranes (in bath soaps and detergents), and at up to 0.15% in baby lotions, oils, and creams. Although there are two uses reported to the VCRP that could result in incidental ingestion (i.e., lipsticks), concentration of use data was not reported for this product type.

Additionally, Caprylhydroxamic Acid is used in cosmetic sprays and could possibly be inhaled. It is reported to be used at 0.075% in both aerosol and pump hair spray formulations. In practice, most droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles <10 μm compared with pump sprays.[10,11] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[12,13] Caprylhydroxamic Acid is also reported in the VCRP to be used in face powders (concentration not reported). Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[14-16]

Caprylhydroxamic Acid is not restricted from use in any way under the rules governing cosmetic products in the European Union.[17]

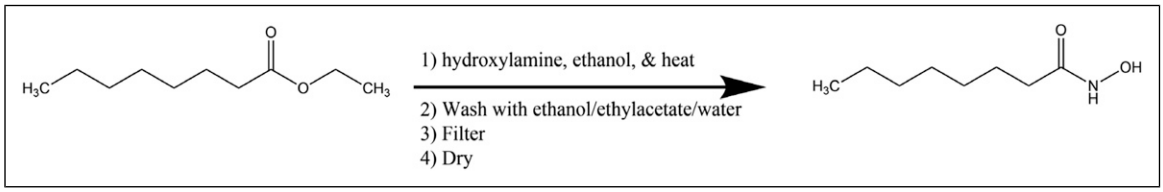

Figure 2. Example of a synthesis route for the commercial production of Caprylhydroxamic Acid, using ethyl caprylate.

Table 2. Frequency (2020) and Concentration (2018) of Use of Caprylhydroxamic Acid.

	# of Uses[8]	Max Conc of Use (%)[9]
Totals[a]	269	0.075–0.3
Duration of use		
Leave-on	*198*	0.075–0.25
Rinse-off	*71*	0.12–0.3
Diluted for (bath) use	*NR*	NR
Exposure type		
Eye area	18	0.11–0.2
Incidental ingestion	2	NR
Incidental inhalation-spray	1; 7[b]; 83[c]	0.075 (aerosol and pump) 0.075–0.23[b]
Incidental inhalation-powder	4; 83[c]; 4[d]	0.12[d]
Dermal contact	243	0.11–0.3
Deodorant (underarm)	1[b]	NR
Hair—non-coloring	23	0.075–0.23
Hair—coloring	NR	NR
Nail	NR	NR
Mucous membrane	6	0.13–0.3
Baby products	7	0.15

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

Risk Assessment. NICNAS estimated the total systemic exposure dose (SED) to Caprylhydroxamic Acid from cosmetic applications.[2] For the assessment, it was assumed that the user is a 60 kg body weight (bw) female, and that dermal absorption is 100% (worst-case scenario). Additionally, it was assumed that Caprylhydroxamic Acid is always used at 0.5% in cosmetic formulations, that it is not used in oral care products, and that there is daily exposure to 6 makeup products, 5 leave-on skin and hair care products (including body lotion), and 4 rinse-off skin and hair cleansing products containing this ingredient, for a total exposure of 15.1 g/d (234 mg/kg bw/d) to products containing Caprylhydroxamic Acid. Based on these parameters, the total SED to Caprylhydroxamic Acid through the use of cosmetics was calculated as 1.17 mg/kg bw/d.

The margin of exposure (MOE) was then calculated using the total SED of 1.17 mg/kg bw/d and a no-observable-adverse-effect-level (NOAEL) of 50 mg/kg bw/d (that was derived in a subchronic oral toxicity study in rats, described later in this report). Using these values, the MOE was calculated to be 43.

A use concentration of 0.3% was then considered in the calculations because an MOE greater than or equal to 100 was not achieved with a concentration of 0.5%. Using 0.3% as the maximum concentration of use, the MOE was calculated to be 71. NICNAS stated that even though this MOE is still below 100, given that the exposure estimate is based on the conservative assumption of 100% dermal absorption of the amount left on the skin following application and the simultaneous use of various products containing the maximum concentration of Caprylhydroxamic Acid, the risk to the public is not considered unreasonable if products contain a maximum of 0.3%.[2] Actual data support a maximum of 42% absorption, as described in the Dermal Penetration section, below.[18]

Non-Cosmetic

Use of Caprylhydroxamic Acid as a growth-promoting feed additive was reported.[19] (No details were provided.) Very little information specific to the non-cosmetic use of Caprylhydroxamic Acid was found in the published literature. However, hydroxamic acids in general have use in numerous applications, including biomedical use as therapeutic agents; agriculturally as insecticides, antimicrobials, and plant growth regulators; and industrially as antioxidants, corrosion inhibitors, for the extraction of toxic elements, as a means of flotation of minerals, and as redox switches for electronic devices.[5]

Toxicokinetics Studies

Dermal Penetration

In Vitro. The rate and extent of dermal absorption of Caprylhydroxamic Acid following topical application of three suspensions (oil-in-water, silicone-in-water, and clear lotion) were examined in vitro using split-thickness human abdominal skin.[18] The concentration of Caprylhydroxamic Acid in each of the three suspensions was *ca* 0.15% (w/w). Split-thickness human skin membranes were mounted into static diffusion cells. 1-[^{14}C]Caprylhydroxamic Acid (specific activity, 360 μCi/mg; 99.6% pure) was used to formulate the three test suspensions, and absorption was assessed by collecting samples of the receptor fluid (phosphate buffered saline containing polyoxyethylene 20-oleyl ether (PEG, *ca* 6%, w/v), sodium azide (*ca* 0.01%, w/v), streptomycin (*ca* 0.1 mg/ml), and penicillin (*ca* 100 units/ml)) prior to dosing and at 2, 4, 6, 8, and 12 h post-dose. At 24 h post-dose, the skin was washed with a concentrated commercial hand wash soap, rinsed with a dilute 2% (v/v) soap solution, and then dried. The process was repeated, the skin samples removed from the diffusion cells, and the stratum corneum was removed by tape stripping. Exposed and unexposed skin was separated, and exposed skin was further separated into the dermis and epidermis.

Dermal absorption of Caprylhydroxamic Acid was greatest with the oil-in-water suspension, followed by the silicone-in-water suspension, and then the clear lotion. With these preparations, the total absorbed dose (cumulative receptor fluid + receptor chamber was) was 41.89% (2971 ng equiv/cm^2), 31.75% (2747 ng equiv/cm^2), and 22.93% (1824 ng equiv/cm^2) of the applied dose, respectively. Dermal delivery (absorbed dose + epidermis + dermis + clingfilm) using these preparations was 51.45% (3649 ng equiv/cm^2), 43.84% (3793 ng equiv/cm^2), and 36.87% (2933 ng equiv/cm^2) of the applied dose, respectively. The total unabsorbed dose (total dislodgeable dose + stratum corneum + unexposed skin) was 43.99% (3120 ng equiv/cm^2), 52.67% (4558 ng equiv/cm^2), and 60.23% (4792 ng equiv/cm^2) of the applied dose for the oil-in-water, silicone-in-water, and clear lotion suspensions of Caprylhydroxamic Acid, respectively.

Absorption, Distribution, Metabolism, and Excretion

In Vitro. Caprylhydroxamic Acid was rapidly hydrolyzed to caprylic acid and hydroxylamine by rat liver homogenates.[20] (Only an English abstract was available for this Japanese paper; therefore, additional details are not presented).

Animal

Oral. Following oral administration of 1-[^{14}C]Caprylhydroxamic Acid (1.27 mg/kg) to rats, hydroxamic acid was not detected in any tissues (except in the GI tract) 2 h after administration.[20] "Considerable amounts" of radioactivity were found in the liver and the heart, but most was excreted as expired [^{14}C]CO_2; approximately 25% of the total radioactivity was excreted as [^{14}C]CO_2 at 2 h. Within 24 h, 6.9% and 0.6% were excreted in the urine and the feces, respectively. (Only an abstract was available; therefore, additional details are not presented).

Toxicological Studies

Acute Toxicity Studies

Oral. The oral LD_{50} of Caprylhydroxamic Acid is reported to be >8820 mg/kg in rats.[2] Another source reported that the oral LD_{50} in rats is >10,700 mg/kg.[21] (Further details were not available).

Subchronic Toxicity Studies

Oral. Groups of 10 male and 10 female Wistar rats were dosed for 13 wk with 0, 100, 500, or 2500 mg/kg bw/d 10% Caprylhydroxamic Acid in lactose (corresponding to 0, 10, 50, and 250 mg/kg bw Caprylhydroxamic Acid, respectively) by gavage.[2,22] The vehicle was 5% aqueous (aq.) gum arabic. There was no mortality attributed to the test article; however, 2 female animals of the mid-dose group died due to dosing errors. Signs of toxicity were observed only in the high dose group, and all the following observations were reported for this group. Clinical observations included "slowness in activity." There were significant decreases in alanine aminotransferase activity and glucose and potassium levels in males, and there was a significant increase in leukocyte count and significant decreases in erythrocyte, hematocrit, and hemoglobin values in males and females. Spleen weights (absolute and relative to bw) were increased in males and females, and adrenal weights were significantly decreased in males. Slight atrophy in the epithelial cells of the renal glomeruli and hemosiderin deposits in the spleen were reported upon microscopic examination. The NOAEL of the test article (10% Caprylhydroxamic Acid in lactose) was determined to be 500 mg/kg bw (corresponding to up to 50 mg/kg bw Caprylhydroxamic Acid).[2]

Developmental and Reproductive Toxicity Studies

Oral

Groups of 18 mated female Wistar rats were dosed with 0, 50, 250, and 500 mg/kg bw/d 10% Caprylhydroxamic Acid (corresponding to 0, 5, 25, and 50 mg/kg bw Caprylhydroxamic Acid, respectively) by gavage on days 9 through 14 of gestation.[2,23] The vehicle was 5% gum arabic solution. Twelve dams of the 0, 50, and 250 mg/kg bw/d groups, and all of the dams of the 500 mg/kg bw/d group, were killed on day 20 of gestation. The remaining dams were allowed to litter naturally. There was no mortality during the study, and there were no clinical signs of maternal toxicity. Body weight gains and feed consumption of the 250 and 500 mg/kg bw/d groups were "a little lower" than those of the controls; fetal weights in these groups were also lower than those in the control group, subsequently resulting in delayed ossification. Neonatal body weights from dams of the 250 mg/kg bw/d dose group were significantly lower at birth and at weaning. Decreased growth that was observed for fetuses and neonates of the higher dose groups was considered to be a result of the slight suppression of maternal body weight gains and feed consumption. Caprylhydroxamic Acid tested at 10% and at doses up to 500 mg/kg bw (corresponding to up to 50 mg/kg bw Caprylhydroxamic Acid) was not teratogenic under the conditions of this study.

Genotoxicity

In Vitro

In an Ames test using *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, and *Escherichia coli* WP2 *hcr trp*, with and without metabolic activation, Caprylhydroxamic Acid in dimethyl sulfoxide (DMSO; 0–2000 μg/plate) showed weak but clear dose-dependent mutagenic activity toward *E. coli* at concentrations up to 1000 μg/plate, but was not mutagenic to *S. typhimurium*.[19] In another Ames test (performed in accord with Organisation for Economic Co-operation (OECD) test guideline (TG) 471), Caprylhydroxamic Acid in DMSO, tested at concentrations of 16–5000 μg/plate using *S. typhimurium* TA1535, TA98, TA100, TA102, and TA97a with and without metabolic activation, was not mutagenic.[24] Solvent and positive controls gave expected results.

Caprylhydroxamic Acid was not genotoxic in a recombination–repair (rec) assay using *Bacillus subtilis* H17 Rec^+ and M45 Rec^-.[19] (No other details were provided.)

The genotoxic potential of Caprylhydroxamic Acid (98.09% pure) was also evaluated in an in vitro mammalian cell micronucleus test using human peripheral blood lymphocytes, with and without metabolic activation, in accord with OECD TG 487.[25] The dose levels tested were 25–450 μg/ml with and without activation for 4 h, and 7.5–50 μg/ml without activation for 24 h. DMSO served as the vehicle. No increase in micronucleated binucleated cells was observed following the 4-hour exposure, with or without activation. With 24 h of exposure (without activation), a statistically significant increase in the percentage of micronucleated binucleated cells was observed with 15 and 30 μg/ml Caprylhydroxamic Acid (0.4% and 0.7% increase, respectively) as compared to the vehicle control; however, these values were within the historical solvent control range (0.01–1.0%). Caprylhydroxamic Acid was not considered genotoxic in this study. Vehicle and positive controls gave appropriate results.

In Vivo

In vivo genotoxicity studies were not found in the published literature, and unpublished data were not submitted.

Carcinogenicity Studies

Carcinogenicity studies were not found in the published literature, and unpublished data were not submitted.

Dermal Irritation and Sensitization

Summaries of in silico structure–activity relationship (SAR) modeling, and in chemico and in vitro testing, were submitted to the Panel.[26] The in silico analysis used three modeling tools, namely, Toxtree, v2.6.13; OECD Toolbox, v4.0.0.26167; and Computer Assisted Evaluation of Industrial Chemical Substances According to Regulations (CAESAR) model. No skin sensitization reactivity domains were identified in the chemical structure using Toxtree and no alerts were identified using the OECD Toolbox, but Caprylhydroxamic Acid was predicted to be a sensitizer using CAESAR (but the prediction had low reliability); it was stated that "the weight of in silico evidence suggests that [Caprylhydroxamic Acid] is not likely to be a skin sensitizer in humans."

The in chemico/in vitro assays that were used included the direct peptide reactivity assay (DPRA; OECD TG 442C), an ARE-Nrf2 luciferase test method (KeratinoSens™; OECD TG 442D), and the human cell line activation test (h-CLAT; OECD TG 442E) and all gave positive results, indicating that Caprylhydroxamic Acid is a potential skin sensitizer. Potency is not indicated, but the researchers did state that the "DPRA results show low reactivity, which is consistent with a less potent sensitizer."

Detailed in vitro and human testing were also submitted to the Panel. The dermal irritation and sensitization studies summarized below are presented in Table 3.

Caprylhydroxamic Acid, tested as received using reconstructed human epidermis tissue containing keratinocytes in an EpiDerm™ skin irritation test (OECD TG 439), was classified as non-irritant.[21] Tissue viability was 102.6%.

In human repeated insult patch tests (HRIPTs), cosmetic formulations containing 0.105% Caprylhydroxamic Acid (54 subjects; 24-hour semi-occlusive patches),[27] 0.15% Caprylhydroxamic Acid (109 subjects, 48-hour occlusive patches),[28] and 0.195% Caprylhydroxamic Acid (52 subjects; 24-hour semi-occlusive patches),[29] an aqueous formulation containing 0.76% Caprylhydroxamic Acid (205 subjects; 24-hour semi-occlusive patches),[30] Caprylhydroxamic Acid at 1.9% in petrolatum (95 subjects; 24-hour occlusive patches),[31] and 100% Caprylhydroxamic Acid (52 subjects; 24-hour semi-occlusive patches),[32] were not considered irritants or sensitizers. In eight HRIPTs completed concurrently in a shared panel (104 subjects; 24-hour occlusive patches), in which 3 formulations containing 0.15% Caprylhydroxamic Acid were tested neat,[33-35] and 5 formulations containing 5–15% Caprylhydroxamic Acid were tested as dilutions in distilled water (with a resulting test concentration of 0.3% Caprylhydroxamic Acid),[36-40] reports of erythema and sometimes edema were noted in several subjects throughout the studies; in particular, one subject exhibited a reaction at challenge to every test material. However, it was the opinion of the researchers that neither the number nor peak level of the responses were inconsistent with similar diluted formulations evaluated under repetitive, occlusive patch conditions; therefore, it was concluded the test material "indicated no clinically significant potential for dermal irritation or allergic contact sensitization." (A summary of the subjects that responded in each of the 8 concurrent tests, and their level of response, is provided in Table 4.) Additionally, in an HRIPT of Caprylhydroxamic Acid, 3.8% in petrolatum (104 subjects; 24-hour occlusive patches), two subjects had scores of 1 for erythema and edema on challenge day 3 ("suggesting induction of allergic contact sensitization") and 1 subject had scores of 2 for erythema and edema on challenge day 3 ("indicative of allergenic contact sensitization induction"); several subjects exhibited barely perceptible erythema, some also erythema and edema (scores of 1), during induction.[41]

Quantitative Risk Assessment

A quantitative risk assessment (QRA) for allergic contact dermatitis for Caprylhydroxamic Acid as used in cosmetic products was conducted; aggregate exposure was not considered in this assessment.[26] All but three of the HRIPTs summarized above were evaluated in determining a weight-of-evidence no-expected-sensitization-induction-level (WoE NESIL) for Caprylhydroxamic Acid; for two studies,[28,32] it was not possible to calculate the dose per unit area exposure, and the third study[30] was not available at the time the WoE NESIL was determined. Accordingly, in examining the outcomes of all of the applicable HRIPTs, the highest concentration tested in which no positive responses were observed (no-observable-effect-level; NOEL) was 1055.6 μg/cm^2; the lowest-observable-effect-level (LOEL) was 2111.1 μg/cm^2. Therefore, a WoE NESIL of 1056 μg/cm^2 was chosen.

To determine a margin of safety (MOS) for skin sensitization for each product category, an acceptable exposure level (AEL) for daily consumer exposure was determined based on the WoE NESIL, to which product category–based sensitization assessment factors (SAFs) were applied. For this assessment, QRA 2.0 SAFs were used.

$$\text{AEL} = \text{WoE NESIL}/\text{total SAF}$$

Consumer exposure levels (CELs) for each product category were determined for the reported maximum concentrations of use for Caprylhydroxamic Acid, as provided in the Council's concentration of use survey, along with published habits and practices data (Table 5). The MOS was then determined by evaluating the AEL/CEL ratio; ratios ≥1 provide an acceptable MOS. Using a NESIL of 1056 μg/cm^2 for Caprylhydroxamic Acid, MOS values ranged from 1.0 (for baby lotions, oils, and creams, not powder) to 269.2 (for bath soaps and detergents; Table 6). Based on the results of this QRA 2.0, the study authors stated that "formulation of these products at their maximal concentration of [Caprylhydroxamic Acid] would present a negligible risk of inducing skin sensitization."

Table 3. Dermal Irritation and Sensitization Studies.[a]

Test Article	Concentration/Dose	Test Population/System	Procedure	Results	Reference
In Vitro					
Irritation					
Caprylhydroxamic Acid, 100% pure	Tested as supplied	Reconstructed human epidermis tissue containing keratinocytes	EpiDerm™ skin irritation test, in accord with OECD TG 439; tissue viability was determined with the MTT assay	Classified as non-irritant; tissue viability was 102.6%	[21]
Human					
Irritation and sensitization					
Eyeliner formulation containing 0.105% Caprylhydroxamic Acid	Applied neat; 0.2 mL Induction and challenge dose[26]: 32.3 μg/cm^2	54 subjects	HRIPT Induction: 24-hour semi-occlusive patch (1 in^2) applied to the upper back 3 x/wk for 3 wk, for a total of 9 applications; test sites were evaluated 24 or 48 h after patch removal Challenge: After a 2-week non-treatment period, a 24-hour patch was applied to a previously untreated test site on the back; test sites were evaluated at 24 and 72 h after application	Not considered an irritant or sensitizer - One subject exhibited barely perceptible erythema after the 1st induction patch, and another subject exhibited barely perceptible erythema after induction patch 4; no other responses were reported	[27]
Facial cream containing 0.15% Caprylhydroxamic Acid	Applied neat; 0.02 mL Dose/unit area could not be calculated[26]	109 subjects	HRIPT Induction: 48-hour occlusive patch applied 3x/wk for 3 wk Challenge: After a 2-week non-treatment period, patches were applied to inducted and previously untreated test sites; test sites were evaluated at 30 min, 24 h, and 48 h after patch removal	Not a sensitizer −1 subject had "low level reaction" (score of 0 or 1) during challenge; no reactions during induction	[28]
Brow thickening powder containing 0.195% Caprylhydroxamic Acid	Applied neat; 200 mg product (0.39 mg Caprylhydroxamic Acid) Induction and challenge dose[26]: 60.0 μg/cm^2	52 subjects	HRIPT Induction: 24-hour semi-occlusive patch (application area 6.45 cm^2) moistened to ensure adherence of the test article applied to the back 3 x/wk for 3 wk, for a total of 9 applications; test sites were evaluated 24 or 48 h after patch removal Challenge: After a 2-week non-treatment period, a 24-hour patch was applied to previously untreated test site on the back; test sites were evaluated upon patch removal and 48 h later	"Did not show potential to induce dermal irritation or allergic contact sensitization" (Individual results were not provided)	[29]
Lotion containing 0.15% Caprylhydroxamic Acid (also, 72.35% water; 5% caprylic/ capric triglyceride; 5% isopropyl myristate; 4.5% arachidyl alcohol (and) behenyl alcohol (and) arachidyl glucoside; 4% petrolatum; 3% cetyl alcohol; 3% stearyl alcohol; 3% glycerin)	Applied neat; 0.2 mL Induction and challenge dose[26]: 83.3 μg/cm^2	114 subjects were selected; 104 subjects completed the study (subjects discontinued for personal reasons, and not due to the test material) (8 test articles were evaluated concurrently with a shared panel)	HRIPT Induction: 24-hour occlusive patch (¾ in^2) applied to the upper back 3 x/wk for 3 wk, for a total of 9 applications; test sites were evaluated 24 or 48 h after patch removal Challenge: After a 2-week non-treatment period, a 24-hour patch was applied to a previously untreated test site on the back; challenge sites were evaluated on day 1 and day 3 post-application in most subjects; however, some subjects (#20–51) were evaluated on day 1 and day 2	Subject #10 exhibited barely perceptible erythema (induction patches 2 and 3); mild erythema with mild edema (induction patch 4); moderate erythema with moderate edema (induction patch 5), resulting in the discontinuation of subsequent patch applications; it was the opinion of the researchers that this pattern of skin reactivity was indicative of a pre-existing hypersensitivity to 1 or more ingredients in the formulation	[33]

(continued)

Table 3. (continued)

Test Article	Concentration/Dose	Test Population/System	Procedure	Results	Reference
Water-in-oil (W/O) thick balm containing 0.15% Caprylhydroxamic Acid (also, 66.35% water; 10% sunflower seed oil; 10% isopropyl palmitate; 5% petrolatum; 3.5% octyldodecanol (and) octyldodecyl xyloside (and) PEG-30 dipolyhydroxystearate; 3% glycerin; 2% beeswax) [concentrations stated as provided]	Applied neat; 0.2 mL	(See above)	HRIPT—same protocol as above	Subject #10 exhibited mild erythema with mild edema (induction patch 4) and moderate erythema with moderate edema (induction patch 5), resulting in the discontinuation of subsequent patch applications; same comment by the researchers as given above Subject #42 had reactions during induction and at challenge: Barely perceptible erythema (induction patches 8 and 9); barely perceptible erythema (day 1 post-challenge); mild erythema and edema (day 2 post-challenge) Several subjects had reactions during induction, but not at challenge: - Subject #12: Mild erythema with mild edema (patch 8); barely perceptible erythema (patch 9) - Subject #73: Barely perceptible erythema (patch 6) - Subject #97: Barely perceptible erythema (patches 4 and 5) - Subject #105: Barely perceptible erythema (patch 2) The researchers concluded "no clinically significant potential for dermal irritation or allergic contact sensitization," adding that "neither the number of responses or the peak level of these responses were inconsistent with similar diluted formulations evaluated under repetitive, occlusive patch conditions" Induction and challenge dose[26]: 83.3 $\mu g/cm^2$ Subject #42 had reactions during induction and at challenge: Barely perceptible erythema (induction patches 5–9; mild erythema with mild edema (day 2 post-challenge) Two subjects exhibited barely perceptible erythema reactions during induction, but not at challenge: - Subject #12: Patches 8 and 9 - Subject #97: Patches 4 and 5 The researcher concluded the test article "did not indicate [d] a clinically significant potential for dermal irritation or allergic contact sensitization," citing the same reasoning as above	[34]

(continued)

Table 3. (continued)

Test Article	Concentration/Dose	Test Population/System	Procedure	Results	Reference
"Wipe juice" containing 0.15% Caprylhydroxamic Acid (also, 94.85% water; 3% propanediol; 2% polysorbate 20)	Applied neat; 0.2 mL Induction and challenge dose[26]: 83.3 μg/cm^2	(See above)	HRIPT—same protocol as above Subject #42 had reactions during induction and at challenge: Barely perceptible erythema (patches 6 and 8); mild erythema with mild edema (day 2 post-challenge) Subject #97 exhibited barely perceptible erythema following induction patches 4 and 5; no reactions were seen at challenge The researchers concluded the test material "indicated no clinically significant potential for dermal irritation or allergic contact sensitization," citing the same reasoning as above		[35]
Formulation containing 5% Caprylhydroxamic Acid (and 30% hexanediol; 65% propanediol)	Tested as a 6% dilution with distilled water (resultant test concentration—0.3% Caprylhydroxamic Acid); 0.2 mL Induction and challenge dose[26]: 166.6 μg/cm^2	(See above)	HRIPT—same protocol as above Subject #42 had reactions during induction and at challenge: Barely perceptible erythema (induction patches 4 and 8); mild erythema (patch 9); barely perceptible erythema (day 1 post-challenge); mild erythema with mild edema (day 2 post-challenge) Several subjects had reactions during induction, but not at challenge: Subject #12: Moderate erythema with mild edema (patch 7); patching was moved to an adjacent site Subject #28: Barely perceptible erythema (patch 5) Subject #52: Barely perceptible erythema (patch 3) Subject #73: Mild erythema (patch 6); barely perceptible erythema (patches 7–9) Subject #97: Barely perceptible erythema (patches 4 and 5) Subject #105: Barely perceptible erythema (patches 2 and 3); this subject completed induction, but was not challenged The researchers concluded the test material "indicated no clinically significant potential for dermal irritation or allergic contact sensitization," citing the same statement as above		[36]

(continued)

Table 3. (continued)

Test Article	Concentration/Dose	Test Population/System	Procedure	Results	Reference
Formulation containing 7.5% Caprylhydroxamic Acid (and 92.5% propanediol)	Tested as a 4% dilution with distilled water (resultant test concentration—0.3% Caprylhydroxamic Acid); 0.2 mL Induction and challenge dose[26]: 166.6 μg/cm^2	(See above)	HRIPT—same protocol as above Subject #42 had reactions during induction and at challenge: Barely perceptible erythema (induction patches 4–8); mild erythema with mild edema (day 2 post-challenge) Several subjects had reactions during induction, but not at challenge: Subject #12: Barely perceptible erythema (patch 8) Subject #52: Barely perceptible erythema (patch 3) Subject #73: Barely perceptible erythema (patches 6–8) Subject #97: Barely perceptible erythema (patches 3 and 6); mild erythema with mild edema (patches 4 and 5) The researchers concluded the test material "indicated no clinically significant potential for dermal irritation or allergic contact sensitization," citing the same statement as above Several subjects had reactions during induction, but not at challenge: Subject #12: Barely perceptible erythema (patches 4 and 5) Subject #28: Barely perceptible erythema (patch 5) Subject #44: Barely perceptible erythema (patch 7); discontinued study at this point Subject #52: Barely perceptible erythema (patches 3 and 4) Subject #73: Barely perceptible erythema (patches 5–7) Subject #97: Mild erythema with mild edema (patches 3–5); Barely perceptible erythema (patches 6–8) The researchers concluded the test material "indicated no clinically significant potential for dermal irritation or allergic contact sensitization," citing the same statement as above		[37]

(continued)

Table 3. (continued)

Test Article	Concentration/Dose	Test Population/System	Procedure	Results	Reference
Formulation containing 10% Caprylhydroxamic Acid (and 75% glyceryl caprylate and 15% glycerin) Induction and challenge dose[26]: 166.6 μg/cm^2	Tested as a 3% dilution with distilled water (resultant test concentration—0.3% Caprylhydroxamic Acid); 0.2 mL	(See above)	HRIPT—same protocol as above	Subject #42 had reactions during induction and at challenge: Barely perceptible erythema (induction patches 5, 6, and 8); mild erythema (patch 9); barely perceptible erythema (day 1 post-challenge); mild erythema with mild edema (day 2 post-challenge)	[38]
Formulation containing 15% Caprylhydroxamic Acid (and 70% phenoxyethanol; 7.5% methylpropanediol; 7.5% water)	Tested as a 2% dilution with distilled water (resultant test concentration—0.3% Caprylhydroxamic Acid); 0.2 mL Induction and challenge dose[26]: 166.6 μg/cm^2	(See above)	HRIPT—same protocol as above	Subject #42 had reactions during induction and at challenge: Barely perceptible erythema (induction patches 5, 6, and 8); mild erythema (patch 9); barely perceptible erythema (day 1 post-challenge); mild erythema with mild edema (day 2 post-challenge) Several subjects had reactions during induction, but not at challenge: Subject #12: Moderate erythema with mild edema (patch 7); patching was moved to an adjacent site Subject #28: Barely perceptible erythema (patch 5) Subject #52: Barely perceptible erythema (patch 3) Subject #73: Barely perceptible erythema (patches 6 and 7) Subject #97: Mild erythema with mild edema (patches 3–5); Barely perceptible erythema (patch 6) The researchers concluded the test material "indicated no clinically significant potential for dermal irritation or allergic contact sensitization," citing the same statement as above	[39]
Formulation containing 15% Caprylhydroxamic Acid (and 71% caprylyl glycol and 14% glycerin)	Tested as a 2% dilution with distilled water (resultant test concentration—0.3% Caprylhydroxamic Acid); 0.2 mL Induction and challenge dose[26]: 166.6 μg/cm^2	(See above)	HRIPT—same protocol as above	Subject #42 had reactions during induction and at challenge: Barely perceptible erythema following induction patches 5–8; barely perceptible erythema day 2 post-challenge Several subjects had reactions during induction, but not at challenge: Subject #12: Moderate erythema with mild edema (patch 7); patching was moved to an adjacent site Subject #73: Barely perceptible erythema (patches 6–8) Subject #97: Mild erythema with mild edema (patches 3–5); Barely perceptible erythema (patches 6–8) The researchers concluded the test material "indicated no clinically significant potential for dermal irritation or allergic contact sensitization," citing the same statement as above	[40]

(continued)

Table 3. (continued)

Test Article	Concentration/Dose	Test Population/System	Procedure	Results	Reference
0.76% Caprylhydroxamic Acid, in an aq. formulation	Applied neat; 0.2 mL Dose/unit area: 380 μg/cm^2	Phase A: 115 subjects Phase B: 116 subjects 205 subjects completed the study (no subjects dropped due to reactions to the test material)	HRIPT completed in 2 phases Induction: 24-hour semi-occlusive patch (¾ in^2) applied to the upper back 3 x/wk for 3 wk, for a total of 9 applications Challenge: After a 2-week non-treatment period, a 24-hour patch was applied to a previously untreated test site on the back; challenge sites were evaluated 24, 48, 72, and 96 h after patching	The researchers stated that no significant dermal reactions were exhibited during induction or challenge (individual results were not provided)	[30]
Caprylhydroxamic Acid powder (98+%)	98.1 g warmed petrolatum was added to 1.9 g of test material; effective test concentration—1.9% Caprylhydroxamic Acid; 0.2 g Induction and challenge dose[26]: 1055.6 μg/cm^2	95 subjects Fitzpatrick skin types: I—23 subjects II—30 subjects III—25 subjects IV—17 subjects	HRIPT Induction: 24-hour occlusive patch (test material was placed on the 3.6 cm^2 absorbent pad portion) applied to the upper back 3 x/wk for 3 wk, for a total of 9 applications Challenge: After a non-treatment period of at least 10 d, a 24-hour patch was applied to a previously untreated test site on the back; challenge sites were evaluated day 1 and day 3 post-application	Not an irritant or sensitizer No reactions were reported during induction or challenge	[31]

(continued)

Table 3. (continued)

Test Article	Concentration/Dose	Test Population/System	Procedure	Results	Reference
Caprylhydroxamic Acid powder (98+%)	96.2 g warmed petrolatum was added to 3.8 g test material; effective test concentration—3.8% Caprylhydroxamic Acid; 0.2 g Induction and challenge dose[26]: 2111.1 μg/cm^2	104 subjects Fitzpatrick skin types: I—4 subjects II—13 subjects III—53 subjects IV—33 subjects V—1 subject	HRIPT Induction: 24-hour occlusive patch (test material was placed on the 3.6 cm^2 absorbent pad portion) applied to the upper back 3 x/wk for 3 wk, for a total of 9 applications Challenge: After a non-treatment period of at least 10 d, a 24-hour patch was applied to a previously untreated test site on the back; challenge sites were evaluated day 1 and day 3 post-application	–1 subject had scores of 1 for erythema and edema on challenge day 3 ("suggesting induction of allergic contact sensitization"); also exhibited barely perceptible erythema with induction patches 6–8, and had scores of 1 for erythema and edema with induction patch 9 –1 subject had scores of 1 for erythema and edema on challenge day 3 ("suggesting induction of allergic contact sensitization"); also exhibited barely perceptible erythema with induction patches 7 and 9 –1 subject had scores of 2 for erythema and edema on challenge day 3 ("indicative of allergenic contact sensitization induction"); also exhibited barely perceptible erythema with induction patches 7 and 8, and scores of 1 for erythema and edema with induction patch 9 –2 subjects had barely perceptible erythema on challenge day 3; one of these subjects also exhibited barely perceptible erythema with induction patches 6–9 - During induction: 1 subject exhibited barely perceptible erythema with patches 5, 8, and 9 and erythema and edema (score = 1) with patches 6 and 7; 2 subjects each exhibited one incident of barely perceptible erythema and one of erythema and edema (score of 1); 2 subjects exhibited 3 incidents of barely perceptible erythema; 1 subject exhibited 2 incidents of barely perceptive erythema; 5 subjects had one incident of barely perceptible erythema	[41]
Caprylhydroxamic Acid, 100%	Amount applied not stated	52 subjects	HRIPT Induction: 24-hour semi-occlusive patch (1 in^2) applied to the upper back 3 x/wk for 3 wk, for a total of 9 applications; test sites were evaluated 24 or 48 h after patch removal Challenge: After a 2-week non-treatment period, a 24-hour patch was applied to a previously untreated test site on the back; test sites were evaluated upon patch removal and at 48 and 72 h	Not an irritant or sensitizer No reactions were reported during induction or at challenge	[32]

[a]Dose/unit area and induction and challenge doses portrayed in μg/cm^2 were not expressed explicitly in the submitted studies, but were calculated separately.[26]
Abbreviations: aq.: aqueous; HRIPT: human repeated insult patch test; MTT: 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide; OECD: Organisation for Economic Co-operation; TG: test guideline.

Table 4. Summary of Reactions Observed by One Panel of HRIPT Subjects to Various Test Formulations Containing Caprylhydroxamic Acid.

Test Formulation	Other Ingredients	Subject #10	Subject #12	Subject #28	Subject #42	Subject #44	Subject #52	Subject #73	Subject #97	Subject #105
Formulations tested neat—contained 0.15% Caprylhydroxamic Acid										
Lotion containing 0.15% Caprylhydroxamic Acid[33]	72.35% water; 5% caprylic/capric triglyceride; 5% isopropyl myristate; 4.5% arachidyl alcohol (and) behenyl alcohol (and) arachidyl glucoside; 4% petrolatum; 3% cetyl alcohol; 3% stearyl alcohol; 3% glycerin	0.5 (P2-3) 1^{EI} (P4) 2^{E2} (P5) Disc (P6+)		1^{EI} (P8) 0.5 (P9)	0.5 (D1) 1^{EI} (D2)			0.5 (P6)	0.5 (P4-5)	0.5 (P2)
Water-in-oil (W/O) thick balm containing 0.15% Caprylhydroxamic Acid[34]	66.35% water 10% sunflower seed oil 10% isopropyl palmitate 5% petrolatum 3.5% octyldodecanol (and) octyldodecyl xyloside (and) PEG-30 dipolyhydroxystearate 3% glycerin 2% beeswax	1^{EI} (P4) 2^{E2} (P5) Disc (P6+)	0.5 (P8-9)		0.5 (P5-9) 1^{EI} (D2)				0.5 (P4-5)	
"Wipe juice" containing 0.15% Caprylhydroxamic Acid[35]	94.85% water; 3% propanediol; 2% polysorbate 20				0.5 (P 6, 8) 1^{EI} (D2)				0.5 (P4-5)	
Formulations tested as dilutions with distilled water; resulting test concentration—0.3% Caprylhydroxamic Acid										
Formulation containing 5% Caprylhydroxamic Acid; tested as a 6% dilution[36]	30% hexanediol; 65% propanediol		2^{EI} (P7) (patching moved to adjacent site)	0.5 (P5)	0.5 (P4, 8) 1 (P9) 0.5 (D1) 1^{EI} (D2)		0.5 (P)	1 (P6) 0.5 (P7-9)	0.5 (P4-5)	0.5 (P2-3)
Formulation containing 7.5% Caprylhydroxamic Acid; tested as a 4% dilution[37]	92.5% propanediol		0.5 (P 8)		0.5 (P 4-8) 1^{EI} (D2)		0.5 (P3)	0.5 (P6-8)	0.5 (P3) 1^{EI} (P4-5) 0.5 (P6)	
Formulation containing 10% Caprylhydroxamic Acid (tested as a 3% dilution)[38]	75% glyceryl caprylate; 15% glycerin		0.5 (P4-5)	0.5 (P5)	0.5 (P5-6, 8) 1 (P9) 0.5 (D1) 1^{EI} (D2)	0.5 (P7) did not continue study	0.5 (P3-4)	0.5 (P5-7)	1^{EI} (P3-5) 0.5 (P6-8)	
Formulation containing 15% Caprylhydroxamic Acid (tested as a 2% dilution)[39]	70% phenoxyethanol; 7.5% methylpropanediol; 7.5% water		2^{EI} (P 7) (patching moved to adjacent site)	0.5 (P5)	0.5 (P5-6, 8) 1 (P9) 0.5 (D1) 1^{EI} (D2)		0.5 (P3)	0.5 (P6-7)	1^{EI} (P3-5) 0.5 (P6)	
Formulation containing 15% Caprylhydroxamic Acid; tested as a 2% dilution[40]	71% caprylyl glycol; 14% glycerin		2^{EI} (P 7) (patching moved to adjacent site)		0.5 (P5-8) 0.5 (D2)			0.5 (P6-8)	1^{EI} (P3-5) 0.5 (P6-8)	

Abbreviations: D: day post-challenge; disc: discontinued patching for this formulation; E: edema; HRIPT: human repeated insult patch test; P: induction patch.
Key to reaction scores: 0.5 = barely perceptible; 1 = mild; 2 = moderate.

Table 5. CEL by Product Category Based Upon Reported Maximum Concentrations of Use for Caprylhydroxamic Acid.[26]

Product Category	Classification	Max Conc of Use (%)	Product Exposure (μg/cm^2)	CEL (μg/cm^2)
Baby lotions, oils, and creams (not powder)	Leave-on	0.15	2421	3.63
Eyebrow pencils	Leave-on	0.2	647	1.29
Eyeliners	Leave-on	0.11	1563	1.72
Eye shadows	Leave-on	0.19	2170	4.12
Other eye makeup preparations	Leave-on	0.2	2170	4.34
Hair conditioners	Rinse-off	0.15	200	0.3
Hair conditioners	Leave-on	0.15	2000	3.0
Hair sprays; aerosol	Leave-on	0.075	1390	1.04
Hair sprays; pump spray	Leave-on	0.075	2200	1.65
Shampoos (non-coloring)	Rinse-off	0.2	170	0.34
Tonics, dressings, and other hair grooming aids	Leave-on	0.075–0.23	990	0.74–2.28
Other hair preparations (non-coloring)	Leave-on	0.15	990	1.49
Bath soaps and detergents	Rinse-off	0.13–0.3	10	0.013–0.03
Body wash, shower gel	Rinse-off	0.13–0.3	15	0.02–0.045
Facial skin cleansing	Rinse-off	0.12–0.15	150	0.18–0.225
Facial skin cleansing	Wipe-off	0.12–0.15	900	1.08–1.35
Face and neck products (not spray)	Leave-on	0.12	2700 (face cream)	3.24
Body creams and lotions	Leave-on	0.12–0.25	1120	1.34–2.80
Hand creams and lotions	Leave-on	0.12–0.25	4200	5.04–10.5
Paste masks and mud packs	Rinse-off	0.15	4200	6.3

Abbreviation: CEL: consumer exposure level.

Table 6. MOS for Skin Sensitization by Product Category Based on Reported Maximum Concentrations of Use of Caprylhydroxamic Acid.[26]

Product Category	NESIL (μg/cm^2)	QRA2 SAF	AEL (μg/cm^2)	CEL (μg/cm^2)	MOS (AEL/CEL)
Baby lotions, oils, and creams (not powder)	1056	300	3.5	3.63	1.0
Eyebrow pencils	1056	100	10.6	1.29	8.2
Eyeliners	1056	100	10.6	1.72	6.2
Eye shadows	1056	100	10.6	4.12	2.6
Other eye makeup preparations	1056	100	10.6	4.34	2.4
Hair conditioners; rinse-off	1056	100	10.6	0.3	35.3
Hair conditioners; leave-on	1056	100	10.6	3.0	3.5
Hair sprays; aerosol	1056	30	35.2	1.04	33.8
Hair sprays; pump sprays	1056	30	35.2	1.65	21.3
Shampoos (non-coloring)	1056	300	3.5	0.34	10.3
Tonics, dressings, and other hair grooming aids	1056	100	10.6	.074–2.28	14.3–4.6
Other hair preparations (non-coloring)	1056	100	10.6	1.49	7.1
Bath soaps and detergents	1056	300	3.5	0.013–0.03	269.2–116.7
Body wash, shower gel	1056	300	3.5	0.02–0.045	175.0–77.8
Facial skin cleansing preparations; rinse-off	1056	100	10.6	0.18–0.225	58.9–47.1
Facial skin cleansing preparations; wipe-off	1056	100	10.6	1.08–1.35	9.8–7.9
Face and neck products (not spray)	1056	100	10.6	3.24	3.3
Body creams and lotions	1056	300	3.5	1.34–2.80	2.6–1.3
Hand creams and lotions	1056	100	10.6	5.04–10.5	2.1–1.0
Paste masks and mud packs	1056	100	10.6	6.3	1.7

Abbreviations: AEL: acceptable exposure level; CEL: consumer exposure level; MOS: margin of safety; NESIL: no-expected-sensitization-induction-level; QRA: quantitative risk assessment; SAF: sensitization assessment factor.

Table 7. Patch Test Results in Patients With Compromised Skin That Had Suspected Contact Allergy to a New Moisturizer Formulation.[44]

New Moisturizer Formulation								
			Cream		Oily cream			Lotion
+++			6		7			4
++			13		11			10
+			13		15			12
?+			2		1			2
Negative			0		2			1
Irritant reaction			0		0			0
No. tested			***34***		***36***			***29***
Caprylhydroxamic Acid (or its potassium salt)								
	0.001%	0.0032%	0.01%	0.032%	0.10%	0.32%	1.0%	3.2%
+++	0	0	0	0	1	4	10	9
++	0	0	0	3	6	15	21	6
+	0	0	1	14	18	17	7	0
?+	0	1	3	6	10	2	1	1
Negative	7	6	8	16	4	1	0	0
Irritant reaction	0	0	0	0	0	0	0	0
No. tested	***7***	***7***	***12***	***39***	***39***	***39***	***39***	***16***
Preservative mixture								
		0.05%		0.15%		0.5%		1.5%
+++		0		0		2		5
++		2		3		6		10
+		7		8		10		16
?+		0		8		10		4
Negative		30		18		10		3
Irritant reaction		0		2		1		1
No. tested		***39***		***39***		***39***		***39***

Ocular Irritation Studies

In Vitro

The ocular irritation potential of a 20% solution of Caprylhydroxamic Acid was evaluated in a bovine corneal opacity and permeability (BCOP) test performed in accord with OECD TG 437.[42] A 4-hour exposure period was followed by a 3-hour incubation period. The vehicle (minimal essential media) served as the negative control; a positive control was not used. The corrected mean opacity score was 10.5, and the corrected mean optical density (permeability) score was 0.108. The resulting in vitro irritancy score of 12.12 corresponds to a classification of mild irritant; a 20% solution of Caprylhydroxamic Acid was not considered a corrosive or severe ocular irritant under the conditions of the test.

A MatTek EpiOcular™ methyl thiazole tetrazolium (MTT) viability assay was also performed to evaluate the ocular irritation potential of Caprylhydroxamic Acid.[43] The chemical was tested neat (100 mg), the test samples were treated in duplicate, and the exposure periods were 16, 64, and 256 min. Appropriate negative and positive controls were used. The ET_{50} (i.e., the time at which the EpiOcular™ tissue viability was reduced 50% compared to control tissues) was 130.8 min, and the ocular irritancy classification for undiluted Caprylhydroxamic Acid was "non-irritating, minimal."

Clinical Studies

Provocative Testing

Patch testing was performed according to the European Society of Contact Dermatitis test guidelines in 39 patients with compromised skin that were suspected of developing contact allergy.[44] Symptoms, which appeared as acute, itchy, often sharply demarcated erythematous eczema, were thought to be due to the use of a moisturizer in Finland that had recently been reformulated; in early 2014, the moisturizer was reformulated to remove parabens. The new moisturizer formulation contained 0.75% of a mixture that consisted of 65–75% phenoxyethanol, 10–20% Caprylhydroxamic Acid, and 5–10% methylpropanediol, resulting in actual concentrations of 0.49–0.56% phenoxyethanol, 0.075–0.15% Caprylhydroxamic Acid, and 0.04–0.075% methylpropanediol in the new formulation.

The test group was patch-tested with the old paraben-containing formulation (as a cream and oily cream); the new formulation containing the preservative mixture (as a cream, oily cream, and lotion); another test formulation that contained phenoxyethanol only; a preservative-free oily cream; 0.05–1.5% of the preservative mixture itself (in petrolatum (pet.)); and 0.001–3.2% Caprylhydroxamic Acid (or its potassium salt; in pet.). Occlusive patches were applied for 2 d, and the test sites were scored upon patch removal and on days 4 and 5. A control group of 20 eczema patients, who had not used the new moisturizer formulation that contained the preservative mixture, was patched-tested with the preservative mixture and with Caprylhydroxamic Acid. A second control group of 13 subjects, all with uncompromised skin, was patch-tested with all the test materials.

Patch test results for the test group are presented in Table 7. In the test group of patients with compromised skin that developed contact allergy, positive reactions were seen with the new moisturizer formulation (that contained the preservative mixture), Caprylhydroxamic Acid, and the preservative mixture itself; however, reactions were not reported with the old moisturizer formulation (which was preserved with parabens), the formulation with phenoxyethanol only, or the preservative-free cream. For Caprylhydroxamic Acid, +++ reactions were reported with test concentrations ≥0.1%, ++ reactions with concentrations ≥0.032%, and + reactions with concentrations ≥0.01%. Patch tests in "all control subjects" gave negative results. The study authors did not elaborate on the lack of reaction by the 33 control subjects to the preservative mixture or Caprylhydroxamic Acid.

As a follow-up, 1% Caprylhydroxamic Acid (pet.) was added to the 2017 epicutaneous preservative series at Helsinki University Central Hospital in an effort to determine if there were any new cases of contact allergy to Caprylhydroxamic Acid in patients with no previous use of the moisturizer series described above; it is not clear if the researchers were referring only to use of the "new" formulation that contained Caprylhydroxamic Acid.[45] In total, 16 patients with a positive patch test reaction were identified, three with a ++ reaction and the remainder with a + reaction. Twelve of the 16 patients that presented with atopic dermatitis, hand eczema, or psoriasis had previously used the moisturizer. Of the remaining 4 patients (2 of which had a ++ reaction), 3 presented with eczema of the face or eyelids, and 1 was a hairdresser with hand eczema. The use of products containing Caprylhydroxamic Acid could not be identified, but makeup or hair products were suspected. The researchers stated that simultaneous contact allergy to other allergens may facilitate the sensitization, and also that further follow-up is needed to clarify the significance of Caprylhydroxamic Acid as a contact allergen.

Case Reports

In Finland, two case reports of contact allergy were attributed to use of a moisturizer that contained Caprylhydroxamic Acid.[46] Although the moisturizer had been reformulated to no longer include a preservative that contained Caprylhydroxamic Acid (it was only included in formulations produced from 2014 to 2016), the patients had used products that had been obtained prior to reformulation. Patch tests were not performed, but the contact allergy was attributed to the Caprylhydroxamic Acid–containing moisturizer based on medical history, use of the old formulation, outbreaks, and clinical presentation.

Summary

Caprylhydroxamic Acid is reported to function in cosmetics as a chelating agent. Hydroxamic acids, such as

Caprylhydroxamic Acid, may exist in both keto and enol tautomeric forms; the keto form is likely to predominate in acidic formulation, while the enol may dominate under alkaline conditions. Hydroxamic acids are capable of the inhibition of a variety of enzymes, including ureases, peroxidases, and matrix metalloproteinases. At very high or low pH, Caprylhydroxamic Acid may be hydrolyzed to caprylic acid and hydroxylamine.

Caprylhydroxamic Acid is most frequently synthesized via the transamidation of either methyl or ethyl caprylate with hydroxylamine to yield Caprylhydroxamic Acid. Methanol or ethanol, respectively, is a byproduct of the process. Caprylhydroxamic Acid is reported to be >99% pure.

According to 2020 US FDA VCRP data and Council survey results, Caprylhydroxamic Acid is reported to be used in 269 formulations at maximum leave-on and rinse-off concentrations of 0.25% in body and hand products and 0.3% in bath soaps and detergents, respectively. It is used in products applied near the eye at up to 0.2%, in lipsticks (concentration of use data not reported), in formulations that come into contact with mucous membranes at up to 0.3%, and in baby lotions, oils, and creams at up to 0.15%. It is also reported to be used in products that could possibly be inhaled; a maximum concentration of use of 0.075% was reported for both aerosol and pump hair spray formulations, and VCRP data indicated that Caprylhydroxamic Acid is used in face powder formulations.

NICNAS estimated the total SED to Caprylhydroxamic Acid from cosmetic applications. Assuming that the user is a 60 kg female, that dermal absorption is 100%, that Caprylhydroxamic Acid is always used at 0.5% in cosmetic formulations, and that there is daily exposure to 15 leave-on and rinse-off skin and hair formulations containing this ingredient, the total SED to Caprylhydroxamic Acid through the use of cosmetics was calculated as 1.17 mg/kg bw/d. Using this SED and an NOAEL of 50 mg/kg bw/d (that was derived in a subchronic oral toxicity study in rats), an MOE of 43 was calculated. Because this is not an acceptable MOE, the calculations were again performed with a maximum use concentration of 0.3% in formulations. With this concentration, the MOE was calculated to be 71. Even though this MOE is still below the generally acceptable value of 100, NICNAS stated, given that the exposure estimate is based on the conservative assumption of 100% dermal absorption, and the simultaneous use of various products containing the maximum concentration of Caprylhydroxamic Acid, the risk to the public is not considered unreasonable if products contain a maximum of 0.3%.

The rate and extent of dermal absorption following topical application of three suspensions containing (oil-in-water, silicone-in-water, and clear lotion) 0.15% Caprylhydroxamic Acid was examined in vitro using split-thickness human abdominal skin. The total absorbed dose of Caprylhydroxamic Acid was greatest with the oil-in-water suspension (41.89%; 3649 ng equiv/cm^2), followed by the silicone-in-water suspension (31.75%; 2747 ng equiv/cm^2), and then the clear lotion (22.93%; 1824 ng equiv/cm^2). Dermal delivery using these preparations was 51.45% (3649 ng equiv/cm^2), 43.84% (3793 ng equiv/cm^2), and 36.87% (2933 ng equiv/cm^2) of the applied dose, respectively.

Caprylhydroxamic Acid was rapidly hydrolyzed by rat liver homogenates to caprylic acid and hydroxylamine. In rats orally administered 1-[^{14}C]Caprylhydroxamic Acid, approximately 25% of the radioactivity was excreted as [^{14}C]CO_2 after 2 h, and by 24 h, 6.9% and 0.6% was excreted in the urine and the feces, respectively.

The oral LD_{50} of Caprylhydroxamic Acid is reported to be >8820 mg/kg in rats. In a 13-week study in which groups of 20 rats were dosed by gavage with up to 2500 mg/kg bw/d 10% Caprylhydroxamic Acid in lactose, with 5% aq. gum arabic as the vehicle, the NOAEL of the test article was determined to be 500 mg/kg bw/d (corresponding to up to 50 mg/kg bw Caprylhydroxamic Acid). Changes in some clinical chemistry parameters and organ weights (specifically an increase in absolute and relative spleen weight) were observed in the high-dose group.

A solution of Caprylhydroxamic Acid (10% in 5% gum arabic solution) was administered to groups of 18 mated rats, at doses up to 500 mg/kg bw/d, on days 9–14 of gestation. The majority of the dams were killed on day 20 of gestation; some were allowed to litter naturally. There was no mortality during the study, and there were no clinical signs of maternal toxicity. Caprylhydroxamic Acid (tested at 10% and at doses up to 500 mg/kg bw, corresponding to up to 50 mg/kg bw Caprylhydroxamic Acid) was not teratogenic.

In the Ames test, Caprylhydroxamic Acid in DMSO (at up to 5000 μg/plate) was not mutagenic to *S. typhimurium*, with or without metabolic activation, but there was weak but clear dose-dependent mutagenic activity toward *E. coli* at concentrations up to 1000 μg/plate. Caprylhydroxamic Acid was not genotoxic in a rec assay using *Bacillus subtilis*, and it was not genotoxic in an in vitro mammalian cell micronucleus test (at doses up to 450 μg/ml) using human peripheral blood lymphocytes, with or without metabolic activation.

Caprylhydroxamic Acid was not irritating or sensitizing in numerous studies. Tested neat, it was classified as non-irritant in an EpiDerm™ skin irritation test in reconstructed human epidermis tissue containing keratinocytes. In HRIPTs, cosmetic formulations containing 0.105% Caprylhydroxamic Acid (54 subjects; 24-hour semi-occlusive patches), 0.15% Caprylhydroxamic Acid (109 subjects, 48-hour occlusive patches), and 0.195% Caprylhydroxamic Acid (52 subjects; 24-hour semi-occlusive patches), an aqueous formulation containing 0.76% Caprylhydroxamic Acid (205 subjects; 24-hour semi-occlusive patches), Caprylhydroxamic Acid at 1.9% in petrolatum (95 subjects; 24-hour occlusive patches), and 100% Caprylhydroxamic Acid (52 subjects; 24-hour semi-occlusive patches), were not considered irritants or sensitizers. In 8 HRIPTs completed concurrently (104 subjects; 24-hour occlusive patches) in which 3 formulations containing 0.15% Caprylhydroxamic Acid were tested neat, and 5 formulations containing 5–15% Caprylhydroxamic Acid were tested as dilutions in distilled water

with a resulting test concentration of 0.3% Caprylhydroxamic Acid, reports of erythema and sometimes edema were noted in several subjects throughout the studies. However, it was the opinion of the researchers that neither the number nor the peak level of the responses were inconsistent with similar diluted formulations evaluated under repetitive, occlusive patch conditions, and thereby they concluded the test material "indicated no clinically significant potential for dermal irritation or allergic contact sensitization." Additionally in an HRIPT of Caprylhydroxamic Acid, 3.8% in petrolatum (104 subjects; 24-hour occlusive patches), two subjects had scores of 1 for erythema and edema on challenge day 3 ("suggesting induction of allergic contact sensitization") and 1 subject had scores of 2 for erythema and edema on challenge day 3 ("indicative of allergenic contact sensitization induction"); several subjects exhibited barely perceptible erythema, some also with erythema and edema (scores of 1), during induction.

A QRA for allergic contact dermatitis for Caprylhydroxamic Acid as used in cosmetic products was conducted; aggregate exposure was not considered, and the NESIL was chosen based on the highest dose/cm^2 that did not cause any sensitization. The results of all the applicable HRIPTs were examined, and accordingly, the highest concentration tested in which no positive responses were observed (NOEL) was 1055.6 μg/cm^2; the LOEL was 2111.1 μg/cm^2. Therefore, a WoE NESIL of 1056 μg/cm^2 was chosen. For each cosmetic product cateory, AELs were determined using this NESIL and appropriate QRA 2.0 SAFs; CELs were determined for the reported maximum concentrations of use for Caprylhdroxamic Acid. MOS values (calculated as AEL/CEL) ranged from 1.0 (for baby lotions, oils, and creams, not powder) to 269.2 (for bath soaps and detergents). Because all product types provided an acceptable MOS (i.e., ≥1), the study authors concluded that formulation of cosmetic products at their reported maximal concentration of Caprylhydroxamic Acid would present a negligible risk of inducing skin sensitization.

According to the results of in vitro ocular irritation studies, Caprylhydroxamic Acid is not expected to be an ocular irritant. In a BCOP test, it was concluded that 20% Caprylhydroxamic Acid was not considered an ocular corrosive or severe eye irritant under the conditions of the test. Additionally, in a MatTek EpiOcular™ MTT viability assay, the undiluted test article was classified as non-irritating to the eye.

In provocative testing, a patch test was conducted using 39 patients with compromised skin that had suspected allergenicity to a specific moisturizer formulation that contained 0.075–0.15% Caprylhydroxamic Acid. In this test group, positive results were reported to the new moisturizer containing the preservative mixture, to the preservative mixture, and to Caprylhydroxamic Acid itself. A "+" reaction was observed with concentrations ≥0.01%, "++" reactions with ≥0.032%, and "+++" reactions with ≥0.1% Caprylhydroxamic Acid. However, when the same patients were tested with an "old" version of the moisturizer that was preserved with parabens, negative results were reported with the old formulation. Additionally, in 33 control subjects (20 with eczema who had not used this specific moisturizer product that contained the preservative mixture, and 13 with uncompromised skin barrier function), negative results were reported to the preservative mixture and to Caprylhydroxamic Acid alone.

Discussion

Caprylhydroxamic Acid is reported to function as a chelating agent in cosmetics; the hydroxamic acid functional group accounts for the chelating property. However, the Panel noted that Caprylhydroxamic Acid has a C8 alkyl chain, and the hydroxamates that are reported to be the most active inhibitors of metalloproteinase enzymes are shorter chain molecules with peptide-mimetic structures that facilitate specific protein binding interactions.

The Panel was concerned with the inconsistent outcomes regarding dermal sensitization. However, upon further review, the Panel determined cases of increased sensitization with the use of a moisturizer in Finland, a product that had been reformulated to include Caprylhydroxamic Acid, appeared to be related to use on damaged skin, which most likely resulted in increased penetration. Therefore, the Panel stated that caution should be taken with use of Caprylhydroxamic Acid in a manner that would result in increased penetration, such as formulation with penetration enhancers. This is especially important in product types with an MOS, based on an AEL/CEL ratio, at or near 1, as calculated in a QRA. According to the results of a QRA that was submitted to CIR, product types with an AEL/CEL of 1 include baby lotions, oils, and creams; the WoE NESIL used in the QRA was 1056 μg/cm^2. This QRA did not consider penetration enhancers or damaged skin, and manufacturers need to take that into account upon formulation.

The Panel noted that carcinogenicity data were absent. However, the fact that the genotoxicity data were largely negative, in conjunction with the lack of structural alerts for carcinogenicity, mitigated concerns regarding carcinogenicity.

Caprylhydroxamic Acid is reported to be used at 0.075% in both aerosol and pump hair spray formulations, and could possibly be incidentally inhaled during customary use. Therefore, the Panel discussed the issue of potential inhalation toxicity. The Panel noted that in aerosol products, most droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredient is used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. 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.

Conclusion

The Expert Panel for Cosmetic Ingredient Safety concluded that Caprylhydroxamic Acid is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Author's Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 555 13th St., NW, Suite 300W, Washington, DC 20004. cirinfo@cir-safety.org

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