Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics

Status:	Scientific Literature Review for Public Comment
Release Date:	February 21, 2019
Panel Meeting Date:	June 6-7, 2019

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date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Monice M. Fiume, Senior Director.

1620 L Street, NW, Suite 1200 ◊ Washington, DC 20036-4702 ◊ ph 202.331.0651 ◊ fax 202.331.0088 ◊
cirinfo@cir-safety.org

INTRODUCTION

This Scientific Literature Review (SLR) is the initial step in preparing a safety assessment of Caprylhydroxamic Acid as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *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Included in this safety assessment are relevant published and unpublished data that are available for each endpoint that is evaluated.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 CIR typically evaluates, is provided on the 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 Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment was found on the National Industrial Chemicals Notification and Assessment Scheme (NICNAS)[2] and European Chemicals Agency (ECHA)[3] websites. These summaries are available on those websites, and when deemed appropriate, information from these summaries has been included in this report.

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. 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.

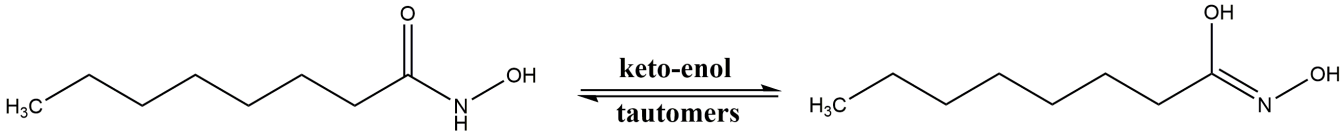

Figure 1. Caprylhydroxamic Acid

The hydroxamic acid functional group makes Caprylhydroxamic Acid an excellent 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]

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.

Physical and Chemical Properties

Caprylhydroxamic Acid is a white to tan crystalline solid,[2,3] with a molecular weight of 159.23 Da.[5] Additional physical and chemical properties are described in Table 1.

Method of Manufacture

While method of manufacture data specific to the production of Caprylhydroxamic Acid as a cosmetic ingredient were not found in the published literature, and unpublished data were not submitted, there are a number of published strategies for the synthesis of this ingredient. For instance, Caprylhydroxamic Acid can be synthesized via a 2-step, one-pot, photocatalytic reaction of caprylaldehyde, diisopropyl azodiformate, and phenylglyoxylic acid, followed by hydroxylamine chlorohydrate and triethylamine.[6] Another facile methodology that could be used to synthesize this ingredient includes the amidation of an acid chloride.[7] Specifically, capryloyl chloride is reacted with hydroxylamine chlorohydrate under alkaline conditions.

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 these ingredients 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 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 2019 VCRP survey data and the results of the concentration of use survey conducted by the Council, Caprylhydroxamic Acid is reported to be used in 227 formulations[8] at maximum leave-on and rinse-off concentrations of 0.25% and 0.3%, respectively.[9] (Table 2) Caprylhydroxamic Acid is used in products applied near the eye at up to 0.2%, 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%. Although there are uses reported to the VCRP that could result in incidental ingestion (i.e., lipsticks), concentration of use data were not reported for these uses.

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, 95% to 99% of the 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 not restricted from use in any way under the rules governing cosmetic products in the European Union.[14]

Exposure 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 make-up 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/day (234 mg/kg bw/day) to products containing Caprylhydroxamic Acid. Based on these parameters, total SED to Caprylhydroxamic Acid through the use of cosmetics was calculated as 1.17 mg/kg bw/day.

Non-Cosmetic

Use of Caprylhydroxamic Acid as growth-promoting feed additive was reported.[15]

Very little information specific to the non-cosmetic use of Caprylhydroxamic Acid was found in the published literature. However, hydroxamic acids have use in numerous applications, including biomedical use as therapeutic agents; 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.[16]

TOXICOKINETICS STUDIES

Dermal Penetration

Based on the physicochemical properties of Caprylhydroxamic Acid, such as the low molecular weight and the octanol/water partition coefficient, percutaneous absorption is likely.[2]

Absorption, Distribution, Metabolism, and Excretion

Given the low molecular weight of Caprylhydroxamic Acid, absorption across the gastrointestinal (GI) tract is possible by passive diffusion through the aqueous pores or micellular solubilization.[2]

Animal

Oral

Orally administered 1-[^{14}C]-Caprylhydroxamic Acid (1.27 mg/kg) was rapidly hydrolyzed by liver homogenates in rats to caprylic acid and hydroxylamine, and hydroxamic acid was not detected in any tissues (except in the GI tract) 2 h after administration.[17] "Considerable amounts" of radioactivity were found in the liver and the heart, but most was excreted as expired $^{14}CO_2$. Approximately 25% of the total radioactivity was excreted as $^{14}CO_2$ at 2 h. Within 24 h, 6.9% and 0.6% was excreted in the urine and the feces, respectively. (Additional details are not presented in that only an English abstract was available.)

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

The oral LD_{50} of Caprylhydroxamic Acid is > 8820 mg/kg in rats.[2] (Details were not available.)

Subchronic Toxicity Studies

Oral

Groups of 10 male and 10 female Wistar rats were dosed by gavage for 13 wks with 0, 100, 500, or 2500 mg/kg bw/day 10% Caprylhydroxamic Acid in lactose.[2,18] The vehicle was 5% aqueous (aq.) gum arabic. There was not mortality attributed to the test article; 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 the following observations were reported for this group. Clinical observations included "slowness in activity." There were significant decreases in alanine amino transferase, glucose and potassium levels in males, and there was a significant increase in leukocyte count and significant decreases in erythrocyte, hematocrit, and hemoglobin counts 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. At microscopic examination, slight atrophy in the epithelial cells of the renal glomeruli and hemosiderin deposits in the spleen were reported. The no-observable-adverse-effect-level (NOAEL) of the test article (10% Caprylhydroxamic Acid in lactose) was determined to be 500 mg/kg bw/day; accordingly, the NOAEL of undiluted Caprylhydroxamic Acid is expected to be 50 mg/kg bw/day.[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/day 10% Caprylhydroxamic Acid[2] in 5% gum arabic by gavage on days 9 through 14 of gestation.[2,19] Twelve dams of the 0, 50, and 250 mg/kg bw/day groups, and all of the dams of the 500 mg/kg bw/day 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/day 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/day dose group were significantly lower at birth and at weaning. Decreased growth that was observed for fetuses and neonates of the higher dose groups were considered to be a result of the slight suppression of maternal body weight gains and feed consumption. Caprylhydroxamic Acid (10%) was not teratogenic.

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 towards *E. coli* at concentrations up to 1000 µg/plate, but not was not mutagenic to *S. typhimurium*.[15] In another Ames test, Caprylhydroxamic Acid in DMSO, tested at concentrations up to 5000 µg/plate with *S. typhimurium* TA1535, TA98, TA100, TA102, and TA97a, was not mutagenic.[2,3] Solvent and positive controls gave expected results.

Caprylhydroxamic Acid was not genotoxic in a rec assay using *Bacillus subtilis* H17 Rec^+ and M45 Rec^-.[15] (No other details were provided.)

The genotoxic potential of Caprylhydroxamic Acid was also evaluated in an in vitro mammalian cell micronucleus test using human peripheral blood lymphocytes, with and without metabolic activation, in accord with Organisation for Economic Co-operation (OECD) test guideline (TG) 487.[3] Dose levels tested using a 4-h treatment period with and without activation were 25 – 450 µg/ml, and with a 24-h treatment period without activation were 7.5 – 50 µg/ml. DMSO served as the vehicle. Caprylhydroxamic Acid was not 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.

OTHER RELEVANT STUDIES

Enzymatic Activity

Data specific to the enzymatic activity of Caprylhydroxamic Acid were found in the published literature. However, in general, hydroxamic acids are capable of the inhibition of a variety of enzymes, including ureases, peroxidases, and matrix metalloproteinases.[16]

Antifungal Activity

The antifungal activity of hydroxamic acids was examined.[20] Caprylhydroxamic Acid had a minimum inhibitory concentration (MIC) of 32 µg/ml against *Trichophyton interdigitale* and *Microsporium gypseum*, of 100 µg/ml against *Saccharomyces sake*, and of 320 µg/ml against *Candida albicans* and *Aspergillus oryzae*. Antifungal activity increased with an increase in carbon number, reaching maximum activity near C10.

DERMAL IRRITATION AND SENSITIZATION

Irritation and Sensitization

In Vitro

The dermal irritation potential of Caprylhydroxamic Acid was evaluated in a reconstructed human epidermis test using non-transformed keratinocytes, in accord with OECD TG 439.[3] Caprylhydroxamic Acid, tested neat, was classified as non-irritant; tissue viability was 102.587%.

Human

A human repeated insult patch test (HRIPT) was completed in 52 subjects to determine the irritation and sensitization potential of Caprylhydroxamic Acid.[2] Semi-occlusive patches of undiluted Caprylhydroxamic Acid were applied for 24 h to the upper back of each subject 3 days/wk for 3 wks, for a total of 9 applications. The test sites were evaluated 24 or 48 h after patch removal. Following a 2-wk non-treatment period, challenge patches were applied to previously untreated test sites on the back for 24 h, and the test sites were evaluated upon patch removal and at 48 and 72 h. Undiluted Caprylhydroxamic Acid was not an irritant or sensitizer in this study.

In another study using 104 subjects, an HRIPT was conducted using occlusive patches of Caprylhydroxamic Acid; the concentration tested was not specified.[3] Responses of scattered, transient barely perceptible-to-moderate erythema, with occasional edema, were noted throughout the study. It was stated 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. No evidence of induced allergic contact sensitization was observed." Additionally, "the test material indicated no clinically significant potential for dermal irritation or allergic contact sensitization." (Details were not provided.)

OCULAR IRRITATION STUDIES

In Vitro

The ocular irritation potential of 20% Caprylhydroxamic Acid was evaluated in a bovine corneal opacity and permeability (BCOP) test performed in accord with OECD TG 437.[2] A 4-h exposure period was followed by a 3-h incubation period. The vehicle (minimal essential media) served as the negative control; a positive control was not used. The in vitro irritancy score was calculated as 12.12; 20% Caprylhydroxamic Acid was not considered an ocular corrosive or severe eye 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.[2,3] The chemical was tested neat, and the exposure periods were 16, 64, and 256 mins. Appropriate negative and positive controls were used. The ET_{50} was 130.8 min, and undiluted Caprylhydroxamic Acid was classified as non-irritating to the eye.

CLINICAL STUDIES

Provocative Testing

Patch testing was performed, according to European Society of Contact Dermatitis test guidelines, in 39 patients with compromised skin that were suspected of developing contact allergy.[21] Symptoms, which appeared as acute, itchy, often sharply demarcated erythematous eczema, were thought to be due to the use of a moisturizer that had recently been reformulated. In early 2014, the moisturizer was reformulated to remove parabens; the new moisturizer formulation contained a preservative mixture that consisted of 65 – 75% phenoxyethanol, 10 – 20% Caprylhydroxamic Acid, and 5 – 10% methylpropanediol. This preservative mixture was added to the new moisturizer formulation at a concentration of 0.75%.

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; the preservative mixture itself diluted in petrolatum (pet.; 0.05% - 1.5%); and Caprylhydroxamic Acid (or its potassium salt) diluted in pet. (0.001% - 3.2%). Occlusive patches were applied for 2 days, 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 3. 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%. Negative results were reported in both the eczema-patient control group and the normal control subjects. The study authors did not elaborate on the lack of reaction by the 33 control subjects to the preservative mixture or Caprylhydroxamic Acid.

Case Reports

In Finland, two case reports of contact allergy were attributed to use of a moisturizer that contained Caprylhydroxamic Acid.[22] Although the moisturizer had been reformulated to no longer include a preservative that contained Caprylhydroxamic Acid (it was only included in formulations produced 2014 – 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

Method of manufacture data specific to the production of Caprylhydroxamic Acid as a cosmetic ingredient were not found. However, in general, Caprylhydroxamic Acid can be synthesized via a 2-step, one-pot, photocatalytic reaction of caprylaldehyde, diisopropyl azodiformate, and phenylglyoxylic acid, followed by hydroxylamine chlorohydrate and trimethylamine. Additionally, it can be synthesized by reacting capryloyl chloride with hydroxylamine chlorohydrate under alkaline conditions.

Caprylhydroxamic Acid is reported to be > 99% pure. At very high or low pH, Caprylhydroxamic Acid may be hydrolyzed to caprylic acid and hydroxylamine.

According to 2019 FDA VCRP data and Council survey results, Caprylhydroxamic Acid is reported to be used in 227 formulations at maximum leave-on and rinse-off concentrations of 0.25% and 0.3%, 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.

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, total SED to Caprylhydroxamic Acid through the use of cosmetics was calculated as 1.17 mg/kg bw/day.

Based on the physicochemical properties of Caprylhydroxamic Acid, such as low molecular weight, both percutaneous absorption and absorption across the GI tract are considered likely. In rats, orally administered 1-[^{14}C]-Caprylhydroxamic Acid was rapidly hydrolyzed by liver homogenates to caprylic acid and hydroxylamine. Approximately 25% of the radioactivity was excreted as $^{14}CO_2$ 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 > 8820 mg/kg in rats. In a 13-wk study in which groups of 20 rats were dosed by gavage with up to 2500 mg/kg bw/day 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/day; accordingly, the NOAEL of undiluted Caprylhydroxamic Acid is expected to be 50 mg/kg bw/day. Changes in some clinical chemistry parameters and organ weights (specifically an increase in absolute and relative spleen weight) were observed in the 2500 mg/kg bw/day group.

Caprylhydroxamic Acid (10% in 5% gum arabic) was administered to groups of 18 mated rats, at doses up to 500 mg/kg bw/day, 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 (10%) 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 towards *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.

Hydroxamic acids are capable of the inhibition of a variety of enzymes, including ureases, peroxidases, and matrix metalloproteinases. Caprylhydroxamic Acid showed antifungal activity; it had an MIC of 32 µg/ml against *Trichophyton interdigitale* and *Microsporium gypseum*.

Caprylhydroxamic Acid was not irritating or sensitizing in several studies. It was classified as non-irritant in a reconstructed human epidermis test using non-transformed keratinocytes. Additionally, undiluted Caprylhydroxamic Acid was not an irritant or sensitizer in an HRIPT study completed with 52 subjects. In an HRIPT with 104 subjects, Caprylhydroxamic Acid (concentration not stated) caused scattered, transient barely perceptible to moderate erythema, with occasional edema, but the researchers concluded that "the test material indicated no clinically significant potential for dermal irritation or allergic contact sensitization."

In provocative testing, a patch test was conducted using 39 patients with compromised skin that had suspected allergenicity to a specific moisturizer formulation; this formulation contained 0.75% of a preservative mixture that included 10 – 20% 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.

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.

INFORMATION SOUGHT

The CIR is seeking the following information on Caprylhydroxamic Acid for use in the resulting safety assessment:

1. Dermal penetration data; if absorbed, additional studies may be requested
2. In vivo genotoxicity data; if positive carcinogenicity studies may be requested.

TABLES

Table 1. Physical and chemical properties

Property	Value	Reference
Physical Form	crystalline solid	2,3
Color	white white to tan	3 2
Odor	mild, characteristic	3
Molecular Weight (g/mol)	159.23	5
Density (g/cm^3 @ 25ºC)	0.3413 (sample not compressed) 0.4789 (sample tamped down)	2,3
Vapor pressure (mm Hg@ 25 ºC)	2.50 x 10^{-6} (estimated)	2
Melting Point (ºC)	≥ 78 to ≤ 81 81	3 2
Water Solubility (g/L @ 23ºC)	1.55	2,3
log K_{ow} (@ 25°C)	1.66 (estimated) 2.827 ± 0.191 (estimated)	2,3 5
Disassociation constants (pKa; (@ 25°C)	9.56 ± 0.20 (estimated)	5

Table 2. Frequency (2019) and concentration (2018) of use of Caprylhydroxamic Acid

	# of Uses[8]	Max Conc of Use (%)[9]
Totals*	**227**	**0.075 – 0.3**
Duration of Use		
Leave-On	*162*	*0.075 – 0.25*
Rinse-Off	*65*	*0.12 – 0.3*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	14	0.11 – 0.2
Incidental Ingestion	2	NR
Incidental Inhalation-Spray	1; 43[a]; 68[b]	0.075 (aerosol and pump) 0.075 - 0.23[a]
Incidental Inhalation-Powder	3; 68[b]; 4[c]	0.12[c]
Dermal Contact	206	0.11 – 0.3
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	18	0.075 – 0.23
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	6	0.13 – 0.3
Baby Products	6	0.15

*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.
[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.
NR – no reported use

Table 3. Patch test results in patients with compromised skin that had suspected contact allergy to a new moisturizer formulation

	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***				

REFERENCES

1. Nikitakis J, Kowcz A. Web-Based International Cosmetic Ingredient Dictionary and Handbook. 2019. http://webdictionary.personalcarecouncil.org/jsp/Home.jsp. Washington, DC: Personal Care Products Council. 2019. Accessed: 02/08/2019.

2. National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Public Report: Octanamide, N-hydroxy- (INCI name: Caprylhydroxamic Acid) (File No.: LTD/1543) 2012 https://www.nicnas.gov.au/__data/assets/word_doc/0005/6773/LTD1543FR.docx Accessed 02/01/2019

3. European Chemicals Agency (ECHA). *N*-Hydroxyoctanamide (CAS No. 7377-03-9) https://echa.europa.eu/en/registration-dossier/-/registered-dossier/25355 2018. Accessed: 02/08/2019

4. Ganeshpurkar A, Kumar D, Singh SK. Strategies for the Synthesis of Hydroxamic Acids *Current Organic Synthesis* 2017;14(0):1-12.

5. Advanced Chemistry Development (ACD/Labs). Software 11.02. 2019.

6. Papadopoulos GN, Kokotos CG. Photoorganocatalytic One-Pot Synthesis of Hydroxamic Acids from Aldehydes. *Chemistry (Weinheim an der Bergstrasse, Germany)* 2016;22(20):6964-6967.

7. BenGuzzi S, El-Warfalli A. Synthesis and characterization of normal and N-substituted octanohydroxamic acid complexes. *Der Chemica Sinica* 2014;5(3):47-50.

8. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program (VCRP) - Frequency of Use of Cosmetic Ingredients. College Park, MD 2019. (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 3 2019; received February 13, 2019.)

9. Personal Care Products Council. Council Concentration of Use Survey: Caprylhydroxamic Acid. 2018. (Unpublished data submitted by the Personal Care Products Council on October 25, 2018.)

10. Johnsen MA. The influence of particle size *Spray Technol Marketing* 2004;14(11):24-27.

11. Rothe H. Special Aspects of Cosmetic Spray Evalulation. 2011. Unpublished data presented at the 26 September CIR Expert Panel meeting. Washington, D.C.

12. Bremmer HJ, Prud'homme de Lodder LCH, Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. RIVM 320104001/2006. Pages1-77.

13. Rothe H, Fautz R, Gerber E, et al. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett* 2011;205(2):97-104.

14. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. 2014. http://ec.europa.eu/growth/tools-databases/cosing/. Accessed: 02/08/2019.

15. Ohta T, Moriya M, Kaneda Y, et al. Mutagenicity screening of feed additives in the microbial system. *Mutat Res, Genet Toxicol Test* 1980;77(1):21-30.

16. Muri E, Nieto M, Sindelar R, Willamson J. Hydroxamic Acids as Pharmacological Agents. *Current Medicinal Chemistry* 2002;9(17):1631-1653.

17. Kobashi K, Takebe S, Hase J. Distribution, metabolism and excretion of caprylo- and nicotinohydroxamic acid. [English abstract only.] *Yakugaku zasshi : Journal of the Pharmaceutical Society of Japan* 1973;93(12):1564-1572.

18. Sugiyama K, Sagami F, Chiba T. Chronic toxicity test of Taselin in rats. (English abstract only) *Jpn J Vet Sci* 1974;36(6):525-538.

19. Suzuki Y, Okada F, Chiba T. Negative result of teratological study on caprylo-hydroxamic acid in rats. *Nihon juigaku zasshi The Japanese journal of veterinary science* 1975;37(5):307-309.

20. Hase J, Kobashi K, Kawaguchi N, Sakamoto K. Antimicrobial activity of hydroxamic acids. *Chem Pharm Bull* 1971;19(2):363-368.

21. Ackermann L, Virtanen H, Korhonen L, et al. An epidemic of allergic contact dermatitis caused by a new allergen, caprylhydroxamic acid, in moisturizers. *Contact dermatitis* 2017;77(3):159-162.

22. Kluger N. Contact allergy to moisturizers in Finland: The tale of the lurking tube in the medicine cupboard. *Contact dermatitis* 2018;78(4):289-290.